Understanding Body Weight Variability in the Context of Weight Management

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The candidate confirms that the work submitted is his/her own, except where work which has formed part of jointly-authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

(1) Chapter 2 includes a joint-authored systematic review and meta-analysis published in Obesity Reviews. The full reference is as follows:

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I was solely responsible for study design, data analysis and manuscript writing. Guidance on the concept was provided from RJS and GF. Additional reviewers (ROD, KB and GF) helped with study selection (as suggested by Cochrane). All named authors provided suggested edits to the final manuscript.

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This study was a re-analysis of data previously collected by the diet, obesity, and genes (DiOGenes) trial. TML, MAVB and AA were involved in the original trial design and responsible for data collection. I was solely responsible for conceptualisation and study design of this secondary analysis, in addition to data analysis and manuscript writing. Guidance on the concept was provided from RJS and GF. All named authors provided suggested edits to the final manuscript.

(3) In Chapter 4, the NoHoW trial is introduced which was a large multi-centre weight loss maintenance trial. The data collected during this trial was used to conduct the remainder of the analyses in this thesis. I took no part in the design of the NoHoW trial as part of this PhD (which was fully designed before the initiation of my PhD), however I did work extensively on data collection, management of the trial conduct at one of the trial centres, data management, data analysis and dissemination for around the first 2 years of my PhD.

(4) Chapter 5 includes an original research article published in The Journal of Medical Internet Research: mHealth and uHealth. The full reference is as follows:

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The study used data collected by the NoHoW consortium. I was solely responsible for conceptualisation and study design, data analysis and manuscript writing. All named authors provided suggested edits to the final manuscript.

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The study used data collected by the NoHoW consortium. I was solely responsible for conceptualisation and study design, data analysis and manuscript writing. All named authors provided suggested edits to the final manuscript.

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Abstract

In the last 5 years, a strong scientific interest in the role of body weight variability (BWV) in health and disease has re-emerged. Due to varied methodologies, the literature is conflicting, yet generally suggests that BWV could be a significant risk factor for disease and mortality. However, the phenomenon remains inadequately measured and poorly understood. This thesis took two discrete but complementary approaches to: (1) understand the aetiology of a weight cycle and (2) understand the measurement of BWV, and its physiological and psychological correlates, with using high-resolution estimates generated through novel technological and statistical procedures.

With regards to (1), two studies examined how the rate, amount and composition of weight loss affect subsequent weight regain and appetite. It was found that the amount and rate of weight loss was directly associated with the magnitude of regain, and that greater proportions of fat-free mass loss predicted greater weight regain and appetite in men but not women.

With regards to (2), five studies using data collected from the NoHoW weight loss maintenance trial aimed to (i) improve the measurement of BWV and use this to investigate the: (ii) predictability of weight fluctuations; (iii) impact of BWV on health markers; (iv) impact of short-term BWV on long-term weight management and (v) psychological and behavioural causes and consequences of BWV.

Briefly, the main findings were that (a) a greater understanding of the measurement (and associated errors) of BWV was achieved; (b) fluctuations in body weight could be predicted by temporal cues (i.e. weekly cycles or holidays); (c) BWV did not affect health markers over 12-months; (d) greater short-term BWV predicted increased weight at 12-18 months and (e) a range of eating behaviour and psychological traits were identified in the aetiology of BWV. To conclude, a full discussion and recommendations for the future study of BWV were provided.

Table of Contents

ACKNOWLEDGEMENTS V

ABSTRACT VI

TABLE OF CONTENTS VII

LIST OF TABLES XII

LIST OF FIGURES XIII

SUMMARY & OBJECTIVES XIV

1. INTRODUCTION 1

1.1 OBESITY 1
1.1.1 REGULATION OF BODY WEIGHT 2
1.1.2 ASSOCIATIONS BETWEEN BMI AND NONCOMMUNICABLE DISEASES 6
1.2 WEIGHT LOSS 8
1.2.1 WEIGHT LOSS PREVALENCE 8
1.2.2 STRATEGIES TO ACHIEVE WEIGHT LOSS 9
1.3 AN IMPETUS FOR WEIGHT REGAIN 11
1.3.1 THE PHYSIOLOGICAL IMPETUS FOR WEIGHT REGAIN 12
1.3.2 THE NECESSITY FOR WEIGHT LOSS MAINTENANCE INTERVENTION 16
1.4 WEIGHT CYCLING 19

CHAPTER 2. ASSOCIATIONS BETWEEN THE AMOUNT, RATE AND COMPOSITION OF WEIGHT LOSS AND SUBSEQUENT WEIGHT REGAIN 21

2.1 INTRODUCTION 21
2.1.1 ASSOCIATIONS BETWEEN THE AMOUNT OF WEIGHT LOST AND REGAINED 22
2.1.2 ASSOCIATIONS BETWEEN THE RATE OF WEIGHT LOSS AND WEIGHT REGAINED 23
2.1.3 CHANGES IN BODY COMPOSITION DURING WEIGHT LOSS 24
2.1.4 THE ROLE OF CHANGES IN BODY COMPOSITION ON APPETITE 25
2.2 ASSOCIATIONS BETWEEN THE RATE, AMOUNT, AND COMPOSITION OF WEIGHT LOSS AS PREDICTORS OF WEIGHT REGAIN: A SYSTEMATIC REVIEW AND META-REGRESSION 27
2.2.1 OBJECTIVES 27
2.2.2 METHODS 28
2.2.3 RESULTS 31
2.2.4 DISCUSSION 47
2.3 ASSOCIATIONS BETWEEN THE PROPORTION OF FAT-FREE MASS LOSS DURING WEIGHT LOSS, CHANGES IN APPETITE AND WEIGHT REGAIN 56
2.3.1 OBJECTIVES 57
2.3.2 METHODS 58
2.3.3 RESULTS 62
2.3.4 DISCUSSION 68
2.3 GENERAL CONCLUSIONS 76

2.4 Progressing to Weight Variability **77**

CHAPTER 3. A REVIEW OF THE LITERATURE ON THE OPERATIONALISATION OF BODY WEIGHT INSTABILITY AND ITS HEALTH CONSEQUENCES **80**

3.1 Definitions of Weight Instability **80**
3.1.1 Weight cycling 81
3.1.2 Body Weight Variability 86
3.2 Associations Between Weight Instability and Health Risk **89**
3.3.1 All-Cause Mortality 97
3.3.2 Cardiovascular Disease 97
3.3.3 Type 2 Diabetes 98
3.3.4 Discussion 99
3.3. Mechanisms Linking Weight Instability to Health Risks **100**
3.3.1 Evidence from Human Studies 101
3.4.2 Evidence from Animal Models 107
3.4.3 Discussion 112
3.4 Associations Between Weight Instability and Weight Management **115**
3.5 Overall Conclusions **116**
3.6 Directions for Future Research **117**

CHAPTER 4: GENERAL METHODS **119**

4.1 The NoHoW study **119**
4.1.1 Rationale 119
4.1.2 Digital Behaviour Change Interventions 120
4.1.2 Aims and Hypotheses 121
4.1.3 Study Design 122
4.1.4 Participant Recruitment 123
4.1.5 The NoHoW toolkit 125
4.1.6 Tracking technologies 125
4.1.7 Physical measurements 127
4.1.8 Self-report measurements 129
4.1.9 Participant demographics 130
4.1.10 Weight history 131
4.2 Processing of body weight data **131**
4.2.1 Data cleaning 131
4.3 Calculation of body weight variability **132**
4.3.1 Coefficient of Variation 133
4.3.2 Mean Absolute Successive Weight Variability 133
4.3.3 Root Mean Square Error 134
4.3.4 Non-linear Mean Deviation 135

CHAPTER 5. ESTIMATING WEIGHT VARIABILITY USING WIFI-CONNECTED SMART SCALES **137**

5.1 Introduction **137**
5.1.1 Remote Tracking 137
5.1.2 The Problem of Missing Data 138
5.1.3 Data Imputation 139

5.1.4 Objectives 140
5.2 Methods 140
5.2.1 Materials and Subjects 140
5.2.2 Analysis overview 141
5.2.3 Data cleaning 142
5.2.3 Simulation of Missing Data 142
5.2.4 Imputation 143
5.2.4 Calculation of Body Weight Variability 145
5.3 Results 145
5.3.1 Imputation Performance 145
5.3.2 Errors in Body Weight Variability Estimates 148
5.4 Discussion 152
5.4.1 Imputation Performance 152
5.4.2 Validation of Body Weight Variability Estimates Under Different Conditions 153
5.4.3 Strengths and Limitations 153
5.5 Conclusions 154

CHAPTER 6. WEEKLY, SEASONAL AND HOLIDAY BODY WEIGHT FLUCTUATIONS 155

6.1 Introduction 155
6.1.1 Body Weight Stability Over the Long Term 155
6.1.2 Body Weight Homeostasis Over the Short Term 156
6.1.3 Temporality, Energy Balance Behaviours and Body Weight 157
6.1.4 Individual Characteristics and Energy Balance Behaviours 158
6.1.5 Measurement of Weight Fluctuation 159
6.1.5 Objectives 159
6.2 Methods 160
6.2.1 Study Design & Participants 160
6.2.2 Participants 160
6.2.3 Anthropometrics Measurements 160
6.2.4 Fitbit Aria Scale 161
6.2.5 Statistical Analysis 161
6.3 Results 163
6.3.1 Weekly Fluctuations in Body Weight 165
6.3.2 Christmas Fluctuation in Body Weight 166
6.3.3 Season Fluctuations in Body Weight 169
6.4 Discussion 172
6.4.1 Weekly Weight Fluctuations 172
6.4.2 Holiday Weight Fluctuations 175
6.4.3 Seasonal Weight Fluctuation 177
6.4.4 Strengths and Limitations 178
6.4.5 Conclusions 179

CHAPTER 7. ASSOCIATIONS BETWEEN BODY WEIGHT VARIABILITY, HEALTH MARKERS AND BODY COMPOSITION 181

7.1 Introduction 181
7.1.1 Body Weight and Cardiometabolic Health 181
7.1.2 Body Weight Variability and Health Outcomes 182
7.1.3 Objectives 183

7.2 Methods 184
7.2.1 Study Design 184
7.2.2 Participants 184
7.2.3 Physiological Measurements 184
7.2.4 Physical Activity 185
7.2.4 Body Weight Variability 186
7.2.5 Statistical Analysis 187
7.3 Results 189
7.3.1 Primary Analysis 189
7.3.2 DXA sub-analysis 191
7.4 Discussion 191
7.4.1 Associations Between BWV and Change in Health Markers and Body Composition 196
7.4.2 Associations Between Weight Change and Change in Health Markers 198
7.4.3 Strength and Limitations 198
7.5 Conclusions 199
7.6 Future Study of Body Weight Variability and Health 200

CHAPTER 8. ASSOCIATIONS BETWEEN SHORT-TERM BODY WEIGHT VARIABILITY AND LONGER-TERM WEIGHT OUTCOMES 201

8.1 Introduction 201
8.1.1 Identification of Weight Outcome Predictors 201
8.1.2 Early Predictors of Weight Outcomes 202
8.1.3 Short-term Body Weight Variability 203
8.1.4 Objectives 204
8.2 Methods 204
8.2.1 Study Design 204
8.2.2 Participants 204
8.2.3 Prior Weight Loss 205
8.2.4 Body Weight 206
8.2.5 Body Weight Variability 207
8.2.6 Statistical Analysis 207
8.3 Results 208
8.4 Discussion 213
8.4.1 Associations between Body Weight Variability and Longer-Term Weight Outcomes 213
8.4.2 Potential Causes of Body Weight Variability 215
8.4.3 Strengths and Limitations 217
8.5 Conclusions 218

CHAPTER 9. AN EXPLORATORY INVESTIGATION OF THE RELATIONSHIPS BETWEEN PSYCHOLOGY, BEHAVIOUR AND BODY WEIGHT VARIABILITY 219

9.1 Introduction 219
9.1.1 Associations Between and Psychological and Behavioural Factors and Self-Reported Weight Cycling 220
9.1.2 Associations Between Psychological and Behavioural Factors and Body Weight Variability 222
9.1.3 Exploratory Research Approaches 223
9.1.4 Objectives 223
9.2 Methods 224
9.2.1 Study Design 224

9.2.2 Participants 224
9.2.3 Body Weight Variability 225
9.2.3 Psychological and behavioural measurements 225
9.2.4 Weight History Measurements 227
9.2.5 Statistical analysis 227
9.3 Results 229
9.3.1 Baseline Regressions 230
9.3.2 Stepwise Regressions 231
9.3.3 Clustering Analyses 232
9.3.4 Bi-directional Relationships 234
9.4 Discussion 235
9.4.1 Stepwise Regressions 236
9.4.2 Clustering Analyses 237
9.4.3 Longitudinal Analysis 237
9.4.4 Strengths and Limitations 238
9.5 Conclusions 239

CHAPTER 10. FINAL DISCUSSION 241

10.1 Summary of PhD Findings 242
10.2 Strengths of the PhD 251
10.3 Limitations of the PhD 253
10.4 Implications of the PhD 254
10.5 New Research Pathways and Future Recommendations 256
10.6 Final Conclusions 257

LIST OF REFERENCES 259

LIST OF ABBREVIATIONS 293

APPENDICES 295

Appendix 2.1. Search Strategy 295
Appendix 2.2: Bias Testing for Systematic Review and Meta-Analysis 296
Appendix 2.3 Test of Collinearity for Model 3 Variables 297
Appendix 2.4: Supplementary Analysis 1 - Associations between appetite perception responses and subsequent weight regain. 299
Appendix 2.5: Supplementary Analysis 2 - Associations of reduction in fat-free mass (FFM) and fat mass (FM) from baseline on weight change and appetite. 301
Appendix 6.1 Tukey Post Hoc Results for Day of Week Comparisons 307
Appendix 6.2 Tukey Post Hoc Results for Christmas Comparisons 310
Appendix 6.3 Tukey Post Hoc Results for Between Season Comparisons 311
Appendix 7.1 – DXA Sub-analysis 313
Appendix 7.2 – Longitudinal Sensitivity Analyses 316
Appendix 8.1. Supplementary Analysis - Associations between body weight variability and concurrent weight change 324
Appendix 8.2. Model 2 Regression Results 325
Appendix 9.1 Correlations Between Psychometric Variables and Body Weight Variability 332

List of Tables

TABLE 2.1	STUDY 1. STUDY CHARACTERISTICS	33
TABLE 2.2	STUDY 1. DESCRIPTIVE RESULTS	37
TABLE 2.3	STUDY 1. RATE AND AMOUNT OF WEIGHT LOSS AS PREDICTORS OF WEIGHT REGAIN	43
TABLE 2.4	STUDY 1. FAT MASS AND FAT-FREE MASS LOSS AS PREDICTORS OF WEIGHT REGAIN	46
TABLE 2.5	STUDY 1. RATE AND AMOUNT OF WEIGHT LOSS AS PREDICTORS OF FAT-FREE MASS LOSS DURING WEIGHT LOSS	48
TABLE 2.6	STUDY 2. PARTICIPANT CHARACTERISTICS	62
TABLE 2.7	STUDY 2. UNIVARIATE REGRESSION ANALYSES PREDICTING WEIGHT REGAIN	65
TABLE 2.8	STUDY 2. SELF-REPORTED APPETITE PERCEPTIONS MEASURED BY VISUAL ANALOGUE SCALE IN RESPONSE TO A FIXED TEST MEAL	69
TABLE 3.1	DEFINITIONS OF WEIGHT CYCLING USED IN THE LITERATURE	82
TABLE 3.2	EPIDEMIOLOGICAL ASSOCIATIONS BETWEEN BODY WEIGHT VARIABILITY AND RISK OF DISEASE OR MORTALITY	90
TABLE 3.3	ASSOCIATIONS BETWEEN INSTABILITY IN BODY WEIGHT AND CHANGE IN HEALTH STATUS IN HUMANS	102
TABLE 3.4	ASSOCIATIONS BETWEEN INSTABILITY IN BODY WEIGHT AND CHANGE IN HEALTH STATUS IN ANIMAL MODELS	108
TABLE 4.1	CRITERIA FOR REMOVAL OF OUTLIERS FROM SMART SCALE DATA	132
TABLE 5.1	STUDY 3. PARTICIPANT CHARACTERISTICS	141
TABLE 5.2	STUDY 3. DESCRIPTION OF TIME SERIES IMPUTATION METHODS USED	144
TABLE 5.3	STUDY 3. IMPACT OF MISSING DATA AND DATA IMPUTATION ON ESTIMATION OF BODY WEIGHT VARIABILITY	150
TABLE 6.1	STUDY 4. PARTICIPANT CHARACTERISTICS	163
TABLE 6.2	STUDY 4. BODY WEIGHT PATTERNS BY DAY OF THE WEEK	168
TABLE 6.3	STUDY 4. BODY WEIGHT PATTERNS ACROSS HOLIDAY PERIODS	171
TABLE 6.4	STUDY 4. BODY WEIGHT PATTERNS ACROSS SEASONS OF THE YEAR	174
TABLE 7.1	STUDY 5. PARTICIPANT CHARACTERISTICS	190
TABLE 7.2	STUDY 5. ASSOCIATION BETWEEN WEIGHT VARIABILITY MEASURES, WEIGHT CHANGE AND CHANGES IN CARDIOMETABOLIC HEALTH	192
TABLE 7.3	STUDY 5. ASSOCIATION BETWEEN WEIGHT VARIABILITY MEASURES, WEIGHT CHANGE AND CHANGES IN BODY COMPOSITION	194
TABLE 8.1	STUDY 6. PARTICIPANT CHARACTERISTICS.	209
TABLE 8.2	STUDY 6. ASSOCIATIONS BETWEEN SHORT TERM WEIGHT VARIABILITY AND LONGER-TERM WEIGHT CHANGES.	212
TABLE 9.1	STUDY 7. PARTICIPANT CHARACTERISTICS.	230
TABLE 9.2	STUDY 7. BASELINE UNIVARIATE AND ADJUSTED ASSOCIATIONS WITH 12-MONTH BODY WEIGHT VARIABILITY.	231
TABLE 9.3	STUDY 7. BASELINE STEPWISE REGRESSION MODELS PREDICTING 12-MONTH BODY WEIGHT VARIABILITY	232
TABLE 9.4	STUDY 7. BASELINE CLUSTERING OF PARTICIPANTS BY PSYCHOLOGICAL AND BEHAVIOURAL VARIABLES	233
TABLE 9.5	STUDY 7. IMPACT OF SUBSEQUENT BODY WEIGHT VARIABILITY ON SUBSEQUENT CHANGE IN PSYCHOLOGICAL AND BEHAVIOURAL FACTORS	234

List of Figures

FIGURE 2.1	STUDY 1. STUDY FLOW DIAGRAM	28
FIGURE 2.2	STUDY 1. META-REGRESSION PLOTS	44
FIGURE 2.3	STUDY 1. INTERACTION BETWEEN RATE AND AMOUNT OF WEIGHT LOSS AND SUBSEQUENT REGAIN	45
FIGURE 2.4	STUDY 2. PARTICIPANT FLOW DIAGRAM	59
FIGURE 2.5	STUDY 2. ASSOCIATION BETWEEN BASELINE BODY FAT AND CHANGE IN BODY COMPOSITION	66
FIGURE 2.6	STUDY 2. ASSOCIATION BETWEEN FAT FREE MASS LOSS AND SUBSEQUENT WEIGHT REGAIN	67
FIGURE 2.7	STUDY 2. ASSOCIATIONS BETWEEN FAT FREE MASS LOSS AND CHANGES IN APPETITE	70
FIGURE 2.8	COMPARISON OF TRADITIONAL AND NEW RESEARCH APPROACHES TO BODY WEIGHT DYNAMICS	78
FIGURE 3.1	DIFFERENCES IN CALCULATING BODY WEIGHT VARIABILITY FROM LINEAR AND NON-LINEAR WEIGHT TRENDS	87
FIGURE 4.1	DESIGN OF THE NOHOW TRIAL	123
FIGURE 4.2	INTERFACE OF THE NOHOW APP	126
FIGURE 4.3	CALCULATING BODY WEIGHT: MEAN ABSOLUTE SUCCESSIVE WEIGHT VARIABILITY	133
FIGURE 4.4	CALCULATING BODY WEIGHT: ROOT MEAN SQUARE ERROR	134
FIGURE 4.5	CALCULATING BODY WEIGHT: NONLINEAR MEAN DEVIATION	136
FIGURE 5.1	STUDY 3. STUDY FLOW DIAGRAM	142
FIGURE 5.2	STUDY 3. ERRORS INTRODUCED BY DIFFERENT METHODS OF DATA IMPUTATION	147
FIGURE 5.3	STUDY 3. EXAMPLES OF DATA IMPUTATION	149
FIGURE 5.4	STUDY 3. ERRORS IN ESTIMATING BODY WEIGHT VARIABILITY FROM MISSING OR IMPUTED DATA SETS	151
FIGURE 6.1	STUDY 4. VARIABILITY IN ENERGY INTAKE AND EXPENDITURE	156
FIGURE 6.2	STUDY 4. PARTICIPANT FLOW CHART	164
FIGURE 6.3	STUDY 4. SCALE USE BY DAY OF THE WEEK AND MONTH OF THE YEAR	164
FIGURE 6.4	STUDY 4. SCALE USE OVER THE DURATION OF THE TRIAL	165
FIGURE 6.5	STUDY 4. WEEKLY BODY WEIGHT FLUCTUATIONS	167
FIGURE 6.6	STUDY 4. CHRISTMAS BODY WEIGHT FLUCTUATIONS	170
FIGURE 6.7	STUDY 4. SEASONAL BODY WEIGHT FLUCTUATIONS	173
FIGURE 7.1	STUDY 5. PARTICIPANT FLOW DIAGRAM	185
FIGURE 7.2	STUDY 5. CALCULATING INITIAL AND CHANGE IN PHYSICAL ACTIVITY	186
FIGURE 7.3	STUDY 5. SCALE USAGE OVER THE TRIAL AND BY DAY AND MONTH	187
FIGURE 8.1	STUDY 6. PARTICIPANT FLOW DIAGRAM	205
FIGURE 8.2	STUDY 6. SCALE USAGE OVER THE TRIAL AND BY DAY AND MONTH	206
FIGURE 8.3	STUDY 6. CHANGES IN BODY WEIGHT OVER THE TRIAL	210
FIGURE 8.4	STUDY 6. ASSOCIATIONS BETWEEN SHORT TERM WEIGHT VARIABILITY AND LONGER TERM WEIGHT OUTCOMES	211
FIGURE 9.1	STUDY 7. PARTICIPANT FLOW DIAGRAM	224

Summary & Objectives

At an individual level, humans exhibit extraordinary stability in body weight over the long-term. Epidemiological evidence provides that over the past few decades, weight gain has occurred at population level in the region of 0.5-1kg per year. Given an estimated consumption of 1-1.2 million kilocalories in the average Western man, the presumption is that energy expenditure and intake are very precisely matched. To give an example, in the UK, the average weight gain over 10 years was 6.7kg, yielding an average daily error between intake an expenditure per day of +25kcal for a decade. Two caveats to the proposed concept that body weight is highly regulated are apparent: (a) obesity (defined as a body mass index; BMI ≥ 30kg/m^2) has become a global pandemic and (b) over shorter periods (i.e. weeks to months), humans show considerable variability in body weight in the region of 1-3kg in the absence of intentional weight change. These two points set the framework for the subsequent thesis.

To begin with the former, obesity rates have increased from 10% to 40% in the past decade and have been forecasted to reach 60% by 2050 though there is some evidence of trend stabilisation in the past few years. Coinciding increases in comorbidity rates relating to type 2 diabetes, heart disease, cancer and a plethora of other conditions have placed a staggering burden on individuals and healthcare systems. Obesity is both preventable and treatable. Weight loss is the primary pathway to treatment and evidence-based approaches for achieving weight loss are widely available. Weight loss associated reductions in risk of obesity-related comorbidities are well established. Nonetheless, the evidence suggests (a) that >40% of adults report trying to lose weight annually in the Western world; (b) >80% of individuals achieving clinically significant weight loss regain most weight within 1-5 years; (c) recent prior loss is a strong predictor of subsequent weight gain.

Given that successful dieting and subsequent weight gain (together termed weight cycling) is a chronic and commonplace phenomenon, the impact of these events on human physiology are not well understood. Indeed, both weight loss and regain cause discrete structural and functional adaptations. During weight loss, changes in body composition occur dynamically in response to various features of weight loss (i.e. the amount of weight lost and rate at which it was lost, the initial body composition and other factors relating to diet, activity and pharmaceuticals). It is likely then that these factors play some role in the

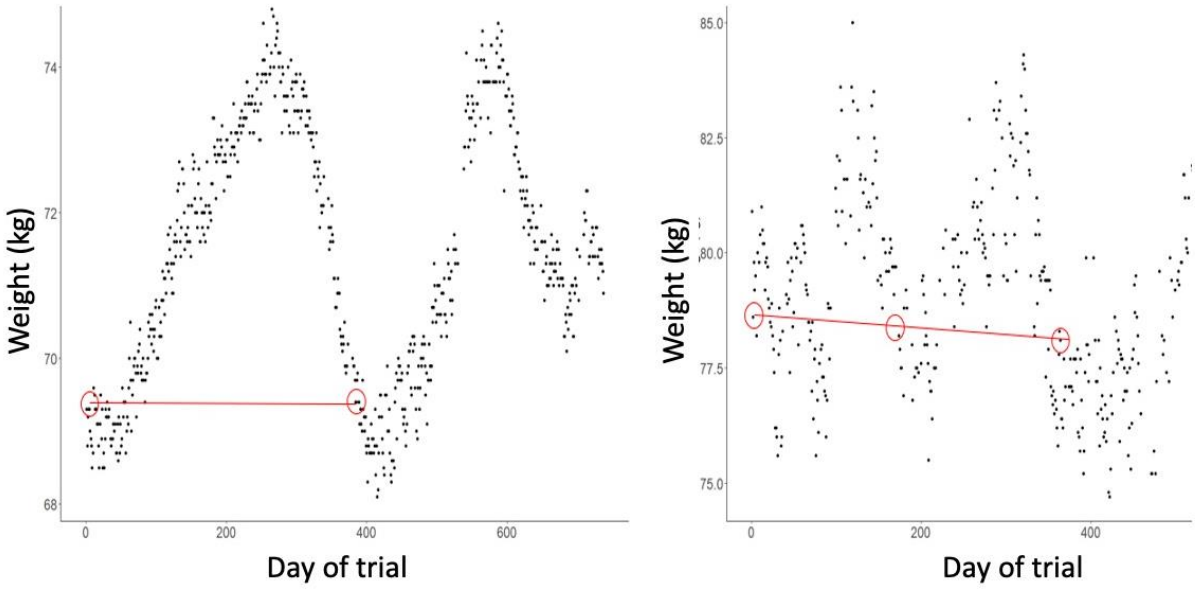
aetiology of the weight regain predisposition. In order to understand human body weight patterns over long periods (years to decades), a single weight cycle can be used as a proxy model for longer-term body weight instability. Importantly, this approach is necessary because detailed data on weight cycling over several years (or cycles) is not widely available. As an initial part of this thesis, a single weight cycle was used as a model for weight instability. This was explored via two studies: firstly, a systematic review and meta-regression exploring the primary features of weight loss (amount, rate and composition) and second through a re-analysis of the DIOGenes study, a large weight loss and maintenance trial, which considered the impact of structural changes occurring during weight loss on weight regain and they're impact on energy balance mediators (specifically appetite) and weight regain. The specific objectives of this chapter were to:

1.1 Examine the associations between the rate, amount and composition of weight loss on subsequent weight regain
1.2 Investigate how proportionate changes in body composition occurring during weight loss impact subsequent weight regain
1.3 Explore how these structural changes may relate to psychological function, specifically changes in appetite during weight loss

Briefly, these investigations showed that (a) greater weight reductions are followed by greater weight regains; (b) the rate at which weight loss occurs may be directly associated with weight regain; (c) changes in body composition during weight loss explain greater variance in weight regain than weight loss alone; (d) specifically, greater proportionate reductions in fat free mass during weight loss was associated with greater weight regain in some individuals and lastly (e) greater proportionate reductions in fat free mass may influence appetite in a direction indicative of increased appetite (in some individuals). These conclusions were reached based on comprehensive examination of 54 groups exhibiting clinical weight loss and subsequent regain using both meta- and individual- level data.

However, a limitation to this traditional approach is the assumption that measuring body weight at 3 time-points (i.e. pre and post weight loss and at follow-up) is representative of human body weight dynamics in free-living environments. Indeed,

traditional study of weight management is dependent on irregular measurement of body weight (i.e. every 6 or 12 months). However, there is considerable unmeasured change in body weight which can and will occur between these timepoints. For example, in the figure below (examples of true body weight patterns taken from participants of the NoHoW trial, discussed later in the thesis), when body weight is measured at 12 (left) or 6 (right) month timepoints (marked with red circles), the impression of weight stability is given, yet it is clear that this far from representative of the actual dynamic of body weight (given that individuals are actually cycling 5-10% body weight between measurements).



This brings us back to the latter point, that humans exhibit considerable body weight variability (BWV). The impact of short and longer-term variability in body weight is not well understood nor well measured yet is of potential scientific interest and thus will form the primary focus of this thesis. The rationale for assuming body weight variability as the primary focus of this work is highlighted in chapter 3 which is a comprehensive literature review with the following aims to:

2.1 Describe and critically evaluate the current measurement and operationalisation of weight instability metrics used previously

2.2 Summarise and evaluate the evidence relating BWV to risk of disease

2.3 Summarise and evaluate the evidence relating BWV to changes in health markers

2.4 Summarise and evaluate the evidence examining the role of BWV in weight management

Briefly, it was found that (a) the methods used to measure instability in body weight are both extremely heterogenous and subject to considerable methodological limitations; (b) the majority of the evidence is in favour of the conclusion that BWV increases the risk of cardiovascular disease, type 2 diabetes and mortality but there are considerable methodological and design flaws which reduce the confidence in these conclusions which are discussed; (c) the associations between BWV and markers of health are not consistent, nor well studied, and generally do not consistently support conclusion (b); and lastly (d) evidence suggests that BWV may function as a risk factor for subsequent weight gain, but this is based on a small number of select studies and replication is required while overcoming existing methodological limitations.

One of the major and unavoidable limitations to the examined literature is the reliance on infrequent measurement of body weight used to statistically calculate BWV. The amount of unmeasured weight change between time points (which varies considerably both between and within individuals) functions to reduce the confidence in conclusions reached. The logical solution to this problem is to frequently and objectively track body weight. Recent technological advancements have facilitated the continuous collection of data in free-living individuals using WiFi-connected smart scales. As part of the NoHoW project, a large European weight loss maintenance trial which is the context of the subsequent investigations described, we used such technologies to track body weight frequently. The trial, methods and tools are described in detail in the general methods section (chapter 4). With this data, the ability to research and understand the phenomenon of BWV is enhanced greatly and there is potential to improve the scientific understanding of the phenomenon. However, these methods are in their infancy. The weight data collected is dense, complex and its intricacies (e.g. high proportions of missing data) may threaten to bias the estimation (and thus study) of BWV. In response to this, in chapter 5, a comprehensive simulation and validation study was devised. The aims of the chapter were to:

3.1 Devise a conservative method of data cleaning and outlier removal

3.2 Test the ability to impute missing body weight data using an array of accessible univariate and multivariate techniques

3.3 Investigate the biases introduced to the calculation of BWV under conditions of incrementally missing and imputed data

The results of this study: (a) defined a conservative cleaning process using evidence-informed limits of physiologically plausible weight change; (b) provided recommendations for the best approaches to imputation of body weight data from smart scales and (c) summarised the errors and biases introduced under conditions of incrementally missing or imputed data. These results informed subsequent studies into BWV.

Given that body weight has not been frequently and longitudinally tracked in research environments previously, the magnitude of the BWV in populations is unclear. It is likely that periods of weight gain and loss are not entirely random. Instead, evidence suggests that energy balance behaviours are often influenced by temporal cues (e.g. weekends, holidays or seasons). For example, energy intake has been shown to increase on weekends and around holidays, and physical activity may decrease in the winter months. These changes in behaviour may be moderated by individual characteristics or location. As such, it could be expected that temporally predictable fluctuations in body weight may be observable in longitudinal and frequent weight data. It is logical as an early step in investigating BWV to attempt to identify deterministic features of the BWV. Importantly, the variability component must be isolated from the overall trend in body weight in order to describe fluctuations independent of overall change, a statistical procedure which is described in full in chapter 3. Accordingly, a descriptive study was conducted on data collected from participants of the NoHoW trial which aimed to:

4.1 Describe fluctuations in body weight according to weekly, seasonal and holiday patterns

4.2 Test how these patterns varied between different groups of individuals (based on age, gender, BMI and country)

Briefly, it was found that (a) predictable fluctuation patterns within a week characterised by weekend weight gain and weekday weight loss; (b) weight fluctuates upwards during the holiday period and reduces (but not entirely) afterwards; (c) consistent season patterns within a year were not evident at group level and (d) group differences relating to individual characteristics were observed.

Next, the literature review in chapter 3 provided evidence that long-term BWV is potentially a risk factor for cardiometabolic disease and mortality, however, the mechanisms linking it to changes in health are unclear and inconsistent. The most common pathway to disease incidence is through detrimental changes to traditional risk factors (including blood pressure, cholesterols, triglycerides and insulin sensitivity). While weight loss is known to improve these markers, the effects of BWV (in particular, after adjustment for overall change in body weight) is not clear and has not been appropriately investigated previously. Furthermore, it has been suggested that weight instability may be a risk factor for increased body fatness, due to repartitioning of mass from fat free tissues to fat during weight loss and regain, however the evidence to support this contention is sparse. In order to explore these potential effects of BWV, chapter 7 aimed to:

5.1 Investigate the impact of weight change on cardiometabolic health markers and body composition

5.2 Investigate the impact of BWV (adjusted for weight change) on cardiometabolic health markers and body composition

It was found that (a) weight loss was associated with improvements in all cardiometabolic health measures and reduced body fat and (b) BWV was not consistently associated with any change in cardiometabolic health or body composition after adjustment for overall weight change, despite the use of 4 measures of BWV and multiple levels of variable adjustment. The implication is that, over the short-medium term (12-months), BWV does not have any measurable impact on health or body composition (based on the limited outcomes that were measured), and that overall weight change is the important weight-related determinant of health.

Weight variability has additionally been implicated for its role in the aetiology of weight gain in a small selection of studies. The suggestion is that BWV can be measured over the short term as a predictive factor in longer-term weight management outcomes, with previous research showing small positive effects (R^2=1-5%) between shorter-term (6-26 week) BWV and longer-term (1-3 year) weight changes. Nonetheless, these results have been shown typically in small, select samples and whether this relationship can be replicated in a large and diverse group of individuals engaged in a weight loss maintenance intervention with the use of WiFi connected smart scales was unclear. Furthermore, optimal measurement duration for BWV, and follow-up period for weight change is unclear and requires further investigation. Accordingly, in chapter 8 aimed to:

6.1 Examine associations between short term (6, 9 and 12- week) body weight variability and longer term (6, 12 and 18-month) weight changes.
6.2 Explore the relationships between exposure and follow-up periods.

It was found that (a) short term BWV (9 and 12 weeks) predicted increased weight at follow-up in most models; (b) greater measurement period of BWV showed increased ability to predict weight change and (c) longer follow-up periods were associated with greater effect sizes. Generally, effect sizes relating to weight changes were modest (<5%). Our results were consistent in direction and magnitude to previous observations, though extended previous research by using a large group of smart scales users engaged in a behaviour change intervention. The limitations of the measurement of BWV and potentially confounding factors which may contribute to the modest effect sizes are discussed.

Most of the previous research concerned with BWV addresses questions relating to physical outcomes (i.e. risk of disease, change in health markers or impact on weight management). Nevertheless, few attempts have been made to explore the psychological and behavioural factors associated with BWV, and most the most relevant research tends to be related to self-reported weight cycling which is substantially different from prospectively measured BWV. As such, there is limited understanding of (a) the factors which predict subsequent BWV and (b) whether prior BWV impacts subsequent change in psychological or behavioural status (i.e. are there causative associations?) As part of the final study, in

chapter 9 an exploratory, data-driven statistical analysis was conducted using psychometric data available in the NoHoW trial which aimed to:

7.1 Identify baseline variables associated with subsequent 12-month BWV
7.2 Generate a baseline model which best explains 12-month BWV
7.3 Explore whether clustering of psychological and behavioural variables at baseline relates to subsequent BWV
7.4 Investigate whether initial (6-month) BWV predicts change in psychometric scores in the subsequent 6-months

A series of psychometric and weight history variables were identified that predict 12-month BWV. The most important psychometric variables in predicting BWV related to uncontrolled eating (e.g. binge eating and disinhibition), weight and body image concerns and negative affect (e.g. depression and mental wellbeing). Weight history variables, particularly weight suppression, predicted subsequent BWV. Unsupervised analytical techniques (clustering and stepwise regression) identified groups of variables at baseline which predicted subsequent 12-month BWV. Lastly, initial BWV predicted increases in binging and disinhibition, and decreases in body image acceptance and mental wellbeing, showing novel evidence of causative associations. Overall, effect sizes were modest (<5%) for single variable associations and the potential reasons for this (in particular, error and heterogeneity in the measurement of BWV) are discussed.

In the final chapter of this thesis, an overarching discussion is presented which considers overlapping themes arising throughout the thesis. The strengths, limitations and implications of the work done during the thesis are discussed in depth, and recommendations for the future study of BWV are presented.

1. Introduction

1.1 Obesity

According to the most recent estimates from the World Health Organization (WHO), the prevalence of obesity (defined as a body mass index [BMI] ≥30kg/m^2) was estimated at ~29.5% of the United Kingdom (UK) population in 2016 and the prevalence of overweight (defined as a BMI ≥25kg/m^2 and < 30kg/m^2) was estimated at ~63% (World Health Organisation, 2016). Mathematical forecasting models predict increases in obesity in coming decades, with over 60% of males and over 55% of females in the Western world predicted to be obese by 2050 (Agha and Agha, 2017). Obesity rates have increased across all regions, age groups and socioeconomic statuses, though there has been a tendency for greater increases in women and older individuals in some regions (Chooi, Ding and Magkos, 2019). Some evidence has shown trend stabilisation in the past few years in some countries, such as those in the Americas, according to data from the Global Burden of Disease study (Chooi, Ding and Magkos, 2019).

The WHO estimates that 2.8 million deaths per year are attributable to overweight and obesity, making it the second greatest risk factor for mortality after smoking (Birch *et al.*, 2019). Associated annual costs of direct and secondary economic impact of obesity are estimated at around $2 trillion in the United States alone (Tremmel *et al.*, 2017). It is a major risk factor for many noncommunicable diseases including type two diabetes (T2D) and cardiovascular disease (CVD) in addition to many site-specific cancers. The associations between BMI and risk of noncommunicable diseases are well-established and linear models have been generated to describe these associations (Bays, Chapman and Grandy, 2007). Associations between BMI and mortality show a non-linear relationship (referred to as the obesity paradox) which describes the tendency for risk of mortality risk to increase at both extremes of BMI, with low BMI being a particular concern in elderly individuals or those with existing health conditions (Hainer and Aldhoon-Hainerová, 2013). Weight loss is known to improve health status, with as little as 5% weight loss generally considered the minimum requirement for clinically significant improvements (Rena R Wing *et al.*, 2011a), however, weight relapse is common (Franz *et al.*, 2007a) and repetitive body weight cycles are likely

to occur in response (Lahti-Koski *et al.*, 2005) thus the effectiveness of weight loss in improving health is limited as long as weight regain remains largely inevitable. Even on a smaller scale, variability in energy balance behaviours over periods of days and weeks produce weight changes. As such, in many individuals, particularly those struggling with weight management, body weight is unstable. This instability will form the focal point of this thesis.

1.1.1 Regulation of Body Weight

1.1.1.1 A Thermodynamic Context

To understand the aetiology of obesity, an appreciation of the basic laws of thermodynamics is helpful. Human metabolism complies with the first law of thermodynamics which states that the total internal energy of a system is the energy added to the system minus the work done by the system. In the study of metabolism, this relationship is referred to as energy balance (EB), whereby the energy added to the system refers to the food we eat, and the work done refers to all energy expended by metabolic and mechanical processes. Obesity is a product of chronic non-regulation of EB. Prolonged periods of energy accumulation result in a storage of energy, and conversely periods of limited energy results in a reduction of these stores. This relationship is commonly illustrated with the equation:

$$\Delta E_S = E_I - E_E$$

Where the rate of energy stored (ES) is a function of the difference between energy in (EI) and energy expenditure (EE). Physiologically, ES reflects the chemical composition of the body and will therefore be determined by all constituent parts of the anatomy. This model of body composition can be divided into two compartments: fat-free mass (FFM; including intracellular and extracellular water stores, skeletal muscle and organs) and fat mass (FM), each of which are differentially altered by the above equation.

Energy expenditure is commonly divided into three elements: (a) resting metabolic rate (RMR); (b) thermic effect of food (TEF) and (c) physical activity energy expenditure (PAEE) which can be further separated into exercise energy expenditure (ExEE) and non-exercise activity thermogenesis (NEAT). RMR is defined as the metabolic rate required to maintain vital physiological functions of an individual that is in rest, awake, in a fasted state, and in a thermoneutral environment. It accounts for 60-85% of an individual's total daily EE (Nielsen

et al., 2000) and is primarily defined by body composition and genetic factors (Bouchard *et al.*, 1993). Fat-free mass accounts for around 70-80% of RMR (Sparti *et al.*, 1997). Energy expenditure is known to decline when weight is lost, with reductions often greater than predicted by measured changes in body composition in a process referred to as adaptive thermogenesis (M. Rosenbaum *et al.*, 2005).

Energy intake is determined by food consumption. Kilocalories (kcal; the universal metric for the energy value of food), or calories for short, are consumed in the form of protein, fat, carbohydrate and alcohol. The caloric values per gram for protein, fat and carbohydrate are estimated at approximately 4kcal, 9kcal and 4kcal respectively. Importantly, a combination of factors including the bioavailability of the specific food, metabolic inefficiencies and heat loss during digestion function to reduce these values meaning that the nutrients consumed are more than those available to the body following digestion.

Energy balance is the difference between the rate of EI and EE. Prolonged positive EBs produce body weight gains, and deficits produce body weight losses. In males, EB is generally reached at approximately 2,500kcal/day on average, and approximately ~2,000kcal/day on average in females, as defined by reference EE values, average PAEE estimates, and a demand for EI to match EE to achieve body weight stability. At population level, small upward trends in body weight (in the region of 0.5-1kg per year) suggest incredible long-term regulation of EB implying discrepancies of only 9-18kcal/day between EI and EE (Speakman *et al.*, 2011). Yet, both the development of obesity and the knowledge that body weight may fluctuate over the short-term by 1-3kg in 2 weeks (Bhutani *et al.*, 2017a) contradict this assumption of tight regulation. These ideas will be expanded on as the thesis proceeds.

1.1.1.2 Early Static Theories

Early research into the regulation of body weight was primarily dominated by three 'static' schools of thought which reflected each macronutrient, although several more theories populated the literature at this time. First, the glucostatic theory, originally developed by Mayer (1955), proposed that fluctuations in peripheral arteriovenous blood glucose concentrations at glucosensitive sites were a tonic controller of EI via a negative feedback loop which moderated subjective hunger or satiety. Shortly after, a string of mechanistic studies in rat models led to results both consistent (VAN ITALLIE, BEAUDOIN

and MAYER, 1953; Stunkard, Van Itallie and Reis, 1955) and inconsistent (BERNSTEIN and GROSSMAN, 1956) with Mayer's hypothesis. Second, Mellinkof et al. (1956) proposed that satiety was related to post-prandial amino acid concentrations. In this study, normal weight individuals ingested a protein meal, and a correlation between circulating amino acid content and subjective satiety was observed. Finally, lipostatic theory was initially presented by Kennedy (1953) and provided that long-term EI was determined by homeostatic signals released from the body's adipose stores which, in turn, acted to moderate fat stores towards a 'set point'. The lipostatic theory was the first to take an adipocentric view of EI; a view that later prevailed from the mid-1990s onwards despite the limitation of a set-point which is inconsistent with the rising prevalence of obesity. Around the same time, Edholm presented a hallmark paper which described a correlation between EE on one day and EI the following day (Edholm *et al.*, 1955), although no correlation existed within a similar day. He later produced similar findings (Edholm *et al.*, 1970), showing a correlation between EE and EI over a period of 2 weeks but not within one day (which is inconsistent with macronutrient static theories). This incongruence is likely due to large variability in PAEE, which varies from day to day but then averages out over several weeks.

1.1.1.3 Set Points and Settling Points

The set point theory suggests that each individual's body has a given weight (or set point) which it attempts to defend throughout the adult life cycle. Modern set point theories emerged from the original suggestions of Kennedy and Edholm who theorized that the body defends a set point, and later developed further following the discovery of adipocyte hormone leptin (Zhang *et al.*, 1994). Leptin was originally shown to reduce EI and increase RMR in mice (Halaas *et al.*, 1995, 1997) and showed a linear relationship with body fat in humans (Considine *et al.*, 1996). Following its discovery, leptin was placed at the forefront of body weight regulation research, with its tonic (long-term) effects in the hypothalamus suggested to regulate EI and thus body weight over the long-term (Morton, 2007). In humans, weight loss associated reductions in leptin coincide with a hyperphagic drive and hypometabolism operating to return the body to a set point (Rosenbaum and Leibel, 2014).

The set point theory has been criticised as it denies a role for human psychology as well as environmental and socioeconomic influences. A variation of the model, termed the

'settling point' theory, suggests that an individual's set point may drift in response to external factors, such as the Western food environment (Müller, Bosy-Westphal and Heymsfield, 2010), and internal factors, such as shifts in -psychological status - including motivations. In this system, first suggested in Payne and Dugdale's mathematical model of weight regulation (Payne and Dugdale, 1977), changes in EI result in stabilising changes in EE (and vice versa), which allows for the set point to drift and reset. Nevertheless, evidence which supports a highly physiological regulatory system remains inconsistent (Müller, Bosy-Westphal and Heymsfield, 2010).

1.1.1.4 Evidence of an Asymmetric Regulatory System

Theories such as the set point theory suggest an inherent physiological feedback loop which defends a current body weight through direct changes in EE and indirect changes to EI (i.e. via appetite). Implied is a bidirectionality in this homeostatic feedback loop, such that both weight loss and gain are defended against. However, when examining both changes in EE and EI in response to weight loss or gain, the evidence of an asymmetric regulatory system which defends against weight loss to a much greater extent than weight gain is evident. When examining metabolic responses to underfeeding (-50% of energy requirements for 3 weeks) or overfeeding (+50% of energy requirements for 2 weeks), Muller et al reported that changes in RMR were around 5 times greater in response to underfeeding than overfeeding (Müller, Enderle and Bosy-Westphal, 2016). Furthermore, weight loss produces reductions in EE which extend beyond that predicted by body composition changes alone via a series of endocrinological changes relating to leptin, thyroidal and sympathetic hormones among others termed adaptive thermogenesis (Müller and Bosy-Westphal, 2013). However, the reverse response is not observed in response to weight gain (Norgan and Durnin, 1980).

Weight loss produces significant increases in appetite (Sumithran *et al.*, 2011; Hintze *et al.*, 2017) driven partially by physiological responses in appetitive hormones in favour of an orexigenic effect. Food reward has also been shown to increase in response to energy deficits (Cameron *et al.*, 2008; Cameron, Goldfield, *et al.*, 2016), as has perceived food palatability and even olfactory responses to food cues (Cameron, Goldfield and Doucet, 2012). Inverse responses have not been evidenced in response to weight gain. Furthermore, acute overconsumption of energy appears not to elicit a compensatory decrease in EI in

subsequent days (Johnstone *et al.*, 1998; Deighton *et al.*, 2019), whereas the effects of caloric restriction are immediate, substantial and predisposes an increased EI (Hubert, King and Blundell, 1998).

Indeed, based on this evidence, it seems fair to assume that physiological or 'homeostatic' regulation of energy balance is inherently asymmetrical in a direction favouring weight gain. This is entirely logical from an evolutionary perspective. Fluctuations in the availability of food caused by seasonal changes, famine and hunting predispose a drive to consume energy and store it as fat. As such, the human body is designed to avoid starvation, but in the Western world where food availability is rarely an issue this survival instinct may be considered obsolete and detrimental. It has been suggested that the Western obesogenic environment camouflages homeostatic regulation of bodyweight (Müller, Bosy-Westphal and Heymsfield, 2010). This is supported by evidence showing that *ad libitum* access to energy-dense, high sugar foods leads to 'passive overconsumption' and weight gain (Blundell and MacDiarmid, 1997), whereas *ad libitum* access to a low energy density diet may reduce weight in free-living adults following massive long-term overfeeding (Pasquet and Apfelbaum, 1994).

1.1.2 Associations between BMI and Noncommunicable Diseases

As mentioned, obesity is a leading cause of noncommunicable diseases, most importantly T2D, CVD and site-specific cancers but also many chronic conditions such as osteoarthritis, liver and kidney disease, sleep apnoea, and depression (Pi-Sunyer, 2009). Obesity forms the single leading cause of T2D, with the risk of incidence being 28 times higher in obese class 1 (BMI 30-35) individuals and 93 times higher in obese class 2 (BMI 35-40) individuals (Barnes, 2011) than normal weight individuals. In obesity, several risk factors which predispose the development of insulin resistance (the underlying cause of T2D) are increased, including non-esterified fatty acids, glycerol, hormones, cytokines and proinflammatory markers (Al-Goblan, Al-Alfi and Khan, 2014). Type 2 diabetes has several co-morbidities, including CVD, to which 50-80% of deaths in those with T2D can be attributed. In line with the rise in obesity rates, it is predicted T2D prevalence will rise from 4.2% in 2007 to over 11% in 2030 (Monesi *et al.*, 2012) and this is expected to be accompanied by a rise in UK NHS spending from £9.8 billion in 2010-11 to £16.9bn in 2035, which will account for almost a fifth of the NHS total budget (Hex *et al.*, 2012).

Understanding the associations between T2D incidence and body weight dynamics is central to curbing of increasing T2D rates.

Cardiovascular disease is the leading cause of death worldwide, accounting for 37% of premature deaths (Kaptoge *et al.*, 2019) and is correlated directly with BMI. Obesity is known to impact many CVD comorbidities such as hypertension, hypercholesterolemia and metabolic syndrome in a manner which increases CVD risk, as well as having a direct and independent effect on CVD risk (Mandviwala, Khalid and Deswal, 2016). Data collected from the Framingham Health study showed that obesity increased the risk of hypertension by 121% and 175% and CVD by 46% and 64% in men and women respectively (Turpie *et al.*, 2002). In contrast to T2D, CVD rates have decreased over the past several decades, with total CVD mortality in the UK down 68% between 1980 and 2013 (Bhatnagar *et al.*, 2016), though this is arguably due to better widescale pharmacological and surgical treatments.

Obesity is also a major risk factor for the development of cancer. In the American Cancer Prevention Study II, >900,000 individuals who were originally free from cancer were followed up for 16 years (Calle *et al.*, 2003). At follow-up, authors reported that BMIs of ≥40kg/m^2 were associated with a 52% and 62% increased risk of cancer incidence in men and women respectively. BMI was also positively associated with mortality rates from esophagus, colon and rectum, liver, gallbladder, pancreas, and kidney cancers. One study suggested that the percentage of total cancers attributable to obesity was ~20% (Preuss *et al.*, 2004). Given that the mechanisms of cancer development often vary between different sites, the underlying processes linking elevated BMI and cancer are not clearly understood, though disturbed regulation of several hormones including insulin, insulin-like growth factor-I, sex steroids, and adipokines may play a role in carcinogenesis (De Pergola and Silvestris, 2013).

The association between BMI and mortality is less clear and has resulted in the 'obesity paradox' which provides that risk of mortality is increased at both extremes of BMI (in individuals considered underweight and obese). The former is often related to old age or underlying disease such as chronic heart failure, hypertension, T2D and kidney disease (Ades and Savage, 2010), and accordingly caution should be taken in providing guidance to gain weight in healthy adults with no underlying conditions. The association of low BMI and high mortality risk could also be explained by unintentional weight loss relating to an underlying condition, and the predisposition towards frailty and low strength which are both linearly

associated with mortality risk (Crow *et al.*, 2018; García-Hermoso *et al.*, 2018). In most non-elderly, healthy individuals, only the direct association between BMI and mortality is relevant.

1.2 Weight Loss

Weight loss is the primary pathway to decreased risk of obesity-diseases. A meta-analysis synthesising data from 54 randomised control trials (RCTs) concluded that weight loss interventions in individuals with obesity have a significant and substantial risk-reducing effect on all-cause, CVD and cancer mortality (Ma *et al.*, 2017a). Five percent weight loss has generally been defined as the standard criterion required to produce clinically significant improvements in health (Williamson, Bray and Ryan, 2015). In the Look AHEAD cohort, 5% weight loss produced clinically significant reductions in haemoglobin A1c (HbA1c), systolic and diastolic blood pressure, triglycerides and increase in high-density lipoprotein cholesterol (HDL-C), although improvements were further enhanced with weight losses over 10-15% in a dose-responsive manner (Rena R. Wing *et al.*, 2011). In the Diabetes Prevention Programme, a weight loss of 5.5% reduced the incidence of T2D by 58% (Diabetes Prevention Program Research Group, 2002) and in another analysis, a 16% reduction in risk was estimated with every 1kg of weight loss (Richard F. Hamman *et al.*, 2006a). As such, in 2014 an expert panel concluded that 5% weight loss 1 year after treatment was deemed the criterion for clinical significance (Jensen *et al.*, 2014).

1.2.1 Weight Loss Prevalence

Despite its known benefits to health, long-term weight loss remains difficult to achieve and, despite the high self-reported prevalence of weight control attempts (Santos *et al.*, 2017), obesity rates continue to rise globally. Determining the prevalence of weight control is difficult as reliance on self-reported measurement is necessary, and the interpretation of the definition of weight control attempt may vary greatly between individuals. Furthermore, it is likely that many of those who report engagement in a weight control attempt actually lose little to no weight. The most comprehensive attempt to quantify this prevalence comes from a systematic review and meta-analysis in which Santos et al examined the prevalence of weight control attempts worldwide, including ~1.2 million participants from 72 studies. They found that around 42% of adults worldwide report making a weight control attempt annually, of which a greater fraction are women, and most

tend to have overweight or obesity. Considerable regional variability was observed, with rates lowest in Africa (~16.6%) and highest in North America (~44%), and generally ethnic minorities showed slightly greater rates. Data from the health survey for England suggests that in the UK, around half of all adults report making at least 1 weight loss attempt each year, increasing from 39% in 1997 (Piernas, Aveyard and Jebb, 2016). The study found that having a health condition was only very modestly associated with weight loss attempts, suggesting that most reasons for dieting seem unrelated to health leaving aesthetic purposes and social desirability as some of the leading reasons for dieting.

Some evidence suggests adolescents and young adults are more motivated by appearance to achieve weight loss, whereas older adults may be more motivated by health benefits, and similarly, females are more likely to be motivated by physical appearance and societal pressures than males (D. F. O. Silva *et al.*, 2018). Differences in dieting prevalence across socioeconomic levels have been observed (Wardle and Griffith, 2001), with greater prevalence in individuals from more affluent areas who are generally more well-educated about obesity and health and having better access to healthier life options (e.g. weight control programs, healthy foods and fitness centres) which help facilitate weight loss (Morland *et al.*, 2002). Further differences can be observed across ethnicities (Zapka *et al.*, 2009) which may be related to cultural norms in dieting, food intake and physical activity (PA) behaviours. For example, South Asians living in the UK are significantly less likely to partake in PA than white individuals (Williams *et al.*, 2011).

1.2.2 Strategies to Achieve Weight Loss

The study of weight loss can be divided into observational and experimental (i.e. randomized control trial; RCT) studies. Observational studies typically rely on self-report questionnaires which collect information on the prevalence, motivations and strategies used to achieve weight loss. From these, large amounts of information can be synthesised on the most popular approaches to weight loss, which can be categorised to nutrition and diet, behaviour or lifestyle, physical activity and more. RCTs test the effectiveness of an approach or multiple approaches compared to a control. Again, RCTs are often divided into diet, exercise, lifestyle/behaviour or combined interventions.

1.2.2.1 Dietary Approaches to Weight Loss

Observational data collected worldwide (Santos *et al.*, 2017) showed that the most prevalent weight control strategies relating to diet included eating more fruit and vegetables, eating low calorie food and beverages, eating low fat products, avoiding high sugar products, increasing water intake and drinking less alcohol. Less commonly used strategies involved eating smaller, more frequent meals, eating breakfast, eating more slowly, limiting snacking and eating less meat. In a meta-analysis conducted on 59 RCTs testing the efficacy of 'fad' diets (including ketogenic diets, the Atkins diet, the Zone diet, low fat diets and others), authors concluded that the differences between all diet types were modest after adjustment for adherence, and recommending any diet which is best adhered to for an individual was best (Johnston *et al.*, 2014), which is a practice often supported (Lemstra *et al.*, 2016; Gibson and Sainsbury, 2017). As well as macronutrient composition, the severity of energy restriction can be manipulated in dietary approaches. The best example is in the case of very-low calorie diets (VLCDs), which typically involve intakes of around 500-800kcal per day and aim to achieve rapid weight loss. In a meta-analysis comparing a range of different weight loss strategies, Franz et al reported substantially greater 6-month weight loss achieved by VLCD (~18%) than any other approach involving diet, exercise or pharmaceuticals (Franz *et al.*, 2007a).

1.2.2.2 Exercise Approaches to Weight Loss

In their meta-analysis, Santos et al reported that in 122,314 participants from 27 studies, ~65% of individuals reported increasing their exercise or activity during a weight control attempt. However, the impact of exercise alone on weight loss is often modest. In one large RCT which compared dietary, exercise and combined approaches over 1 year, weight loss in the diet and combined arms were 8.5% and 10.8% respectively, whereas exercise alone produced only 2.4% weight loss (Foster-Schubert *et al.*, 2012). Furthermore, Swift et al reviewed the role of exercise in weight loss, concluding that weight loss interventions typically have modest effects in the region of ~2kg, and that practitioners should ensure realistic expectations in individuals beginning an exercise intervention for weight loss (Swift *et al.*, 2014). Considerable individual variability in response to exercise interventions has been shown in a recent meta-analysis of exercise trials (Williamson, Atkinson and Batterham, 2018) concluding that the true interindividual response in the trials

analysed ranged from -2.8kg to +3.6kg. Importantly, exercise may have more beneficial effects on body composition, strength and fitness compared to dietary approaches for a given weight loss, meaning that improvements in health status may occur at a greater rate when exercise in included (Clark, 2015).

1.2.2.3 Behavioural Approaches to Weight Loss

Behaviour change interventions attempt to instil and solidify behaviours supportive of weight loss, often by targeting psychological processes (e.g. motivation). While diet and exercise are behaviours, they are dealt with discretely from behaviour change approaches in the context of interventions. One of the most evidenced behavioural approaches associated with improved weight control is self-regulation (Teixeira *et al.*, 2015a), which involves the active tracking of diet, physical activity and body weight (or a combination). Self-weighing in particular has been consistently associated with improved weight outcomes (Madigan *et al.*, 2015a; Zheng *et al.*, 2015a). One systematic review reported that self-monitoring of diet, regardless of the method used to record (e.g. paper diary or online web app), was associated with improvements in weight (Burke, Wang and Sevick, 2011). Other behaviours such as commitment making (Coupe *et al.*, 2019), goal setting, planning and developing coping strategies (Teixeira *et al.*, 2015a) have been shown to improve weight outcomes, as has practicing acceptance, commitment and mindfulness, reducing avoidance and practising psychological flexibility (Lillis and Kendra, 2014). Nonetheless, behaviour change interventions alone may have limited effectiveness, with one meta-analysis reporting a mean weight loss of -1.4kg at 12-months in 15 behaviour change RCTs (Booth *et al.*, 2014), and as such they are often combined with dietary and exercise interventions.

1.3 An Impetus for Weight Regain

Despite the increasing prevalence of self-reported weight control attempts in the general population, BMI continues to rise in most of the world. It follows that weight loss must be generally unsuccessful in the long-term for most individuals. In one comprehensive meta-analysis, Franz et al. found that regardless of the method used to reduce weight (which included dietary, exercise and pharmacological approaches), body weight takes the same trajectory, characterised by a peak weight loss around 6-months and gradual weight regain over the subsequent 6 months to 4 years (Franz *et al.*, 2007a). The issue of weight

regain has been studied from physiological, biopsychological and genetic perspectives as well as psychological and behavioural standpoints, and indeed involves complex interactions between all of these factors. Crucially, weight regain does not occur in a vacuum but instead forms a single weight cycle in what, for many, is an ongoing battle with weight loss and regain which may span most of one's life. Understanding the causes of weight regain can provide vital information in understanding longer-term weight cycling.

1.3.1 The Physiological Impetus for Weight Regain

The physiological adaptations which occur in response to weight loss have been studied and reviewed (MacLean *et al.*, 2011; Ochner *et al.*, 2013; Sumithran and Proietto, 2013; Greenway, 2015; Casanova *et al.*, 2019). Biological adaptations can only modify EE and EI. Modifications to EE may be both physiological (i.e. reductions in RMR or TEF) and behavioural (changes in PA behaviours) whereas modifications to EI cannot be direct as food intake is entirely behaviourally determined, however, several physiological and neural changes function to predispose increased EI. These changes generate a double burden on weight-reduced individuals who simultaneously experience a reduction in the amount of energy they can consume (to maintain weight) and an increase in the energy they are driven to consume, resulting in a weight-loss induced energy gap which is central to the aetiology of weight regain.

1.3.1.1 Changes to Energy Expenditure with Weight Loss

The most obvious reduction in EE is a product of the reduced mass of metabolically active tissues, namely components of FFM including skeletal muscle and organ tissue. Given that each of these tissues have a well-defined energy rate (Wang *et al.*, 2010), the reduction in EE can be estimated from measured changes in body composition (although often a blanket value for FFM is used, rather than considering reductions in separate FFM compartments). As such, reductions in RMR are roughly predictable for a given amount of weight loss. However, as discussed earlier, there is an additional adaptive response (termed 'adaptive thermogenesis') which has been observed to reduce EE beyond predicted reductions, with one study reporting that 30% of the reduction in EE was due to adaptive thermogenesis (Tremblay and Chaput, 2009). Furthermore, a meta-analysis showed that formally-obese individuals had significantly (~5%) lower RMR than weight-matched never-

obese controls, with this effect persisting even years after weight loss (Astrup *et al.*, 1999). This adaptive response is thought to be driven by reductions in leptin, thyroid and sympathetic hormones and can be reversed acutely and instantaneously by leptin administration (Rosenbaum and Leibel, 2010). Whether metabolic adaptation alone is a barrier to weight loss maintenance has been questioned, with a recent study suggesting that the effect was too modest, and did not persist for long enough to be considered a barrier (Martins *et al.*, 2020). Changes in TEF (which typically comprises around 10-15% of EE) coincide proportionately with reductions in total energy consumption, however there is some evidence to suggest that it might decrease further in response to the same meal (Roberts *et al.*, 1996; Luscombe *et al.*, 2002), with reductions of around 13-23% greater-than-expected reported.

Energy expended in response to activity may reduce for physiological reasons (i.e. increased mechanical work efficiency) or behavioural reasons (i.e. reduced intentional activity or exercise). One study reported that mechanical work efficiency (that is, the energy required for a given movement) increased by ~20% (Michael Rosenbaum *et al.*, 2005), with these effects being reversed following leptin administration in two studies (Michael Rosenbaum *et al.*, 2005; Galgani *et al.*, 2010). The evidence on the impact of weight loss on intentional physical activity is less consistent. Indeed, weight loss is often accompanied by increases in activity (to achieve the initial weight loss), which may need to continually increase as weight loss proceeds to maintain an energy deficit. As such, it could seem that weight loss increases activity, though this association is not necessarily evidence of an effect. Bonomi et al showed that weight loss of ~13.4% in 66 individuals with overweight and obesity resulted in a 9% increase in daily activity counts, which was weakly associated with weight loss (Bonomi *et al.*, 2013) with similar results observed elsewhere (Weinsier *et al.*, 2000). Regarding unintentional activity, a recent systematic review provided that weight loss results in reduced NEAT in 15 of 36 studies included, though suggesting that heterogeneity in the definitions and measurement of NEAT limited comparison (A. M. Silva *et al.*, 2018).

1.3.1.2 Changes to Energy Intake Determinants with Weight Loss

Weight loss affects EI largely via changes to behaviour rather than as a direct physiological effect. Nonetheless, a plethora of adaptations to weight loss are known to

increase in subjective sensations of appetite and hunger, as well as increase sensory stimulation, food reward and addiction-like neural mechanisms. In extreme cases such as starvation, weight loss can produce significant changes to personality such as a persistent obsession with food and even violent attempts to acquire food [Stubbs & Turicchi 2020, in press].

The most commonly cited biopsychological adaptation is the reduction in leptin which accompanies reduced FM. Reductions in leptin occur within 24-48 hours of caloric restriction (Leibel, 2002) instigating what could be considered a 'starvation response' acting on both EE and EI in the direction of a positive energy balance. Leptin's action on two arcuate nucleus neuropeptides (namely the orexigenic neuropeptide Y and anorexigenic proopiomelanocortin peptides) in the hypothalamus functions to increase hunger and food intake, though these behavioural effects are more pronounced in animal models (Zhan *et al.*, 2013). Reductions in leptin can also reduce plasma glucose and increase plasma insulin, two further changes which stimulate appetite (Hussain and Khan, 2017). In humans with leptin deficiency, exogenous leptin administration is shown to approximately half satiation time, double satiety time and half the energy required to produce satiation (McDuffie *et al.*, 2004). However, whether leptin concentrations are a strong determinant of ad libitum energy intake under normal conditions is less clear (Hussain and Khan, 2017).

A string of other peptides, including ghrelin, peptide YY (PYY), cholecystokinin (CCK), glucagon-like peptide 1 (GLP-1), insulin and catecholamines respond acutely to energy balance and feeding, and have each been shown to respond to weight loss in a manner indicative of an increased appetitive response. Peptide YY, CCK, GLP-1 and insulin are all appetite-reducing hormones which increase following a meal to cause satiation and decrease between meals stimulating hunger. Ghrelin, the only orexigenic hormone of those listed, has an inverse effect. While their response is generally considered acute, longer-term weight changes can cause more long-lasting changes in circulating concentration. Weight loss has been shown to reduce GLP-1, CCK and insulin responses and increase ghrelin responses in a seminal study in which these adaptations persisted for 1 year follow ~13.5kg weight loss (Sumithran *et al.*, 2011), with similar observations made by several other groups (Nymo *et al.*, 2017; DeBenedictis *et al.*, 2020).

These physiological changes coincided with increased subjective appetite ratings (Sumithran *et al.*, 2011; Nymo *et al.*, 2017). Increases in both fasting and postprandial

appetite ratings have been observed in response to weight loss. In a comprehensive review of appetitive responses to weight loss in women, Hintze et al., reported increases of 5-38% in fasting hunger and 10-51% in motivation to eat, as well as 14-60% decrease in fasting fullness following prolonged energy restriction (Hintze *et al.*, 2017). They also reported altered postprandial responses, with most, but not all evidence, showing decreased fullness after a meal following caloric restriction. Importantly, the extent to which appetite ratings translate into measured EI has been questioned; in one systematic review of 462 studies, authors concluded that appetite ratings were only sufficiently associated with EI in 6% of the included studies (Holt *et al.*, 2017).

Some evidence suggests that addiction-like neural mechanisms are exaggerated following weight loss or in weight-reduced individuals (Ochner *et al.*, 2013), predisposing increased EI. One study showed that when comparing obese, formally-obese and lean individuals, neural responses (regional cerebral blood flow) in areas of the brain associated with reward were reduced in the obese and formally-obese groups compared to the lean group, suggesting persistence of abnormal neural responses (DelParigi *et al.*, 2004). However, one recent systematic review suggested that wanting and liking for food decrease following weight loss (Oustric *et al.*, 2018), though this could potentially be explained by habituation to lower food quantities following weight loss.

1.3.1.3 Functional Changes in Body Composition

As discussed, weight loss elicits a response in human physiology which acts to reverse the weight loss achieved. Weight loss is composed of both reductions in both FM and FFM. FM forms a relatively consistent component of body composition in terms of chemical structure, metabolic rate and energy value, whereas FFM is highly heterogeneous, and includes all non-fat tissues such as skeletal muscle, bone, organs, total body water, glycogen and gut weight, the metabolic rate of each varying greatly. Many of the effects of weight loss have been attributed to reductions in FM, due to the knowledge that FM is directly correlated with leptin, and leptin reductions show considerable effects on both EE and appetitive factors. Beyond leptin, the adipocyte may play a role in the aetiology of weight regain due to changes in its anatomy and accompanying cellular stress, inflammation and metabolism. In their recent comprehensive review of the role of adipose tissue in weight regain following weight loss, van Baak and Mariman describe how cell shrinkage and

extracellular remodelling occurring with weight loss provides a series of adaptations which downregulate the metabolic capacity of the tissue (including inhibition of lipolysis and reductions in the release of fatty acids) and predispose subsequent increases in FM (van Baak and Mariman, 2019).

Nonetheless, in terms of structural and functional integrity, certain components of FFM, particularly organs followed by skeletal muscle, are more vital than FM. As such, one would expect reductions in FFM to also elicit adaptive responses to reduce EE or increase EI, however, little scientific evidence supports a functional role of FFM loss in the aetiology of weight regain. In a re-analysis of the seminal Minnesota Starvation study (Keys *et al.*, 1950), Dulloo and colleagues analysed changes in (directly measured) energy intake and body composition during starvation and refeeding periods in 12 initially lean men (Dulloo, Jacquet and Girardier, 1997a). They showed that a reduction in both FM and FFM correlated directly with the hyperphagic response observed during the ad libitum refeeding period, and that the correlation between FFM recovery and hyperphagia persisted following complete recovery of FM. Together, these suggest an integrated model of autoregulation of body composition, in which the drive to eat persists beyond FM recovery and, perhaps, until FFM is fully recovered (the study did not continue to complete FFM recovery). Importantly, this study was conducted in initially lean mean (initial BMI ~ 22kg/m^2), who were predisposed to rapid FFM losses given the lack of FM as a buffer. Little evidence exists supporting a functional role of FFM in overweight individuals, though one recent study showed that in 57 overweight and obese subjects who achieved a mean 8.6kg weight loss by dietary intervention, the proportion of weight lost as FFM correlated with the degree of weight regain, suggesting that FFM may also have a mechanistic role in energy balance regulation following weight loss (Vink *et al.*, 2016).

1.3.2 The Necessity for Weight Loss Maintenance Intervention

There is an acknowledgement that (a) following weight loss, ongoing clinical care is necessary to achieve weight loss maintenance (WLM) in many individuals and (b) the approach to achieving WLM should be specifically tailored to the maintenance phase (Hall and Kahan, 2018). While quantifying the physiological impact (e.g. slowing of metabolic or peptide-based adaptations) is relatively simple, understanding the downstream behavioural mechanisms of weight regain is much more complex. An important starting point is to

compare the impact of changes in EE and EI on weight regain. Using a validated mathematical model to estimate free-living EI over 52 weeks in a weight loss intervention, Polidori et al showed that for each 20-30kcal/day of metabolic slowing (occurring at around every 1kg of weight loss), free-living EI increased by 100kcal/day (Polidori *et al.*, 2016). Similar results have been shown from related mathematical models of body weight (Hall *et al.*, 2011). Put simplistically, around three-quarters of the energy gap generated by weight loss and driving weight regain is thought to be attributable to changes in EI.

1.3.2.1 Eating Behaviour and Diet

This places modifying eating behaviour at the forefront of WLM interventions. Interventions can target eating behaviour directly by providing a structured or unstructured dietary plan. In one of the largest dietary WLM studies, the DiOGenes study which was conducted in 8 centres across Europe in 733 adults, diets varying in protein content and glycaemic index were provided for 26 weeks. Subjects in the low protein and high glycaemic index group regained regained weight (1.7kg) whereas others did not, and a stratified analysis revealed individuals assigned to a high protein group regained ~0.9kg less than the low protein arm, with similar results associated with low glycaemic index groups (Larsen *et al.*, 2010). In a more recent systematic review of long-term WLM, low carbohydrate, low glycaemic index and high protein diets were generally associated with some positive effect on WLM. The study also revealed that some dietary behaviours such as not being awake late at night, drinking lower amount of sugar-sweetened beverages, and following a healthy pattern were also useful (Soeliman and Azadbakht, 2014). In another systematic review, self-reported eating behaviour factors were related to successful weight loss maintenance (Varkevisser *et al.*, 2019) including cognitive restraint, cutting junk foods, using meal replacements, baseline healthy eating (and increases in healthy eating). Dietary factors associated with improved WLM included increases in fruit and veg consumption, decreases in sugar sweetened beverage consumption, increases in protein intake and decreases in carbohydrate and fat intake.

1.3.2.2 Physical Activity and Exercise

Mathematical models of body weight regulation in the WLM phase suggest that PA plays a much lesser role in the aetiology of weight regain than EI (Thomas *et al.*, 2012). Nonetheless, some contrasting evidence has suggested a key role of PA in preventing weight

regain. In their systematic review, 21 studies examined associations of change in PA and WLM, of which 76% reported a direct association (with increased PA) (Varkevisser *et al.*, 2019). In another study, increased cardiovascular fitness was associated with WLM (Wingo *et al.*, 2013). One study showed that over 30 months following a weight loss intervention, individuals with >2,500kcal/week exercise EE had significantly less weight regain than those who burned <2500kcal/week by exercise (2.9kg vs 6kg respectively) (Tate *et al.*, 2007). In a more recent study, WLMers (n=25, maintaining a mean 26.2kg weight loss for a mean of 9 years), weight-matched controls (n=27) and overweight/obese (n=28) groups had EE estimated by doubly labelled water over 2 weeks. PAEE was estimated by subtraction from total EE (minus 10% for TEF). It was found that WLMers had ~200kcal/d greater PAEE than both obese and weight-matched controls, suggesting that almost a decade after substantial weight loss, significantly greater PAEE was required to continue WLM (Ostendorf *et al.*, 2019).

Physical activity may also improve weight management by helping to regulate appetite. In one recent systematic review, it was shown that greater amounts of PA improves the matching of EE and EI, with low levels of PA (physical activity level 1.4–1.69 or <150 mins of exercise/week) resulting in a dysregulated EI (Beaulieu *et al.*, 2016), and in another review the same group suggested that acute bouts of exercise may reduce the reward associated with high-energy foods, an effect that may also extend to long term PA (Beaulieu, Oustric and Finlayson, 2020).

1.3.2.3 Behaviour change approaches

A range of behaviour change taxonomies have been applied to the study of WLM. One consistent observation arising from this literature is the direct association between self-regulatory processes and successful WLM (Wing *et al.*, 2006). A systematic review of self-regulatory mediators of WLM (Teixeira *et al.*, 2015b) identified a range of psychological processes and behaviours which were associated with successful weight management in interventions with a behaviour change component. Authors reported that increased autonomous motivation and self-efficacy, coupled with greater self-regulatory skills (such as self-monitoring but also skills related to planning and coping) were important mediators of success. In particular, self-weighing (Zheng *et al.*, 2015a) and self-monitoring of physical

activity and diet (Burke, Wang and Sevick, 2011) are central self-regulatory behaviours in successful weight management.

While self-regulation of weight and energy balance behaviours are shown to be important in successful WLM, these behaviours may be undermined by failures in emotional control and negative affect. In the early stages of development of the NoHoW project, a 3-country study questioned 2000 adults from UK, Portugal and Denmark (the loci of the project) who had recently lost weight on relationships between eating behaviour, emotional control and self-regulation (Sainsbury *et al.*, 2019). They found that individuals who showed greater difficulties regulating emotions regained more weight and used fewer self-regulatory strategies. Emotional control is consistently associated with weight control, often mediated by uncontrolled eating behaviour (Shriver *et al.*, 2019).

Identified as two key (and dependent) mediators of weight management, self-regulation and emotion regulation had not previously been jointly investigated in a WLM intervention. Given the knowledge (a) self-monitoring is a highly consistent predictor of better weight management and that (b) that difficulties controlling emotions and negative affectivity may function to undermine self-regulatory processes, the need to develop an intervention which jointly tests both the behaviour (monitoring) and the underlaying emotional cognitions was conceived recently as part of the NoHoW trial (examined in chapters 4 onwards).

1.4 Weight cycling

The processes of weight loss and, more recently, weight regain have been studied extensively in weight loss studies with either a follow-up period or an active WLM intervention. As such, the causes of weight regain are becoming increasingly understood. As mentioned previously, a concept which will form a key aspect of the present thesis, this struggle to manage body weight does not occur as a single weight cycle as it is typically studied but instead is likely to be indicative of a long-term struggle to manage weight which may span the majority of the adult lifespan. Understanding the determinants of weight regain may partially aid in addressing this problem, however, the prevalence, causes and consequences of weight cycling remain unclear.

In chapter 2, a detailed analysis of a single instance of weight loss and regain is conducted using two studies: a comprehensive meta-analysis of existing studies in which weight loss and regain is demonstrated and a re-analysis of individual-level data from the DiOGenes trial. Both studies attempt to place emphasis on the defining factors of a weight loss attempt (namely the rate, amount and composition of weight loss), and how these factors influence further weight regain. In doing so, a single weight cycle is used as a model for longer-term weight cycling, given the lack of data on weight cycling over the longer-term.

In chapter 3, a comprehensive review of the literature is provided aiming to understand these factors in greater detail, and the chapters following this address key issues surrounding how this instability in body weight can be defined, and its causes and consequences. The thesis develops the idea that weight cycling is a traditional idea of weight loss and regain, however, in reality individual's body weight trajectories are not V- or U-shaped, but instead show indiscriminable patterns varying in the amount, rate and duration of weight loss and weight regain. This variability in body weight assumes the central focus of this thesis and is an extension of historical weight cycling literature, first studied by Kelly Brownell and Lauren Lissner in the late 1980s to early 1990s (Brownell *et al.*, 1986; Lissner *et al.*, 1990).

Chapter 2. Associations Between the Amount, Rate and Composition of Weight Loss and Subsequent Weight Regain

Detailed, long-term data on weight cycling is lacking, and as such understanding its determinants is difficult. However, many studies have examined the process of weight loss and regain, and this data can be used to inform a model of weight cycling by using a single cycle as a model for longer-term weight cycling.

The following chapter is structured around two related scientific publications: (a) a systematic review and meta-analysis published in Obesity Reviews (Turicchi *et al.*, 2019) and (b) a re-analysis of the Diet, Obesity and Genes (DiOGenes) trial, published in The American Journal of Clinical Nutrition (Jake Turicchi, O'Driscoll, Finlayson, Duarte, Hopkins, *et al.*, 2020). In both papers, I was solely responsible for conception, analysis, draft writing and the final published manuscript. In both papers, secondary authors (see articles for list of authors) may have provided feedback for editing. In the meta-analysis, three additional authors (R.O.D., G.F. and K.B.) helped with the systematic review process (e.g. paper screening) as required.

2.1 Introduction

The coinciding prevalence of both dieting (Santos *et al.*, 2017) and increasing rates of obesity (Agha and Agha, 2017) may indicate many attempts to achieve or subsequently maintain weight loss are of limited success. Evidence suggests that the latter in particular is a concern for the global management of obesity (Soleymani, Daniel and Garvey, 2016), such that weight gain commonly follows weight loss. Furthermore, a weight loss attempt does not occur in a vacuum, but instead is generally indicative of a longer-term problem with controlling body weight, the consequence of which is, for many, repetitive cycles of loss and regain (also termed weight cycling).

The problem of failure in WLM has been studied from physiological, psychological, behavioural and environmental perspectives. It seems evident that understanding and addressing the problem has many layers of complexity. Research suggests that weight loss functions to both decrease EE (Müller, Enderle and Bosy-Westphal, 2016) and increase EI and appetite (Nymo *et al.*, 2018). The former is largely a physiological adaptation and the

latter a behavioural one (though most likely partially related to biopsychological changes). Given that these adaptations are a response to weight loss, the question of how to describe the features of a given weight loss episode is relevant. Weight loss can be described in terms of its magnitude (i.e. kg or %), rate (e.g. kg/week) and a composition (i.e. the proportionate reductions in both FM and FFM, which can be further broken down to constituent components). It is likely that magnitude, rate and composition of weight loss relate to the changes in EI and that predispose people to weight regain. Indeed, it has been suggested that functional changes in different body structures influence physiological function which in turn act as cues for behaviour particularly in relation to negative energy balances [Stubbs & Turicchi 2020, in press]. However, the impact of each of these three characteristics of weight loss on subsequent weight regain is not well understood and the literature relating to each is discussed below.

2.1.1 Associations Between the Amount of Weight Lost and Regained

Given that weight loss causes resistant adaptive responses, it follows that it typically results in weight regain. Indeed, such a view is central to the set point (or settling point) theories (Speakman *et al.*, 2011) which states that the body is under strong genetic and humoral control which aims to return the body to a given weight, or that the interference of the western diet environment may modify this to a new 'settling point' (Müller, Bosy-Westphal and Heymsfield, 2010) marked by a new homeostatic equilibrium. Given the assumption that physiological resistance increases in line with weight loss, straying further from a set point may increase the risk of weight regain. However, a contrasting viewpoint is that individuals who succeed in achieving more weight loss are likely to have developed and solidified the behavioural skills, psychological processes and lifestyle changes which allowed them to reach that point, and thus are more equipped to achieve successful WLM, compared to an individual who achieved only minor weight loss (Elfhag and Rossner, 2005; Wadden *et al.*, 2011).

The evidence relating to the association between the amount of weight loss and subsequent 'successful' WLM is inconsistent. One key distinction between studies reporting this association is the manner in which researchers define 'success' in WLM. Some studies may choose to define success as, for example, maintenance of ≥5% weight loss (Foster *et al.*, 1997), or another binary definition. In this case, 'successful' weight loss maintenance in

these studies is likely to be a function of losing more initial weight, yet individuals with greater weight loss may actually regain more weight than some unsuccessful individuals. For example, an individual who lost 15% body weight and regained 9% would still be considered successful, whereas an individual who lost 6% and regained 2% would be unsuccessful despite regaining substantially less weight. To overcome this, one approach used the fraction of weight lost which was subsequently regained and found no difference in this fraction during follow up between those losing 5-10% (55% regained) and those losing >10% (49% regained) body weight (Barte *et al.*, 2010).

Several studies have identified greater initial weight loss as a predictor of successful WLM (Jeffery, Wing and Mayer, 1998; Astrup and Rössner, 2000; van Baak *et al.*, 2003; Elfhag and Rossner, 2005; Handjieva-Darlenska *et al.*, 2010a; Wadden *et al.*, 2011; Sawamoto *et al.*, 2017). Some of these use associations between continuous loss and regain as an outcome (Jeffery, Wing and Mayer, 1998; Handjieva-Darlenska *et al.*, 2010a), whereas some used defined cut-offs such as 5% reduction at a given timepoint (Wadden *et al.*, 2011). The explanations given by authors for this result are consistent with those mentioned earlier (solidifying beneficial behaviours, strategies and lifestyle changes). In contrast, a fewer number have shown associations between increased weight loss and weight regain (McGuire *et al.*, 1999; Sbrocco *et al.*, 1999), or no effect (Barte *et al.*, 2010). However, no previous meta-analysis has synthesised the evidence on the impact of the magnitude of weight lost on that subsequently weight regained.

2.1.2 Associations Between the Rate of Weight Loss and Weight Regained

The rate of weight loss is generally less well studied in relation to subsequent WLM than the amount of weight lost. One area of literature where the rate is particularly noteworthy is in relation (VLCDs; often allowing 500-800kcal per day and lasting for short durations typically around 4-12 weeks). Indeed, in two meta-analyses, it was reported that VLCDs produce significantly greater short-term, but not long-term, weight losses than less severe calorie restrictions (Gilden Tsai and Wadden, 2006; Franz *et al.*, 2007b) largely driven by the rapid rate of weight regain. Similarly, several other studies have associated VLCDs with greater weight regains (Wadden, Foster and Letizia, 1994; Paisey *et al.*, 2002; Lutes *et al.*, 2008). In one study, two groups were given a moderate (1,200kcal/day) and severe (420kcal/day) diet. Weight losses at 52 weeks were 11.9kg and 21.5kg respectively,

however, during the next 26 weeks the severe restriction group regained ~11kg whereas the moderate restriction group did not significantly change weight (Wadden, Foster and Letizia, 1994). It could be that greater rates cause more substantial biopsychological adaptations, or simply that lifestyle changes need to be more abrupt and significant therefore less sustainable, and indeed a combination of both is likely.

Conversely, one study found when comparing slow (<0.23 kg/week, n = 89), moderate (≥0.23 and <0.68 kg/week, n = 104) and fast (≥0.68 kg/week, n = 69) weight loss groups, The fast and moderate groups were 5.1 and 2.7 times more likely to achieve 10% weight losses at 18 months than the slow group, though this was largely driven by much greater initial weight loss (Nackers, Ross and Perri, 2010). Indeed, it is hard to disentangle the effects of rate and amount of weight loss on weight regain as in studies examining severe deficits (e.g. VLCDs), rapid weight losses often coincide with large reductions in weight. One study which addressed this problem found that when comparing similar weight losses (~8.5kg) achieved by low calorie diet (LCD) and VLCD (i.e. generating the same total energy deficit over different time periods), there were no significant differences in weight regain at 9-month follow-up (Vink *et al.*, 2016), suggesting that perhaps any rate effects are related to the magnitude of weight loss. Nonetheless, no systematic review or meta-analysis has investigated the association of rate of weight loss as a continuous variable on subsequent magnitudes of weight regain (before and after adjustment for total weight loss).

2.1.3 Changes in Body Composition During Weight Loss

In a two-compartment model of body composition, weight loss is comprised of reductions in FM and FFM. Fat mass is a relatively consistent compartment, in that while it may be distinctively situated (e.g. subcutaneous vs visceral compartments), it is of relatively constant composition and thus energy value. Fat free mass on the other hand includes all compartments excluding FM, including skeletal muscle, organ tissue, bone, water, glycogen, gut weight and more. Each of these compartments vary considerably in their energy value (and has a null energy value in the case of water). The proportionate loss of FFM is modified by a range of factors, including but not limited to: initial body composition (Hall, 2007), the amount of weight lost (Heymsfield *et al.*, 2011), the degree of energy deficit (and thus the rate of weight loss (Chaston, Dixon and O'Brien, 2007)), macronutrient composition of the diet (Kim *et al.*, 2016) and physical activity.

Structural changes occurring during therapeutic weight loss has been deconstructed to three overlapping physiological stages by Heymsfield and colleagues (Heymsfield *et al.*, 2011). Phase 1 is characterised by rapid initial reductions in FFM due to initial loss of glycogen, associated body water and nitrogen (from some tissues such as the liver). The rate of FFM depletion decelerates and the contribution of glycogen and water to FFM loss decrease throughout phase 1, stabilising around 4-6 weeks marking the beginning of phase 2. Phase 2 is characterised by increases in the relative contribution of FM loss and gradual plateau of FFM loss. During phase 2, the contribution of FFM loss to weight loss decreases along exponential decay curves that are influenced the factors cited above, including the rate at which rate is lost (or, in other words, extent of energy deficit) (Chaston, Dixon and O'Brien, 2007). The reduction in FFM loss serves to protect against reductions in organ weight which may cause perturbations to physiological functioning and, in extreme cases such as starvation (as we reviewed extensively). Differential changes in organ weights have been discussed and we have reviewed structural changes in FM and FFM compartments extensively (Stubbs & Turicchi 2020, in press).

In their systematic review, Chaston et al concluded from data collected in 26 dietary and behavioural interventions that the degree of caloric restriction (and thus rate of weight loss) was a significant predictor of the proportionate reductions in FFM occurred during the weight loss (R^2=0.31, P=0.006). Again, this comparison is made solely from comparing LCD and VLCDs. Nonetheless, no study has reviewed whether the rate of weight loss as a continuous variable across a wide range of energy deficits is associated with proportionate reductions in FFM loss.

2.1.4 The Role of Changes in Body Composition on Appetite

Weight loss is generally considered to have an orexigenic effect in most (Sumithran *et al.*, 2011; Hintze *et al.*, 2017; Sayer *et al.*, 2018) but not all studies (Andriessen *et al.*, 2018a). It follows that appetite-stimulating signals must be released in response to reductions in at least one but likely many body tissues. Early research on appetite regulation took an adipocentric view by proposing that leptin was the central regulating orexigenic hormone through which changes in appetite and energy intake were moderated (Friedman, 2011) via its action on hunger and satiety related ARC-neurons. It follows, theoretically, that reductions in FM should reduce leptin and stimulate appetite. Yet, recent work has

evidenced a direct association between FFM and energy intake based on cross-sectional data (Blundell *et al.*, 2012; Weise *et al.*, 2013; Cameron, Sigal, *et al.*, 2016; Vainik *et al.*, 2016; McNeil *et al.*, 2017; Jang and Bu, 2018), a relationship which is often reversed, weaker or not observed in relation to FM (Weise *et al.*, 2013; Hopkins *et al.*, 2016). The implication of this association suggests that (a) as FFM increases, appetite and associated EI increases and conversely (b) as FFM decreases, appetite and associated EI decreases. The latter is inconsistent with the increased appetitive response to weight loss, and in response to this inconsistency the concept of both 'active' and 'passive' influences of FFM on EI has been proposed (Dulloo *et al.*, 2017; Stubbs *et al.*, 2018). The passive role of FFM which occurs at or around energy balance refers to a direct, tonic link between FFM and EI, shown to be mediated by energy requirements (Hopkins *et al.*, 2016). The active role is asserted as the activation of a drive to eat as a product of reduced FFM in a pathway not mediated by energy requirements (i.e. a signal coming directly from FFM tissue) in order to preserve the structural integrity of the compartment.

Importantly, most of this evidence stems from cross-sectional data. Active and passive influences of FFM on EI are largely hypothesised yet very little data exists to support this contention. Longitudinal data on body composition and appetite (or preferably EI) are required to test these hypotheses. To my knowledge, only one study, The Minnesota Starvation Study (Keys *et al.*, 1950) has examined the influence of changes in FM and FFM compartments in relation to appetite and energy intake changes occurring during weight loss. In a re-analysis of the study, Dulloo and colleagues showed that the prior depletion of both FM and of FFM were independently associated with the subsequent hyperphagic response (which persisted until the repletion of FFM despite an overshoot of FM) (Dulloo, Jacquet and Girardier, 1996). This suggests that dynamic changes in the proportion of FM:FFM changes during energy deficits may impact subsequent appetite and EI, and given that hyperphagia persisted until FFM but not FM was restored, it is logical to hypothesise that greater proportionate losses of FFM are the determining factor in the hyperphagia response. Importantly, these results were observed under extreme conditions of weight loss, and no evidence has tested this hypothesis in overweight and obese individuals undergoing therapeutic weight loss, yet it is likely that weight loss produces substantially different physiological responses in individuals with obesity compared to individuals with normal weight or underweight.

What follows is two complementary studies examining how the three components of a weight loss episode (amount, rate and composition) of weight loss discussed influence the process of weight regain. The first study is based on meta-data extracted from 52 weight loss groups, and the second study is a re-analysis of the DiOGenes weight loss and maintenance trial using individual-level data, which builds on the results of the first study by examining a potential mechanism through which proportionate changes in body composition influence the process on weight regain (through adaptations to appetite perceptions).

2.2 Associations between the rate, amount, and composition of weight loss as predictors of weight regain: A systematic review and meta-regression

2.2.1 Objectives

The following study is concerned with investigating determinants of weight regain following therapeutic weight loss interventions in individuals with overweight and obesity. Specifically, the association between each of the 3 components of weight loss (discussed above; amount, rate and composition) with subsequent weight regain in the follow-up period were examined using meta-regression to synthesise the existing evidence. In order to investigate this, enough weight loss (considered as ≥ 5% which is generally deemed as clinically significant (Rena R Wing *et al.*, 2011b)) and also some weight regain (considered as ≥ 2%, given that normal body weight fluctuation is around 1-2% (Bhutani *et al.*, 2017a)) was required.

The objectives of this study were to:

1. Systematically review weight loss studies reporting amount, rate and composition of weight loss which feature subsequent weight regain during the follow-up period
2. Use meta-regression to determine the association between these characteristics of weight loss and the amount of weight subsequently regained.
3. Use meta-regression to examine the associations between rate and amount of weight loss on loss of fat-free mass

It was hypothesized that both the amount and rate of weight loss would be associated with greater weight regains, as would greater reductions in FFM. Furthermore, it was

hypothesized that both greater rates and amounts of weight loss would be associated with greater reductions in FFM.

2.2.2 Methods

This review was prospectively registered on PROSPERO (ID: CRD42018106638). A study flow diagram is shown in **figure 2.1.**

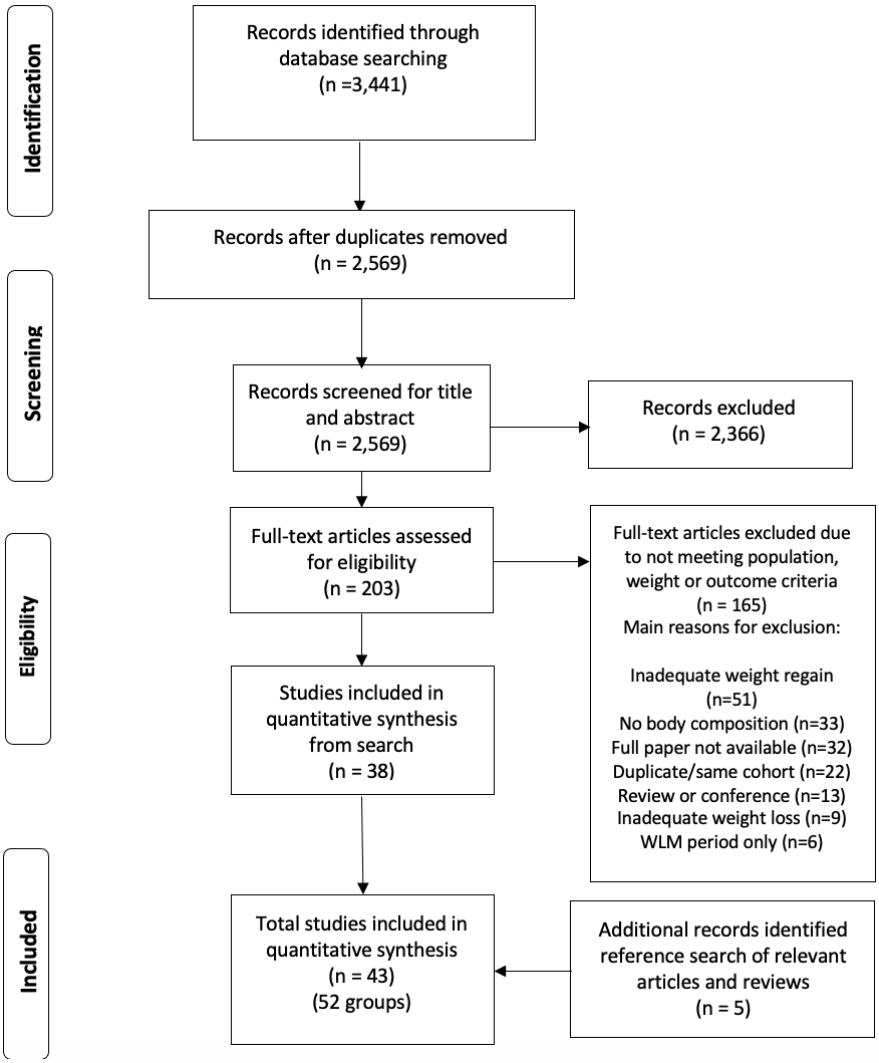


Figure 2.1. *PRISMA study flow chart detailing identification, screening, eligibility and inclusion processes. Reasons for exclusions included*

2.2.2.1 Inclusion and Exclusion Criteria

Studies included were primary research in the English language published up until the 27th July 2018 in humans. Study participants were limited to adults (≥18 years) but included all age and ethnic groups as well as those with pre-existing health conditions (e.g. cardiovascular disease or type 2 diabetes). The minimum weight loss duration was set at 4

weeks to limit the confounding effect of initial water and glycogen losses which may be recorded as loss in FFM (see (Heymsfield *et al.*, 2011) for more information). Studies included were weight loss intervention studies in which clinically significant weight loss (≥5%) was achieved and subsequent weight regain (≥2% of baseline weight) occurred during the follow-up period. Only studies which reported weight regain were included to examine predictive factors associated with the magnitude of weight regain. Inclusion of studies with successful weight loss maintenance (or further weight loss) during the follow up period would have allowed for no variability in the dependent variable with which to generate predictive models of weight regain. A minimum of 2% weight regain (vs. baseline) was required as short-term weight fluctuations of 1-2% are common (Bhutani *et al.*, 2017b), therefore this allowed us to be more certain individuals had regained weight. Studies included measured body composition before and after weight loss, and, if reported, following weight regain. Studies were excluded if weight loss was achieved by pharmacological, surgical or moderate to vigorous exercise interventions as these methods may alter the relationship between weight loss and changes in body composition (Chaston, Dixon and O'Brien, 2007). Studies in healthy weight individuals (BMI <25 kg/m^2) were excluded due to a lack of weight loss studies in the group. Studies in athletes were excluded as the dynamic of weight loss in this group varies from the target population (i.e. rapid weight loss is used to target water and glycogen depletion [36]).

2.2.2.2 Literature search

A literature search was carried out on the 27th of July 2018. MEDLINE, EMBASE and PubMed databases were searched, and the search strategy employed can be found in appendix 2.1. Grey literature was searched for thesis articles and a reference search of relevant articles and reviews was conducted to make sure no relevant material was omitted.

2.2.2.3 Study selection

References were extracted into Microsoft Excel (2016; version 1805) and duplicates were removed. A title and abstract screen was conducted initially to remove studies unrelated to the topic by two authors (JT and ROD). All remaining studies were subject to a full paper screen conducted by the lead author (JT) and one secondary author (ROD, KB or GF). Discrepancies were resolved by discussion between authors.

2.2.2.4 Data extraction

Data relevant to the population (sample size, gender, age and BMI), intervention type, intervention and follow-up duration, weight lost, weight regained (absolute and relative values) and body composition at a minimum of two points (baseline and following weight loss) were extracted. Body composition following weight regain was extracted if provided. Body composition data relating to a 2-compartment model (e.g. FM and FFM) was extracted. Data relating to 4-compartment models reported in some studies was not extracted (Jebb *et al.*, 2007; Bosy-Westphal *et al.*, 2013) as these studies were limited in number and therefore not enough data was available to generate statistical models. Where a single study had more than one discrete group (Pasman, Westerterp-Plantenga and Saris, 1997; Nicklas *et al.*, 2001; Uusi-Rasi *et al.*, 2010; Soenen *et al.*, 2012; Vink *et al.*, 2016; Byrne *et al.*, 2018) these were treated as separate groups in the analysis.

2.2.2.5 Risk of bias

A modified Downs and Black scale was used to assess risk of bias independently by two authors (J.T. and R.O.D.). The Downs and Black instrument is an established tool for determination of the quality of a study within a systematic review and meta-analysis (Deeks *et al.*, 2003). Two questions related to randomisation were removed as randomisation to groups was not relevant to our outcomes and two questions specific to case-control and cohort studies were removed. Three aspects of bias were assessed: reporting (10 questions), external validity (3 questions) and internal validity (8 questions). The maximum possible score was 21. High, medium and low risk of bias were assessed as follows: high (>7 reporting; >1 external validity; >5 internal validity); medium (>3 reporting; >1 external validity; >3 internal validity) and low (<3 reporting; <1 external validity; <3 internal validity).

2.2.2.6 Data Analysis

Study characteristics are described as median (range), and outcomes as mean (standard deviation; SD). Where missing, SDs were calculated from standard errors. If SDs were not provided at all time points, they were imputed from previous time points using last observation carried forward. A random effects meta-regression model was selected prior to analysis due to anticipated high levels of unexplained variance between studies. All meta-regressions were performed using the restricted maximum likelihood method with

Hartung-Knapp adjustment. Both of these approaches are recommended as conservative methods and therefore the risk of type 1 errors was minimized (IntHout, Ioannidis and Borm, 2014). Two unstandardized outcome variables were used: (1) weight regain (the absolute difference between weight following loss and at follow-up) and (2) fat-free mass loss (the absolute difference between FFM at baseline and following weight loss). Absolute amount (kg) and rate of weight loss (kg/week; calculated as the weight lost divided by weight loss duration) were used to predict both outcomes (1) and (2). Additionally, the interaction between rate and amount was entered in both of these models. Absolute FFML and FML were used to predict outcome (1). Pre-post correlations were calculated if SD of change was provided as per Cochrane guidelines (Higgins JPT, Green S, 2011) or where raw data was provided by authors (Bosy-Westphal *et al.*, 2013). A pre-post correlation value of 0.9 was used in the analysis as it was most common from calculated correlations. A sensitivity analysis was conducted between the lowest and highest calculated correlation (0.7 - 1.0) and this did not change the significance of any results. Results are presented as unstandardized regression coefficients and 95% confidence intervals, p-values, R2 values, measure of heterogeneity ($Tau^{2,}$ which is a commonly used metric of heterogeneity in random-effects meta-analysis (Higgins, 2008)) and all models are presented both with and without adjustment for baseline BMI. Body mass index was chosen as a covariate due to its known interaction with body composition changes (Hall, 2007). All meta-regression plots are presented in **figure 2.2**. The meta-regression was conducted using Comprehensive Meta-Analysis Software (v3.0; Biostat, Englewood, NJ).

2.2.3 Results

The database search returned a total of 3,441 results of which 2,569 were not duplicates. Of these, 203 were retrieved for full text screening, resulting in the inclusion of 43 studies which comprised of 52 eligible groups. The main reasons for exclusion included inadequate weight regain and lack of body composition measurement.

2.2.3.1 Study Characteristics

Study characteristics are presented in **table 2.1**. Three studies included two independent groups (Nicklas *et al.*, 2001; Vink *et al.*, 2016; Byrne *et al.*, 2018) and three studies included three independent groups (Pasman, Westerterp-Plantenga and Saris, 1997;

Uusi-Rasi *et al.*, 2010; Soenen *et al.*, 2012). Each group used one or more of the following methods to achieve weight loss: calorie restriction (n=20), very-low calorie diet (n=19), low calorie diet (LCD; n=15), behaviour change intervention (n=2), high protein diet (n=2), high-fibre diet (n=2), alternate day fasting (n=1), high fat diet (n=1), low carbohydrate diet (n=1) and Medifast diet (n=1). Body composition was measured using dual energy X-ray absorptiometry (DXA; n=21); water displacement (n=6); deuterium dilution (n=7); bioelectrical impedance (BIA; n=5) and air displacement plethysmography (ADP; n=4). In 27 studies there was a passive follow-up period where no contact with participants occurred (van der Kooy *et al.*, 1993; Wadden *et al.*, 1996; Nagy *et al.*, 1998; Westerterp-Plantenga, Kempen and Saris, 1998; Fogelholm *et al.*, 1998; Gallagher *et al.*, 2000; Nicklas *et al.*, 2001; Van Aggel-Leijssen *et al.*, 2002; Byrne *et al.*, 2003; McAuley *et al.*, 2006; Jebb *et al.*, 2007; Linna *et al.*, 2007; Vogels and Westerterp-Plantenga, 2007; Diepvens *et al.*, 2007; WANG *et al.*, 2008; Goyenechea *et al.*, 2009; Matsuo *et al.*, 2010; Beavers *et al.*, 2011; Senechal *et al.*, 2011; Bosy-Westphal *et al.*, 2013; Verhoef *et al.*, 2013; Waters *et al.*, 2013; Christensen *et al.*, 2013; Von Thun *et al.*, 2014; Aubuchon *et al.*, 2016; Vink *et al.*, 2016; Catenacci *et al.*, 2016; Dandanell *et al.*, 2017) whereas 16 studies conducted an active WLM intervention (Pasman, Westerterp-Plantenga and Saris, 1997; Brinkworth *et al.*, 2004; Due *et al.*, 2004; Lejeune, Kovacs and Westerterp-Plantenga, 2005; Lien *et al.*, 2009; Uusi-Rasi *et al.*, 2010; Davis *et al.*, 2010; Márquez-Quiñones *et al.*, 2010; Soenen *et al.*, 2012; Verhoef *et al.*, 2013; Pownall *et al.*, 2015; Vadiveloo *et al.*, 2016; Borel *et al.*, 2017; Ryan, Serra and Goldberg, 2018; Byrne *et al.*, 2018). The median weight loss period was 13 (4 – 52) weeks and the median follow-up period was 44 (18 – 249) weeks. The median sample size was 27 (5-506), yielding a total of 2,379 participants, of which 66% were female.

2.2.3.2 Participant Characteristics

At baseline, groups had a median age of 44.8 (34.5-70.6) years and a median BMI of 32.9 (27.3-38.5) kg/m^2. Baseline outcome values are reported in **table 2.2**. The initial body weight was 92.9 (9.9) kg, FM was 38.4 (5.6) kg and FFM was 53.4 (7.6) kg.

2.2.3.3 Weight and Body Composition Changes

Changes in body weight and composition during loss and regain are reported in **table 2.2**. The mean weight loss was 10.1 (3.0) kg which accounted for 10.9% of initial bo

Table 2.1. Study characteristics

Study	Sample size (gender)	Age (years)	BMI (kg/m^2)	Weight loss intervention	Follow-up period	Body composition method	Weight loss duration (weeks)	Follow-up duration (weeks)
Aubuchon 2016	13 (W)	32.9 (4.2)	32.9 (4.2)	VLCD	Passive	DXA	12	26
Beavers 2011	78 (W)	58.8 (5.1)	33.4 (3.8)	CR	Passive	DXA	20	52
Borel 2017	144 (M)	48 (8)	30.9 (3.1)	CR	Nutritional and physical activity counselling	DXA	52	104
Bosy-Westphal 2013	27 (21W)	36.4 (5.9)	35.4 (4.5)	LCD	Passive	ADP	13	26
Brinkworth 2004	38 (23W)	34.5 (7.7)	34.5 (7.7)	CR	Dietary guidance	DXA	12	52
Byrne 2003	40 (W)	36.3 (6.0)	29 (11.1)	CR	Passive	DXA	22	52
Byrne 2018 (continuous)	13 (M)	40 (5.2)	34 (3.6)	Continuous CR	Dietary guidance	ADP	16	32
Byrne 2018 (intermittent)	15 (M)	40.3 (7.6)	34 (4.3)	Intermittent CR	Dietary guidance	ADP	16	32
Camps 2013	91 (69)	40.2 (9)	31.8 (3)	VLCD	Passive	ADP	8	44
Catenacci 2016 (ADF)	13 (10)	39.6 (9.5)	35.8 (3.7)	ADF CR	Passive	DXA	8	24
Christensen 2016 (control)	64 (51)	61.7 (6.8)	37.9 (5.3)	LCD or VLCD	Passive	DXA	16	52
Dandanell 2017	23 (13W)	34 (9.6)	35 (4.8)	CR + CBT	Passive	BIA	12	249
Davis 2010 (MD group)	45 (34)	43 (10.2)	38.5 (6.8)	Medifast diet CR	Medifast maintenance	BIA	16	24
Diepvens 2007 (placebo)	28 (W)	41.2 (9.3)	28.5 (2.2)	VLCD	Passive	Deutrium dilution	8	18

Due 2004 (HP)	25 (19)	39.8 (8)	30 (1.9)	High protein CR	Dietary counselling	DXA	26	26
Fogelholm 1998	5 (W)	41.2 (4)	37 (3.1)	LCD + VLCD	Passive	Water displacement	12	39
Gallagher 2000	11 (W)	63.4 (8.5)	33.6 (2.7)	LCD	Passive	DXA	16	66
Goyenechea 2009	12 (6)	37.7 (7.1)	32.3 (5.5)	LCD	Passive	BIA	7	25
Jebb 2007	58 (W)	46.8 (8.9)	31.6 (2.5)	LCD	Passive	DXA	12	40
Lejeune 2005	60 (M/W)	45.1 (10.4)	29.3 (2.5)	VLCD	Dietary counselling	Deutrium dilution	4	26
Lien 2009	27 (16W)	51	32.6	CR + behaviour change	Personal counselling or interactive website	DXA	26	26
Linna 2007	48 (M)	42.7	32.9	VLCD	Passive	Water displacement	26	130
Marquez-Quionones 2010	38 (W)	40.5 (4.3)	32.3 (6.9)	Dietary CR	Dietary intervention	DXA	8	26
Matsuo 2010	54 (W)	55.6 (4.8)	27.3 (1.9)	CR	Passive	BIA	15	90
McAuley 2006 (HF group)	31 (W)	45 (7.9)	36 (3.9)	High fat CR	Passive	BIA	26	26
Nagy 1998	14 (W)	58.4 (5.9)	27.7 (1.6)	LCD	Passive	Water displacement	15	208
Nicklas 2001 (ALA)[1]	14 (W)	57 (3.7)	33.3 (4.9)	CR	Passive	DXA	26	52
Nicklas 2001 (PRO)[1]	56 (W)	61 (7.5)	31.8 (4.5)	CR	Passive	DXA	26	52
Pasman 1997 (A)[2]	10 (W)	44.8 (7.3)	33.9 (2.8)	VLCD	High fibre diet	Deutrium dilution	8	60
Pasman 1997 (B)[2]	10 (W)	38.9 (7)	32.7 (3.6)	VLCD	High fibre diet	Deutrium dilution	8	60
Pasman 1997 (Control)	11 (W)	40.5 (7.1)	32.9 (4.7)	VLCD	Passive	Deutrium dilution	8	60

Pownall 2015	506 (305)	58.6 (7)	35.3 (5.4)	CR	Dietary guidance	DXA	52	156
Ryan 2018	24 (W)	45-76	32.3 (4.4)	CR	Dietary counselling	DXA	26	26
Senechal 2011	19 (W)	61.2 (6.0)	31.8 (4.0)	CR	Passive	DXA	15	52
Soenen 2012 (HPLC)	33 (M/W)	50 (12)	36.6 (4.6)	LCD: HPLC	HPLC diet	Deutrium dilution	12	36
Soenen 2012 (NPNC)	33 (M/W)	50 (12)	36.2 (4.7)	LCD: NPNC	NPNC diet	Deutrium dilution	12	36
Soenen 2012 (NPLC)	33 (M/W)	50 (12)	37 (5.4)	LCD: NPLC	NPLC diet	Deutrium dilution	12	36
Uusi-rasi 2010 (Large)[3]	20 (W)	42.1 (3.7)	33.3 (3.3)	VLCD thenLCD	Dietary counselling	DXA	12	36
Uusi-rasi 2010 (Medium)[3]	21 (W)	39.2 (5.6)	33.1 (4.5)	VLCD then LCD	Dietary counselling	DXA	12	36
Uusi-rasi 2010 (Low)[3]	21 (W)	38.3 (5.7)	34.4 (5.5)	VLCD then LCD	Dietary counselling	DXA	12	36
Vadiveloo 2016	186 (M/W)	52.3 (8.9)	33 (4)	CR	Dietary counselling	DXA	26	78
Van Aggel-Leijssen 2002	15 (M)	38.6 (6.5)	32 (2.2)	VLCD	Passive	Water displacement	12	40
Van der Kooy 1993	32 (15W)	39 (7)	30.9 (2.3)	CR	Passive	Water displacement	13	67
Verhoef 2013	98 (73W)	20-50	31.0 (3.2)	VLCD	Dietary guidance	Deutrium dilution	8	44
Vink 2016 (LCD)	57 (30W)	51.8 (14.3)	31.3 (3.8)	LCD	Passive	ADP	12	36
Vink 2016 (VLCD)	58 (30W)	50.7 (11.4)	31.0 (3.0)	VLCD	Passive	ADP	5	36
Vogels 2007	90 (M/W)	49.6 (9.7)	30.5 (3.5)	VLCD	Passive	Deuterium dilution	6	104
Von Thun 2014	20 (W)	60.1 (5.2)	28.9 (3)	CR	Passive	DXA	26	78
Wadden 1996	12 (W)	38.8 (3.4)	36.7 (2.1)	VLCD	Passive	Water displacement	16	116

Wang 2008 (Diet group)	15 (W)	58.6 (5.2)	33	CR	Passive	DXA	20	52
Waters 2013	16 (M/W)	70.6 (3.7)	36 (6.4)	VLCD	Passive	DXA	26	104
Westerterp-Plantega 1998	27 (W)	19-53	31.7 (2.6)	CR	Passive	Deutrium dilution	16	52

Table 2.1. *Sample size is presented as number of participants (number of women). M or W denotes a single gender sample. Age and BMI are presented as means (SD) and, where missing, were not provided. Abbreviations: M, men; W, women; CR, calorie restriction; LCD, low-calorie diet; VLCD, very low-calorie diet; CBT, cognitive behavioural therapy; HPLC, high protein low carbohydrate; NPNC, normal protein normal carbohydrate; NPLC, normal protein low carbohydrate; HF, high fat; MD, Medifast, DXA, dual energy X-ray absorptiometry; ADP, air displacement plethysmography.* [1]*Pro and Ala refer to two genetic variants of the peroxisome proliferator–activated receptor gene..* [2]*A; high fibre supplementation, B; medium fibre supplementation..* [3]*Low, medium and high weight loss groups*

Table 2.2. Absolute and relative changes in weight, FFM and FM during weight loss and regain

Study	Pre-weight loss			Post-weight loss			Follow-up			Relative changes in weight, FFM and FM					
	W1	FFM1	FM1	W2	FFM2	FM2	W3	FFM3	FM3	WL (%)	FML (%)	FFML (%)	WG (%)	FMG (%)	FFMG (%)
Aubuchon 2016	89 (13.9)	54.6	34.4	80.5 (12.6)	53.1	27.4	88.5 (9.8)	54.7	33.8	9.6	20.3	2.8	9.0	18.7	2.9
Beavers 2011	89.8 (11.1)	52.2 (5.7)	39.6 (6.8)	78.2 (10.7)	48.6 (6.1)	31.4 (8.0)	81.9 (13.5)	48.4 (5.9)	33.9 (9.0)	12.9	20.7	6.9	4.1	6.3	-0.4
Borel 2017	91.0 (16.2)	65.1 (7.0)	27.3 (3.7)	85.8 (14.6)	64.4 (6.7)	21.6 (6.7)	89.6 (16.3)	64.2 (6.5)	23.5 (4.0)	5.7	20.9	1.0	4.2	7.0	-0.3
Bosy-Westphal 2013	105.6 (18.9)	58.4 (8.3)	47.2 (5.0)	96.6 (18.9)	56.1 (9.0)	38.6 (7.1)	102.2 (18.9)	60.0 (12.6)	45.0 (12.8)	8.5	18.2	4.0	5.3	13.6	-0.1
Brinkworth 2004	98.8 (15.9)	53.3 (9.9)	41.1 (10.9)	90.5 (15.9)	50.9	35.0	94.7 (15.9)	51.4	38.9	8.4	14.8	4.5	4.3	9.5	0.9
Byrne 2003	93.7 (4.2)	51.9 (16.2)	38.7 (16.2)	88.3 (3.9)	50.7 (16.2)	34.6 (16.2)	90.7 (4.1)	49.8 (16.2)	38.3 (16.2)	5.8	10.6	2.3	2.6	9.5	-1.7
Byrne 2018 (continuous)	78.3 (7.4)	40.1 (4)	31.7 (4.4)	65.4 (6.4)	38.8 (4)	20.5 (4)	71.6 (8.3)	39.2 (4.3)	27.0 (5.9)	16.5	35.3	3.2	7.9	20.5	1.0
Byrne 2018 (intermittent)	110.2 (9.3)	67.7 (4.8)	42.5 (8.9)	100.2 (9.3)	66.6	35.9	107.2 (9.3)	68.0	41.5	9.1	15.5	1.6	6.4	13.2	2.1
Camps 2013	108.6 (13.5)	64.4 (8.6)	44.2 (11)	93.1 (13.5)	62.8	31.9	97.5 (13.5)	62.5	35.0 (11)	14.3	27.8	2.5	4.1	7.0	-0.5
Catenacci 2016 (ADF)	92.9 (12.6)	54.2 (10.1)	38.7 (7.2)	83.3 (11.4)	52.4 (9.8)	30.9 (6.9)	87.5 (13.4)	53.8 (9.9)	33.7 (7.8)	10.3	20.2	3.3	4.5	7.2	2.6
Christensen 2016 (control)	94.8 (15.9)	53.2 (10.1)	37.7 (9.4)	86.5 (15.9)	50.0 (9.7)	33.9 (9.0)	89.1 (16.2)	52.1	33.5	8.8	10.1	6.0	2.7	-1.1	3.9
Dandanell 2017	105 (16.1)	54.1 (9.3)	48.0 (10.3)	91.7 (16.1)	52.1 (9.3)	37.8	96.7 (16.1)	52.9	42.0 (10.3)	12.7	21.3	3.7	4.8	8.8	1.5

Davis 2010 (MD group)	107.0 (19.2)	65.0 (3.0)	42.0 (3.0)	94.0 (14.4)	62.0 (3.0)	32.0 (3.0)	101.0 (19.2)	60.0 (4.0)	41.0 (4.0)	12.1	23.8	4.6	6.5	21.4	-3.1
Diepvens 2007 (placebo)	111.6 (25.7)	63.8 (11.4)	47.8 (7.7)	98.0 (23.9)	61.3	36.8	103.6 (25.2)	62.3 (10.0)	41.3	12.2	23.1	4.0	5.0	9.6	1.6
Due 2004 (HP)	79.0 (8.6)	48.3 (4.5)	30.2 (6.2)	71.3 (8.3)	46.1 (4.1)	25.3	74.3 (9.0)	48.1	26.1 (7.0)	9.7	16.2	4.6	3.8	2.6	4.1
Fogelholm 1998	87.0 (14.3)	54.6 (8.1)	28.5 (5.8)	77.6 (14.3)	53.4 (8.1)	20.9 (5.8)	80.8 (14.3)	53.7 (8.1)	23.9 (5.8)	10.8	26.7	2.2	3.7	10.5	0.5
Gallagher 2000	96.3 (8.5)	51.6 (8.9)	44.7 (8.9)	85.8 (8.5)	48.1	37.7	91.6 (8.5)	50.4	41.2	10.9	15.7	6.8	6.0	7.8	4.5
Goyenechea 2009	86 (8.1)	45.7 (3.0)	40.3 (6.0)	77.4 (8.9)	44.3 (3.1)	33.2 (6.5)	83.0 (10.6)	45.1 (3.4)	37.9 (8.4)	10.0	17.6	3.1	6.5	11.7	1.8
Jebb 2007	89.3 (28.4)	58.0	31.3	83.8 (24.4)	56.3	27.5	86.5 (27.7)	56.4	30.1	6.2	12.2	2.9	3.0	8.4	0.1
Lejeune 2005	85.8 (8.5)	48.0 (5.2)	37.8 (6.0)	75.9 (8.7)	45.7 (6.7)	30.2 (6.6)	80.8 (9.9)	45.9 (5.1)	34.9 (7.2)	11.5	20.1	4.8	5.7	12.4	0.4
Lien 2009	83.4 (10.4)	52.1 (9.1)	31.4 (5.9)	77.3 (9.9)	49.9 (8.8)	27.2 (6.2)	80.3 (11.6)	51.1 (9.3)	29.0 (7.1)	7.3	13.4	4.2	3.6	5.7	2.3
Linna 2007	99.9 (9.5)	61.7 (8.0)	35.3 (6.0)	93.6 (9.5)	60.2 (8.0)	31.5 (6.0)	95.9 (9.5)	60.6 (8.0)	33.1 (6.0)	6.3	10.7	2.3	2.3	4.6	0.5
Marquez-Quionones 2010	105.3 (10.3)	68.8 (7.6)	36.8 (7.6)	90.6 (9.8)	64.1 (7.6)	26.8 (7.9)	100.3 (11.7)	66.9 (8.1)	33.7 (8.1)	14.0	27.2	6.8	9.2	18.8	4.1
Matsuo 2010	91.4 (12.9)	51.5	39.9	82.2 (11.7)	50.6	31.6	86.1 (12.3)	50.5	35.6	10.1	20.8	1.8	4.3	9.8	0.0
McAuley 2006 (HF group)	66 (7.1)	41.9 (3.9)	24.1 (4.7)	57.4 (6.4)	40.7 (3.4)	17 (3.8)	59.6 (7.3)	40.3 (3.8)	19.6 (4.8)	13.0	29.5	2.9	3.3	10.8	-1.0
Nagy 1998	97.2 (10.4)	52.4	44.8 (6.8)	88.7 (10.5)	49.4	39.3 (7.2)	91.8 (11.3)	50.4	41.4 (7.3)	8.7	12.3	5.7	3.2	4.7	1.9

Nicklas 2001 (ALA)[1]	72.7 (8.1)	43.0 (4.5)	29.7 (4.5)	60.7 (7.8)	40.5 (4.0)	20.3 (4.7)	64.9 (11.8)	44.8 (4.5)	27.1 (8.4)	16.5	31.6	5.8	5.8	22.9	10.0
Nicklas 2001 (PRO)[1]	90.9 (14.6)	42.6 (5.2)	42.2 (11.2)	83.3 (13.8)	42.3 (5.2)	37.6 (10.9)	88.7 (13.8)	NA	NA	10.9	0.7	5.9	5.9	NA	NA
Pasman 1997 (A)[2]	82.7 (11.2)	39.3 (3.7)	37.0 (8.2)	74.3 (11.2)	39.2 (3.7)	31.0 (8.2)	77.1 (11.2)	NA	NA	16.2	0.3	3.4	3.4	NA	NA
Pasman 1997 (B)[2]	89.9 (12)	51.6	38.3	78.6 (10.2)	49.3	29.3	85.6 (13.1)	49.6	36.0	12.6	23.4	4.5	7.8	17.5	0.5
Pasman 1997 (Control)	87 (5.9)	49.1	37.9	77.3 (6.1)	47.4	29.9	88.4 (10.1)	49.0	39.4	11.1	21.1	3.4	12.8	25.1	3.2
Pownall 2015	89.4 (12.6)	51.3	38.1	78.3 (10.6)	49.8	28.5	85.0 (12)	51.9	33.1	12.4	25.2	3.0	7.5	12.0	4.2
Ryan 2018	88 (14.7)	45.3 (5.9)	41.1 (9.3)	80.0 (9.8)	43.8 (5.4)	35.4 (9.8)	82.0 (14.7)	43.4 (5.9)	36.4 (9.8)	9.1	13.9	3.3	2.3	2.4	-0.9
Senechal 2011	79.3 (11.1)	40.3 (4.5)	36.7 (8.4)	68.6 (10.2)	39.1 (3.8)	27.8 (3.8)	71.1 (12.4)	39.0 (4.1)	30.5 (9.4)	13.5	24.3	3.0	3.2	7.4	-0.2
Soenen 2012 (HPLC)	108.1 (21.7)	63.2 (14.3)	44.9 (11.4)	93.4 (17.2)	60.4 (12.2)	33.0 (7.0)	96.5 (17.1)	59.8 (11.9)	36.7 (7.3)	13.6	26.5	4.4	2.9	8.2	-0.9
Soenen 2012 (NPNC)	105.3 (18.6)	57.7 (11.1)	47.6 (12.2)	94.6 (17.9)	55.6 (10.8)	39.0 (8.6)	97.1 (16.6)	56.2 (10.7)	40.9 (8.9)	10.2	18.1	3.6	2.4	4.0	1.0
Soenen 2012 (NPLC)	107.2 (17.7)	58.5 (9.8)	48.7 (11.6)	95.0 (17.2)	56.3 (9.1)	38.7 (7.9)	97.5 (17.1)	57.3 (9.9)	40.2 (8.4)	11.4	20.5	3.8	2.3	3.1	1.7
Uusi-rasi 2010 (Large)[3]	92.1 (12.4)	47.9 (6.1)	40.6 (7.0)	77.8 (10.8)	45.0 (4.7)	29.4 (7.3)	81.1 (10.5)	45.2 (5.4)	32.4 (7.1)	15.5	27.6	6.1	3.6	7.4	0.4
Uusi-rasi 2010 (Medium)[3]	92.0 (16.5)	45.5 (7.0)	42.7 (10.1)	82.3 (14.5)	43.9 (5.5)	35.0 (10.0)	86.7 (15.4)	44.0 (6.3)	38.9 (10.5)	10.5	18.0	3.5	4.8	9.1	0.2
Uusi-rasi 2010 (Low)[3]	94.0 (15.1)	47.3 (5.5)	43.1 (11.3)	88.4 (13.9)	47.4 (5.2)	37.8 (10.8)	92.9 (14.2)	46.9 (5.6)	42.3 (10.9)	6.0	12.3	-0.2	4.8	10.4	-1.1

Vadiveloo 2016	92.4 (15.0)	55.4 (11.9)	36.6 (9.2)	84.2 (15.0)	55.2	28.3	88.4 (15.0)	55.6	32.2	8.9	22.7	0.4	4.5	10.7	0.7
Van Aggel-Leijssen 2002	92.6 (9.5)	55.9 (11.6)	36.2 (6.4)	83.6 (9.5)	55.1	27.6	88.1 (9.5)	55.6	31.6	9.7	23.8	1.4	4.9	11.0	0.9
Van der Kooy 1993	93.8 (16.0)	59.2	34.6	86.9 (16.0)	54.8	32.1	89.5 (16.4)	56.5	33.0	7.4	7.4	3.0	2.8	2.8	2.8
Verhoef 2013	103.6 (11.7)	68.3 (9.6)	35.2 (5.6)	88.2 (9.6)	66.2	22.0 (5.1)	95.3 (9.6)	68.0 (8.5)	27.3	14.9	37.5	3.1	6.9	15.1	2.6
Vink 2016 (LCD)	91.1 (8.1)	56.7	34.4 (5.7)	78.1 (8.1)	54.6	23.5	90.0 (8.1)	57.2	32.8 (5.7)	14.3	31.7	3.7	13.1	27.0	4.6
Vink 2016 (VLCD)	92.5 (12.7)	53.8	38.7 (7.6)	83.0 (11.3)	51.8	31.2 (7.5)	86.8 (13.2)	53.2	33.6 (8.6)	10.3	19.4	3.7	4.1	6.2	2.6
Vogels 2007	89.4 (15.1)	57.2 (13.3)	32.1 (8.3)	82.1 (13.3)	54.6 (11.6)	27.6 (6.4)	89.0 (14.8)	56.2 (11.8)	31.0 (7.3)	8.2	14.0	4.5	7.7	10.6	2.8
Von Thun 2014	75.3 (7.0)	42.3	33 (4.8)	69.1 (3.3)	40.6	28.5 (6.7)	73.2 (3.3)	42.0	31.2 (6.6)	8.2	13.6	4.0	5.4	8.2	3.2
Wadden 1996	98 (11.1)	54 (7.6)	44 (7.3)	79.1 (10.4)	50.3 (6.0)	28.2 (7.0)	99.1 (11.8)	54.7 (6.6)	43.3 (8.3)	19.3	35.9	6.9	20.4	34.3	8.1
Wang 2008 (Diet group)	92.3 (10.3)	53 (3.1)	40.7 (8.0)	79.5 (11.3)	51.5 (3.4)	32.5 (8.5)	84.2 (14.4)	NA	NA	20.1	2.8	5.1	5.1	NA	
Waters 2013	101.5 (14.2)	59.9 (8.6)	40.9 (12.3)	91.4 (14.2)	56.7 (7.9)	34.8 (12.3)	94.5 (14.8)	56.9 (8.3)	37.6 (11.9)	10.0	14.9	5.3	3.1	6.8	0.3
Westerterp-Plantega 1998	85.9 (9.6)	49.9 (4.7)	36.6 (18.7)	75.2 (11.4)	47.5 (4.7)	27.5 (8.1)	81.4 (12.47)	48.8 (4.7)	32.3 (9.4)	12.5	24.9	4.8	7.2	13.1	2.6

Table 2.2. *Absolute and relative changes in weight, FFM and FM during weight loss and regain. Relative changes are calculated relative to baseline. Where data is missing it was not reported. Abbreviations: W, weight; FFM, fat-free mass; FM, fat mass; WL, weight loss; FFML, fat-free mass loss; FML, fat mass loss; WG, weight gain; FFMG, fat-free mass gain; FMG, fat mass gain, LCD, low-calorie diet; VLCD, very low-calorie diet; HPLC, high protein low carbohydrate; NPNC, normal protein normal carbohydrate; NPLC, normal protein low carbohydrate; HF, high fat; MD, Medifast, DXA.* [1]*Pro and Ala refer to two genetic variants of the peroxisome proliferator–activated receptor gene.* [2A]*; high fibre supplementation, B; medium fibre supplementation.* [3]*Low, medium and high weight loss groups*

weight. During weight loss, FFM and FM were reduced by 1.9 (1.0) kg and 7.8 (2.7) kg respectively, resulting in a 19.6% proportion of the weight lost as FFM. The mean rate of weight loss was 0.79 (0.39) kg/week equalling 0.86%/week. A total of 5.0 (3.0) kg, or 5.4% was regained in the follow-up period, comprised of 1.1kg (3.1) FFM and 4.0 (2.7) kg FM, providing a proportionate weight gain of 21.6% FFM.

2.2.3.4 Effect of Extent and Rate of Weight Loss on Weight Regain

Results for the effect of amount and rate of weight loss on weight regain are reported in **table 2.3** and meta-regression plots can be found in **figure 2.2 (A-B).** Both the amount of weight loss (β=0.50 (0.25, 0.74), R^2 = 0.29, p<0.001) and the rate of weight loss (β=2.06 (0.01, 4.11), R^2 = 0.06, p=0.049) were positively associated with weight regain in univariate and BMI-adjusted analyses. After adjustment for the amount of weight lost, the rate of weight loss was no longer a significant predictor of weight regain (p=0.42). However, the amount of weight loss remained significantly associated with weight regain when controlling for the rate of weight loss (p=0.001).

In model 2, the interaction term (rate x amount) was positively associated with weight regain (p=0.042) (**figure 2.3**), although this reduced to a non-significant trend after adjustment for BMI (p=0.09).

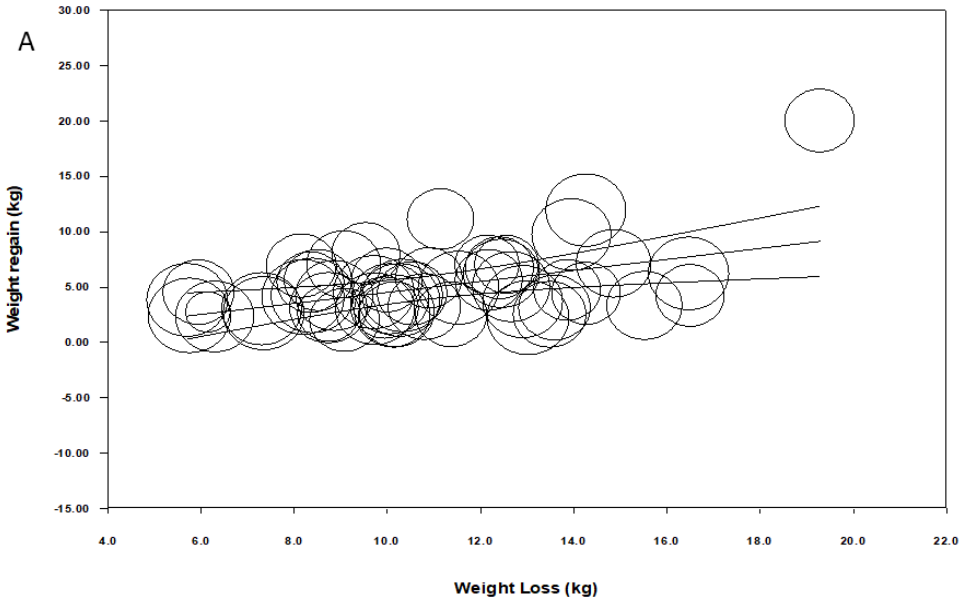
2.2.3.5 Effect of Fat Free Mass and Fat Mass Loss on Weight Regain

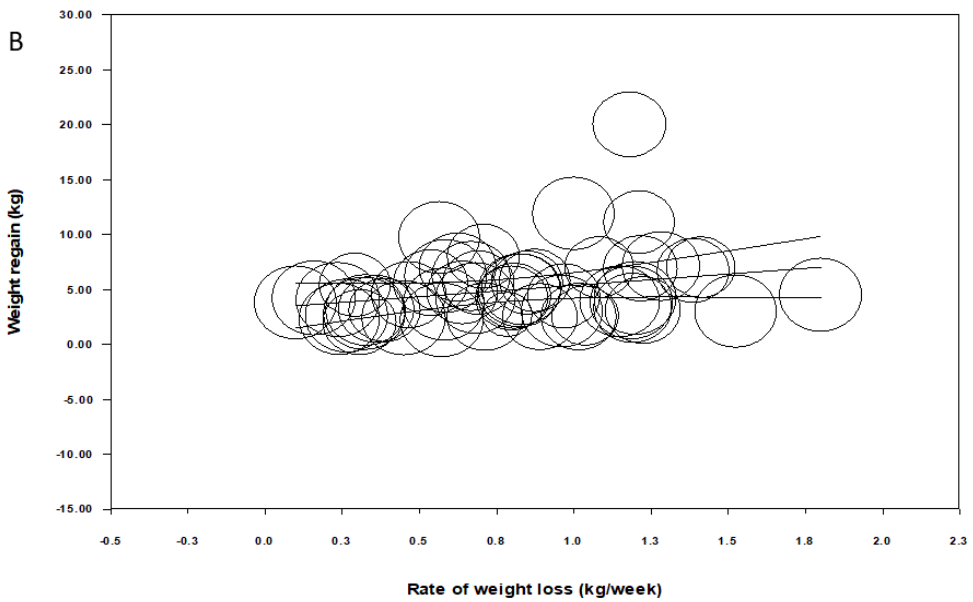
Results for the effect of FFML and FML on weight regain are reported in **table 2.4** and meta-regression plots can be found in **figure 2.2 (C-D)**. In a univariate analysis, both FFML (β=1.04 (0.20, 1.87), R^2 =0.12, p=0.017) and FML (β=0.61 (0.35, 0.87), R^2=0.37, p<0.001) predicted weight regain and these results remained similar after adjustment for BMI. After adjustment for FFML, FML remained significantly associated with weight regain (p<0.001) but FFML was no longer associated with weight regain after adjustment for FML (p=0.15). These results were similar when adjusted for baseline BMI.

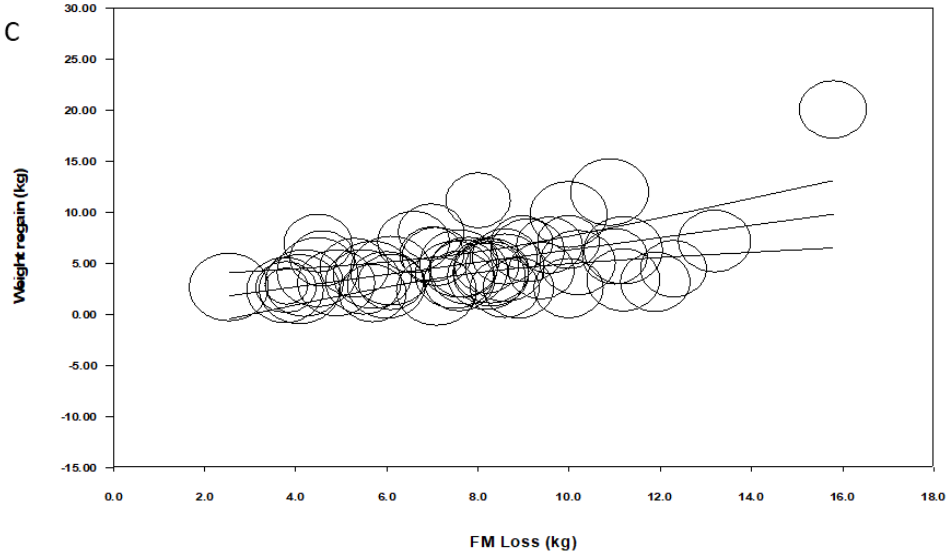
Table 2.3. Rate and amount of weight loss as predictors of weight regain (n=52)

	Unadjusted				Adjusted for baseline BMI			
	β (95% CI)	R^2	Tau^2	p-value	β (95% CI)	R^2	Tau^2	p-value
Predictors (univariate)								
Weight loss (kg)	0.50 (0.25, 0.74)	0.29	5.23	<0.001	0.50 (0.24, 0.76)	0.28	7.61	<0.001
Rate of WL (kg/wk)	2.06 (0.01, 4.11)	0.06	6.94	0.049	2.05 (0.00, 4.10)	0.06	7.38	0.049
Model 1		0.28	5.32	<0.001		0.28	5.56	0.002
Weight loss (kg)	0.46 (0.13, 0.72)	0.29		0.001	0.47 (0.19, 0.74)			0.001
Rate of WL (kg/wk)	0.80 (-1.17, 2.77)	-0.01		0.420	0.73 (-1.30, 2.77)			0.470
Model 2		0.35	4.83	<0.001		0.33	4.97	<0.001
Weight loss (kg)	0.11 (-0.30, 0.53)	0.29		0.568	0.09 (-0.43, 0.62)	0.31		0.720
Rate of WL (kg/wk)	-3.41 (-7.89, 1.05)	-0.01		0.420	-3.83 (-9.65, 1.98)	-0.01		0.190
Amount *x* rate	0.45 (0.02, 0.89)	0.07		0.042	0.50 (-0.10, 1.08)	0.04		0.090

Table 2.3. *Effect sizes are unstandardized β coefficients representing unit change per 1kg weight regain. Model 1 included amount and rate of weight loss. Model 2 included amount and rate of weight loss and their interaction. Abbreviations: WL, weight loss*


A
Weight regain (kg)
30.00
25.00
20.00
15.00
10.00
5.00
0.00
-5.00
-10.00
-15.00
4.0
6.0
8.0
10.0
12.0
14.0
16.0
18.0
20.0
22.0
Weight Loss (kg)


B
Weight regain (kg)
30.00
25.00
20.00
15.00
10.00
5.00
0.00
-5.00
-10.00
-15.00
-0.5
-0.3
0.0
0.3
0.5
0.8
1.0
1.3
1.5
1.8
2.0
2.3
Rate of weight loss (kg/week)


C
Weight regain (kg)
30.00
25.00
20.00
15.00
10.00
5.00
0.00
-5.00
-10.00
-15.00
0.0
2.0
4.0
6.0
8.0
10.0
12.0
14.0
16.0
18.0
FM Loss (kg)

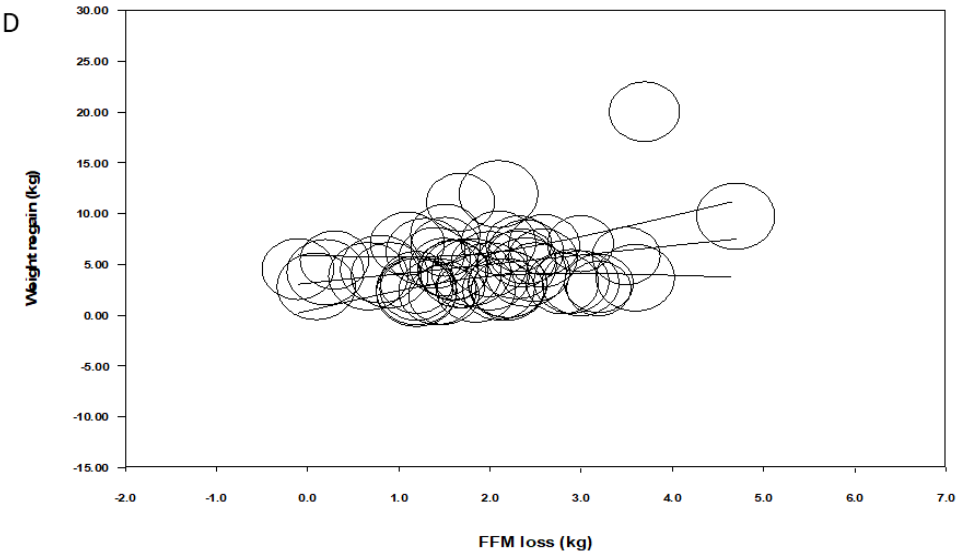

D
Weight regain (kg)
30.00
25.00
20.00
15.00
10.00
5.00
0.00
-5.00
-10.00
-15.00
-2.0
-1.0
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
FFM loss (kg)

Figure 2.2. *Linear meta-regression plots showing (A) the association between weight loss and weight regain, (B) the association between the rate of weight loss and weight regain, (C) the association between fat mass loss and weight regain and (D) the association between fat free mass loss and weight regain. Abbreviations: FM; fat mass, FFM, fat free mass*

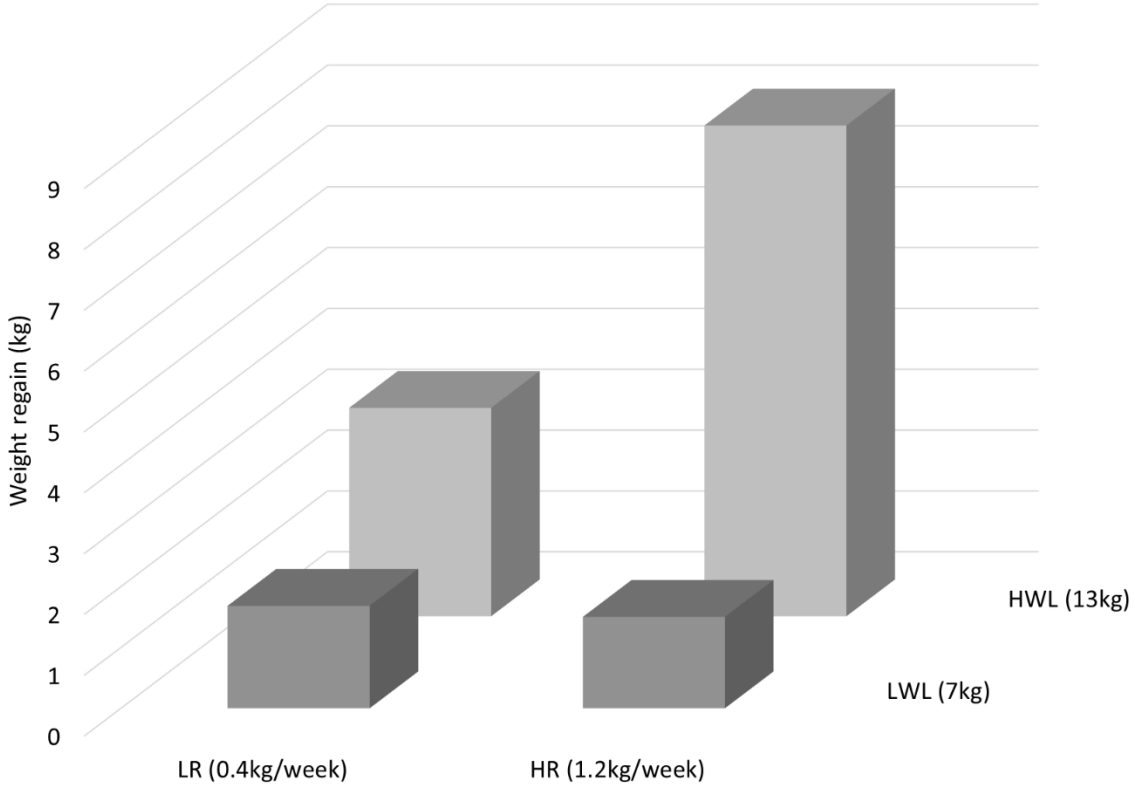


Figure 2.3. *Interaction between rate and amount of weight loss and subsequent regain illustrated using a 3D bar chart with two groups with two levels. Simple slopes analysis was used: one standard deviation was added (high) and removed (low) from the mean value for each moderating variable. This was then entered into the interaction regression equation to generate weight regain values under 4 possible conditions. Abbreviations: LR, low rate; HR, high rate, LWL, low weight loss; HWL, high weight loss*

Table 2.4. Fat mass and fat-free mass loss as predictors of weight regain (n=52)

	Unadjusted				Adjusted for BMI			
	β (95% CI)	R^2	Tau^2	p-value	β (95% CI)	R^2	Tau^2	p-value
Predictors (univariate)								
FFM loss (kg)	1.04 (0.20, 1.87)	0.12	6.51	0.017	1.0 (0.10, 1.89)	0.10	6.68	0.030
FM loss (kg)	0.61 (0.35, 0.87)	0.37	4.62	<0.001	0.60 (0.33, 0.87)	0.35	4.76	<0.001
Model 1		0.40	4.45	<0.001		0.37	4.88	<0.001
FFM loss (kg)	0.55 (-0.20, 1.32)	0.03		0.150	0.54 (-0.28, 1.35)	0.02		0.170
FM loss (kg)	0.54 (0.27, 0.81)	0.37		<0.001	0.57 (0.27, 0.87)	0.35		<0.001

Table 2.4. *Effect sizes are unstandardized β coefficients representing unit change per 1kg weight regain. Model 1 included both FFM and FM loss. Abbreviations: FFM; fat-free mass; FM, fat mass*

2.2.3.6 Effect of Extent and Rate of Weight Loss on Fat Free Mass Loss

Results for the effect of amount and rate of weight loss on FFML are reported in **table 2.5**. The amount of weight lost was positively associated with the degree of FFML (β=0.20 (0.11, 0.30), R2 = 0.37, p<0.001) whereas the rate of weight loss was not associated with FFML (β=0.56 (-0.22, 1.34), R2 = 0.04, p=0.15). These results remained similar after adjustment for BMI. When both amount and rate of weight loss were entered, amount (p=0.003) but not rate (p=0.92) of weight loss was associated with FFML in both unadjusted and BMI-adjusted models. In model 2, rate of weight loss, as well as the interaction between rate and amount showed a trend after adjustment for BMI (p=0.072 for both).

2.2.3.7 Risk of Bias

Results for risk of bias can be found in appendix 2.2. One study had high risk of bias (Diepvens *et al.*, 2007), four studies had low risk of bias (Van Aggel-Leijssen *et al.*, 2002; Goyenechea *et al.*, 2009; Beavers *et al.*, 2011; Waters *et al.*, 2013) and all other studies had medium risk of bias. No studies were deemed to worthy of exclusion due to bias.

2.2.4 Discussion

This is the first systematic review and meta-regression to investigate the associations between the amount, rate and composition of weight loss and weight regain following clinically significant weight loss in overweight and obese participants engaged in weight management interventions. Using this approach, 43 studies were examined which included 52 groups comprising 2,379 individuals. The average durations of the study were typical of therapeutic weight loss interventions, with a weight loss period of ~3 months and a follow-up period of ~9 months. It was found that both the amount and rate of weight loss were positively associated with the amount of weight regain, and further, that a significant interaction between both factors predicted weight regain. Specifically, rate of weight loss became a stronger predictor of weight regain at larger amounts of weight loss but had minimal effect at lower amounts. Second, both FFML and FML were predictors of weight regain, although the effect of FFML was attenuated after adjustment for FML. Lastly, amount, but not rate, of weight loss was positively associated with FFML, and observed a trend for their interaction to predict FFML.

Table 2.5 Rate and amount of weight loss as predictors of fat-free mass loss during weight loss (n=52)

	Unadjusted				Adjusted for BMI			
	β (95% CI)	R^2	Tau^2	p-value	β (95% CI)	R^2	Tau^2	p-value
Predictors (univariate)								
Weight loss (kg)	0.20 (0.11, 0.30)	0.37	0.45	<0.001	0.19 (0.09, 0.29)	0.37	0.45	<0.001
Rate of WL (kg/wk)	0.56 (-0.22, 1.34)	0.04	0.70	0.150	0.57 (-0.18, 1.33)	0.12	0.63	0.130
Model 1		0.36	0.46	<0.001		0.35	0.46	0.002
Weight loss (kg)	0.2 (0.10, 0.30)	0.37		0.003	0.18 (0.07, 0.29)	0.37		0.002
Rate of WL (kg/wk)	0.15 (-0.57, 0.88)	-0.01		0.920	0.10 (-0.65, 0.84)	0.02		0.790
Model 2		0.37	0.45	<0.001		0.40	0.71	0.001
Weight loss (kg)	0.38 (0.13, 0.63)	0.37		0.004	0.38 (0.138, 0.63)	0.37		0.003
Rate of WL (kg/wk)	1.84 (-0.58, 4.26)	-0.02		0.130	2.25 (-0.218, 4.71)	-0.02		0.072
Loss*Rate	-0.21 (-0.48, 0.06)	0.02		0.120	-0.25 (-0.52, 0.02)	0.03		0.072

Table 2.5. *Effect sizes are unstandardized β coefficients representing unit change per 1kg FFM lost. Model 1 included amount and rate of weight loss. Model 2 included amount and rate of weight loss and their interaction. Abbreviations: WL, weight loss*]

2.2.4.1 Amount of Weight Loss on Weight Regain

This study aimed to determine whether the magnitude of weight loss was associated with the magnitude of weight regain. The phenomenon of weight gain following weight loss is very common and thus prior weight loss is considered a probable predictor of weight gain, regardless of the method of weight loss (Franz *et al.*, 2007b). However, whether there is a direct association between the magnitude of weight lost and subsequently regained under conditions of therapeutic weight is less clear. In the present study, greater weight loss predicted greater weight regain. This is in contrast to other findings which have suggested that greater weight loss during a weight loss intervention is associated with more successful weight loss maintenance (Björvell and Rössner, 1992; Jeffery, Wing and Mayer, 1998; Astrup and Rössner, 2000; van Baak *et al.*, 2003; Elfhag and Rossner, 2005; Wadden *et al.*, 2011) and, in their conceptual review on factors associated with weight loss maintenance, Elfhag and Rossner (2005) identified greater initial weight loss as a key predictor of successful weight loss maintenance (Elfhag and Rossner, 2005). In contrast, some studies have reported that greater weight loss has been associated with greater weight regain (Foster *et al.*, 1997; McGuire *et al.*, 1999), (Sbrocco *et al.*, 1999) or found to have no association (Barte *et al.*, 2010; Gilis-Januszewska *et al.*, 2018; Ing *et al.*, 2018). As mentioned earlier, the reason for the discrepancy between these findings may be due to the manner in which authors define 'successful' weight loss maintenance. Some studies may choose to define success as, for example, maintenance of ≥5% weight loss (Wadden *et al.*, 2011), or another binary definition. In the present case, both loss and regain were used as continuous variables, using meta-regression to assess their association to avoid this limitation.

Our observations are generally consistent with the set or settling point theories (Speakman *et al.*, 2011; Müller, Geisler, Heymsfield, *et al.*, 2018) which suggests that the body naturally defends a given weight as well as other ideas suggesting that an asymmetric regulation of energy balance protects against weight loss thus driving weight regain via adaptative responses (Müller, Enderle and Bosy-Westphal, 2016; Blundell, 2018). Following ~11% weight loss, about half of this was regained (~5.4%). However, it has been shown that weight regain can take several years (Kraschnewski *et al.*, 2010) and given that the median follow-up period in reported studies was 44 weeks it may be that the process of regain was

ongoing in many individuals. While the reasons for this tendency to regain weight are not fully understood, a range of physiological homeostatic pathways as well as psychological and behavioural determinants have been implicated in influencing weight relapse (see MacLean *et al.*, 2011; Sumithran and Proietto, 2013; Greenway, 2015) for reviews). Indeed, the present results are in line with the idea that the greater the amount of weight loss achieved, the greater physiological resistance to weight loss individuals undergo.

Importantly, studies in which weight loss maintenance was achieved (based on group averages) during the follow-up phase were not included. The inclusion of these studies would have resulted in a significant reduction in the variability of the outcome variable (weight change at follow-up) and this would have constricted the model's ability to identify predictive factors. As such the present analysis provides associations with weight regain, but not necessarily weight loss maintenance success.

2.2.4.2 Rate of Weight Loss on Weight Regain

This study aimed to determine whether the rate of weight loss was associated with the magnitude of weight regain. A significant and direct association was observed between the rate at which weight was lost and the amount subsequently regained. The effect of rate of weight loss on subsequent regain is unclear; it has long been suggested that gradual weight loss brought on by small changes in lifestyle produce more manageable changes for long-term maintenance (Wadden, Foster and Letizia, 1994; Sbrocco *et al.*, 1999; Lutes *et al.*, 2008) and as such this advice has been adapted into some public health guidelines (Dietitians Association of Australia, 2012). Despite this, some evidence has challenged this contention by suggesting that rapid weight loss is not associated with weight regain (Toubro and Astrup, 1997; Purcell *et al.*, 2014; Vink *et al.*, 2016) and, in some cases may actually provide more beneficial long-term weight outcomes (Nackers, Ross and Perri, 2010). In each of these studies, authors compared two discrete rates (e.g. rapid vs gradual (Purcell *et al.*, 2014) or LCD vs VLCD (Vink *et al.*, 2016)), showing that rate did not affect the magnitude of regain. However, often the follow-up durations of these studies may not permit enough time for greater weight recover (e.g. 9 months in Vink et al), thus limiting the ability to make a comparison between different energy deficits

In the present analysis, studies employing a wide range of caloric deficits ranging from 500 calorie VLCDs (Pasman, Westerterp-Plantenga and Saris, 1997; Van Aggel-Leijssen *et al.*, 2002; Diepvens *et al.*, 2007; Vogels and Westerterp-Plantenga, 2007; Camps, Verhoef and Westerterp, 2013; Verhoef *et al.*, 2013) to less stringent, mild caloric restrictions of around 25% over longer periods of half a year to one year (Nicklas *et al.*, 2001; Due *et al.*, 2004; Von Thun *et al.*, 2014; Pownall *et al.*, 2015; Vadiveloo *et al.*, 2016; Borel *et al.*, 2017; Ryan, Serra and Goldberg, 2018) were included. Consequently, a high variability in the rate of weight loss was observed, ranging from 0.1 to 1.8kg/week allowing us to use rate as a continuous covariate rather than a binary or categorical variable (as is the case when comparing two rates). Moreover, this is the first study to investigate the continuous relationship between rate of weight loss and subsequent regain. Further study is required using individual level data to confirm the effect of the rate of weight loss on weight regain, preferably with longer follow-up durations in the region of 2-3 years to follow weight regain to be more appropriately assessed.

Importantly, the effect of rate was attenuated when both amount and rate of weight loss was entered in the same model. This is likely because of collinearity between both the rate and amount of weight loss. In studies in which a VLCD was used to reduce weight, often large amounts of loss are reported in a very short time, resulting simultaneously in a large loss at a considerable rate, which may together predispose regain. For example, in one study (Lejeune, Kovacs and Westerterp-Plantenga, 2005), a VLCD was used to reduce body weight by 11.5% in 4 weeks, of which around half was regained in the following 26 weeks. It seems likely that the amount of weight lost is the primary determinant of physiological resistance to weight loss encountered (both in terms of energy expenditure and intake), explaining why the effect of rate is ameliorated.

Interestingly, a significant interaction was observed between the amount and rate of weight loss in predicting weight regain. This was the first study to investigate the interaction between both factors in relation to subsequent weight regain. As **figure 2.3** suggests, for individuals losing small amounts of weight, the rate of weight loss is of minimal importance. As weight loss increases, so does the influence of the rate on subsequent weight regain. This interaction may have important clinical implications for making a weight control attempt as it indicates that if an individual intends to make a substantial weight loss attempt they may wish to consider a more conservative method, whereas if only a small amount of weight loss

is required, the rate at which it is less important for subsequent regain. In particular, this could be have implications in areas where large amounts of weight lost by VLCD are recommended, such as in diabetes treatment (Capstick *et al.*, 1997; Bhatt *et al.*, 2017).

2.2.4.3 Composition of Weight Loss on Weight Regain

To further examine the relationship between changes in the structure of the body during weight loss and subsequent weight regain, both FML and FFML were examined as predictors of weight regain. When entered separately, both FML and FFML predicted weight regain both in unadjusted and BMI-adjusted models. However, the association between FFML and weight regain became non-significant after accounting for changes in FML. Importantly, the combination of FML and FFML in a single model explained substantially greater amounts of variance in subsequent regain than when weight loss alone is entered (R^2= 40% vs 29% respectively). These data are suggestive of a mechanistic or functional role of changes in body composition in the aetiology of weight regain in samples with overweight and obesity who are engaged in therapeutic weight loss attempts. This points to potentially similar mechanisms as detected by Dulloo et al in the Minnesota study (Dulloo, Jacquet and Girardier, 1996). However, if such mechanisms are existent in these samples under these weight loss conditions, they are likely to be far more muted than seen in response to semistarvation in subjects if a body mass index close to reference man at the outset of semistarvation.

The finding that FML was positively associated with weight regain is a replicable finding underpinned by established physiological mechanisms. Indeed, adipocentric theories of body weight control have been central to energy balance research as early as 1953 when Kennedy posited that fat mass was the key physiological regulator of body weight. Further, it was suggested that the tissue operates via a lipostatic feedback signal (Kenndey, 1953), later discovered to be the adipocyte hormone leptin (Zhang *et al.*, 1994), which is known to be released from adipose tissue and is therefore highly correlated with fat mass (Shimizu *et al.*, 1997). Reductions in leptin which occur during weight loss (Rosenbaum *et al.*, 1997) are known to both decrease energy expenditure (M. Rosenbaum *et al.*, 2005) and increase appetite (Keim, Stern and Havel, 1998; Mars *et al.*, 2006) thus predispose increased EI, and these changes may persist for years following weight loss (Sumithran *et al.*, 2011; Fothergill, Guo, Howard, Jennifer C. Kerns, *et al.*, 2016a), ultimately influencing weight regain.

The observation that reductions in FFM was associated with weight regain to a lesser extent than FM requires further examination. Weight loss is typically considered to be comprised of around 25% FFML (Heymsfield *et al.*, 2014) based on reference values, which is similar to what was observed in this study (7.8kg FML vs 1.9kg FFML). Importantly, the mean reductions in FFM are modest and FFML is also likely to be confounded by water and glycogen loss, particularly in shorter duration studies. Moreover, due to variability in the measurement of body composition between studies, the error associated with body composition measurement is inconsistent. For example, significant underestimation of FFML during WL has been observed in densitometry compared to BIA (Deurenberg, Weststrate and Hautvast, 1989), and inconsistent associations have been observed between BIA and DXA, with some studies observing an overestimation of FM during weight loss by BIA (Aslam *et al.*, 2009; Li *et al.*, 2013), and others an underestimation of FM (Verdich *et al.*, 2011). This is a key limitation in the present investigation of the functional role of FFM. The changes in FFM detected and reported in this analysis were close to the measurement error for this tissue and probably within the measurement error given that different two-compartment body composition techniques were used. The implication of this is that if weight losses were greater or more consistent measures were made across studies, the contribution of FFML to weight regain may have been more pronounced.

Limited evidence exists examining the association of FFML during weight loss on subsequent weight regain. It has been posited that FFML during weight loss may be a key regulator of EI which is thought to increase to restore structural integrity of FFM compartments (Dulloo, Jacquet and Girardier, 1997b; Stubbs *et al.*, 2018). Early evidence supporting this contention was initially collected during the Minnesota Starvation study and later re-analysis revealed that while loss of both FM and FFM had independent effects of regain, though hyperphagia and regain persisted following full recovery of FM and proceeded towards FFM recovery. In their more recent study, Vink et al., (2016) added support to this model, reporting a positive relationship between FFML and weight regain following loss. According to the 'Leeds model' of body composition and appetite control (Blundell *et al.*, 2012; Hopkins *et al.*, 2016; Stubbs *et al.*, 2018), under conditions of energy balance both FFM and FM exert a tonic pull on EI through its contribution to RMR, whereas under conditions of sustained negative energy balance (e.g. during weight loss), both compartments exert an active drive on EI to recover lost tissue through discrete

mechanisms. Nevertheless, this model is based largely on cross-sectional data in individuals at energy balance. In the present analysis, longitudinal data on changes in weight and body composition during loss and regain was collected. From our results, it appears that both compartments may potentially play discrete roles in influencing future relapse, although this effect was particularly evident for FM. It is likely the analysis was limited in observing a more pronounced role of FFML due to the minor amounts of FFML which occurred in studies, as well as a series of methodological limitations related to body composition methods. Further longitudinal studies at individual level with greater manipulation of FFM are required to investigate the effects of functional changes in body composition in relation to weight regain following weight loss.

2.2.4.4 Amount and rate of weight loss as predictors of FFML

This study aimed to determine whether the amount and rate of weight loss were associated with the magnitude of FFML. A strong linear relationship between the amount of weight loss achieved and FFML was observed. This is not surprising given that weight loss can only be a function of FML and FFML and thus FFML must occur continuously with weight loss. Alternatively, the rate of weight loss was not associated with FFML but there was a trend towards an interaction effect which demonstrated stronger associations between the rate of weight loss and FFML when absolute amounts of weight loss were smaller.

Despite limited evidence, articles in the lay press commonly suggest that “losing weight too fast can be detrimental to your overall health and damaging to your lean mass” (Nall, 2017). Similar to evidence investigating the effect of rate of weight regain, studies investigating the effect of rate of weight loss on FFML rely heavily on a comparison between VLCDs and other, more mild forms of caloric restriction. In a systematic review by Chaston et al., (2007) authors concluded that VLCDs resulted in greater FFML than other calorie restricted diets based on descriptive data, although no statistical tests were conducted to infer this (Chaston, Dixon and O’Brien, 2007). Similarly, in two more recent studies, it was found that when comparing weight-matched rapid weight loss by VLCD over 5 weeks to more gradual weight loss over 12-15 weeks, rapid weight loss resulted in greater FFML (Vink *et al.*, 2016; Ashtary-Larky *et al.*, 2017). Alternatively, the present study aimed to investigate the continuous relationship between rate of weight loss and FFML. Indeed, it may be the case that greater FFML only begins to occur in the context of a very substantial negative

energy balance (e.g. a VLCD). In this analysis, a wide range of rates were included to assess variability in FFML and found no linear relationship. It was hypothesized that the rate of weight loss would affect both FFML and weight regain, and that FFML may have provided the physiological signal to drive weight regain, but our results were not able to support this model.

2.2.4.5 Limitations

The present study has some limitations. Firstly, as with all meta-analyses, the results were limited by use of group level, rather than individual data. While this approach may lend greater power to the observed results, it was not possible to incorporate variability within studies in some covariates (e.g. BMI) into our models. Furthermore, it was not possible to adjust for factors such as exercise or dietary composition (both during weight loss and follow-up) which may affect the composition of weight loss and subsequent regain. However, caution was taken in excluding all exercise interventions to avoid capturing exercise-induced changes in body composition and by using a random effects statistical model as considerable between-study heterogeneity was anticipated. Next, FFML was minor in most studies which resulted in limited variability to fully explore its effect on weight regain. Future studies exploring the hypothesized functional effects of FFML (Dulloo *et al.*, 2017) should manipulate the magnitude of FFML. Importantly, a variety of body composition methods were used (including DXA, water displacement, deuterium dilution, BIA and ADP), and this may limit comparability between studies. Furthermore, weight loss (and, more so, the composition of the weight loss) predicted weight regain, but the data was not available to explore a mechanism (particularly in relation to changes in body composition). Lastly, the analysis was limited to an overweight and obese sample due to the sparsity of weight loss studies in lean individuals. The inability to investigate the effects of weight cycling on body composition in lean individuals has been discussed previously and is a known limitation in this area (Bosy-Westphal and Müller, 2014). It is hypothesised that the observed effect of FFML on energy intake and weight gain following weight loss is stronger in lean individuals (Dulloo, 2017), although the data was not available to test this.

2.2.4.6 Conclusion

This systematic review examined changes in body composition during clinically significant weight loss and regain, and meta-regression was used to examine their

association with the amount and rate of weight lost and subsequent weight regain. The amount of weight lost was found to be positively associated with weight regain, while the rate of weight loss appeared only to be significant when high levels of weight loss occurred. The amount, but not the rate of weight loss affected the amount of FFML observed. Significant effects of both the amount and rate of weight loss were observed, as well as their interaction, on weight regain. Importantly, loss of both FM and FFM compartments explained greater variance in predicting subsequent weight regain than weight loss alone, suggesting a potentially functional role of changes in body composition during weight loss. Heterogeneity of methods between studies as well as restriction to an overweight and obese cohort limited the present analysis. This review underlines the need for more studies aimed at investigating the relationship between rates of weight loss and changes in body composition as potential processes underpinning weight regain. Further research on the role of functional body composition in lean individuals would provide additional mechanistic insight.

2.3 Associations between the proportion of fat-free mass loss during weight loss, changes in appetite and weight regain

In the previous study, some evidence to suggest that structural changes in body composition which occur during weight loss may have functional importance in the aetiology of weight regain was found, additive to that explained by the magnitude of weight loss alone. However, it was not possible to fully elucidate this effect in the previous study for several reasons. The magnitude of reductions in FFM were modest (~1.9kg on average), and this is limiting for two reasons: (a) this value is within measurement error in some devices and (b) it is close to the fluctuation which could be expected in non-energy balance related tissues (i.e. water, glycogen and gut weight) (Bhutani *et al.*, 2017b). Furthermore, various aspects of the analysis could not be controlled for due to a limited ability to adjust meta-regression models (given the number of studies equals the sample size thus n is limited), such as considerable heterogeneity in (i) the weight loss period (ranging from 4 to 52 weeks); (ii) the follow-up period (ranging from 18 to 249 weeks); (iii) the method of body composition measurement; (iv) the weight loss method or type of diet used and (v) the type

of follow-up period (i.e. whether an active or passive follow-up was used). Together, these limitations cloud the observations made.

Furthermore, associations between changes in body composition and psychological or behavioural adaptations which may help to explain weight regain were not examined. Indeed, a common response to weight loss is increased appetite (Sumithran *et al.*, 2011; Hintze *et al.*, 2017; Sayer *et al.*, 2018) (with some exceptions (Andriessen *et al.*, 2018a)). Given that weight loss is comprised of coinciding reductions in FM and FFM, it is likely that both of which may exert independent or integrated effects on appetite and thus energy intake. One concept, arising initially from Dulloo's reanalysis of the Minnesota Starvation study (Dulloo, Jacquet and Girardier, 1996) and more recently evolving into a working hypothesis relating to active and passive roles of FFM (Dulloo *et al.*, 2017; Stubbs *et al.*, 2018), suggests that greater proportionate reductions in FFM occurring during weight loss actively drive a hyperphagic response, the behavioural outcome being increased ad libitum energy intake. The suggested reason for this is that large losses in FFM may threaten the structural integrity of vital organs (Heymsfield *et al.*, 2011).

To date, evidence that proportionate FFM changes are associated with hyperphagia subsequent to weight loss comes from small, select studies during relatively extreme energy deficits (Keys *et al.*, 1950; Friedl *et al.*, 2000). It is unclear if such effects are apparent in groups with overweight or obesity engaged in therapeutic weight loss programmes. One recent study reported that greater fractional loss of FFM (%FFML) was predictive of subsequent weight regain in 2 groups of obese individuals undergoing a moderate and severe caloric restriction (Vink *et al.*, 2016), although the mechanisms relating changes in body composition to weight regain were not investigated. Below, a study is described which attempts to address this lack of evidence relating to the functional roles of FFM during weight loss.

2.3.1 Objectives

The following work was a post-hoc analysis of the DiOGenes study. The aims of the investigation were to:

1) Test the relationships of changes in body composition experienced during an 8-week LCD in individuals losing ⩾8% body weight on weight outcomes at 26-week follow up;

2) Examine the effects of these body composition changes on appetite perceptions in response to a structured test meal conducted before and after weight loss

It was hypothesised that greater proportionate reductions in FFM would result in (1) greater weight regain at 26-week follow-up and (2) changes in self-reported appetite perceptions indicative of increased appetite in response to a fixed test meal.

2.3.2 Methods

2.3.2.1 Study Design

The present study was a post-hoc analysis of the data collected as part of the DiOGenes study (http://www.diogenes-eu.org/, Clinical Trial Registry number NCT00390637) (Larsen *et al.*, 2010). The DiOGenes study was a European multi-centre randomised control trial designed primarily to test the effect of five diets (low-protein, low-glycemic index (LPLGI), high-protein, low-glycemic index (HPLGI), low-protein high-glycemic index (LPHGI), high-protein, high-glycemic index (HPHGI) and a control group (CON)) on weight loss maintenance outcomes over the 26-week weight loss intervention following at least 8% reduction in body weight over an 8-week period achieved by LCD (Modifast; Nutrition et Sante, Revel, France). The DiOGenes study protocol and primary results have previously been published elsewhere (Larsen *et al.*, 2010; Moore *et al.*, 2010). The present sub-study is concerned with data collected at clinical investigation day (CID) 1 which occurred prior to weight loss intervention; CID2 at the end of 8 weeks immediately following the LCD and weight change at CID3, after 26 weeks of the weight loss maintenance intervention.

2.3.2.2 Participants

All participants were recruited to the DiOGenes study between November 2005 and April 2007 from eight European centres, of which three had the necessary data available for the present analysis and were located in Copenhagen, Denmark; Cambridge, UK; Potsdam, Germany. Participants had either overweight or obesity (BMI between 27 and 45 kg/m^2 at baseline) and were between 18 and 65 years old. Further information on inclusion and exclusion criteria can be found elsewhere (Larsen *et al.*, 2010). In the present study, to test hypothesis (1), only participants who completed the 8-week LCD with at least 8% weight loss (set originally by the DiOGenes study) and had DXA measurements at CID1 and CID2 and a measurement of body weight at CID3 were included. To test hypothesis (2), those eligible

for (1) and had additional measurements of appetitive ratings during a standardised test-meal at CID1 and CID2 were included. A participant flow diagram is given in **figure 2.4**. Procedures followed in the DiOGenes study were in accordance with the Declaration of Helsinki and approved by local ethics committees in all participating countries. Written informed consent was obtained from all participants.

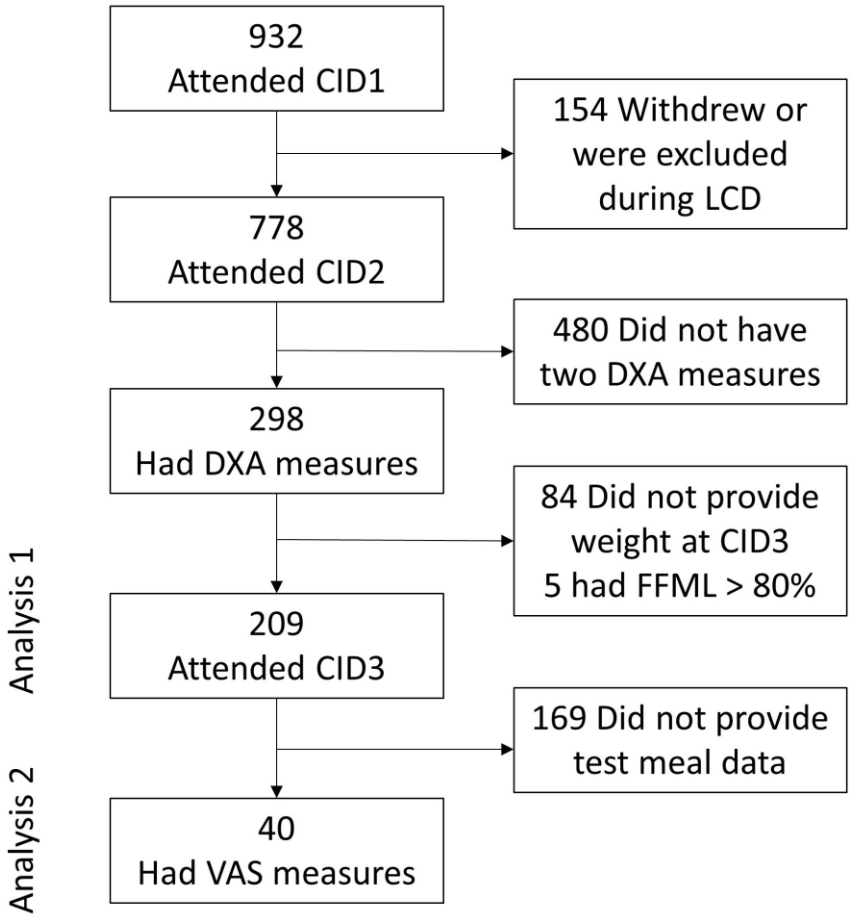


Figure 2.4. *Participant flow diagram*

2.3.2.3 Anthropometric Measurements

Body weight, waist circumference and body composition were measured as described previously (Larsen *et al.*, 2010). Body composition was measured using a 2-compartment model (i.e. FM and FFM) by DXA.

2.3.2.4 Standardised Test Meal and Appetite Ratings

Full details of the test-meal protocol are provided elsewhere (Andriessen *et al.*, 2018a). Briefly, a homogenous pasta-based test meal providing 1.6 MJ of energy, of which 61% of

carbohydrate, 26% was fat and 13% was protein was given around lunch time at CID1 and CID2. Participants were requested to fast overnight before each test meal and could drink a maximum of 1 dl water before the test. Participants were instructed to consume all of the test meal and were free to drink water ad libitum. Visual analogue scale (VAS) ratings were obtained at 15 minutes before and then at 15, 30, 60, 90, 120, 150, and 180 min after the start of the test meal. The visual analogue scale (VAS) for appetite measurement consisted of a series of 100 mm horizontal lines anchored with extreme appetite perceptions on both ends of each line (e.g. not at all hungry-very hungry). They were used to answer each of the following 4 questions: how hungry are you? (not at all hungry-very hungry), how full do you feel? (not at all full-very full), how strong is your desire to eat? (not at all strong-very strong), how much food do you think you can eat? (none at all-a large amount) (Flint *et al.*, 2000).

2.3.2.5 Statistical Analyses

Mean and SD for participant characteristics and key variables are provided in **table 2.6**. All variables reported were assessed for normality by visual inspection of QQ plots and histograms. Analyses were run for all participants and separately for each sex due to known differences in body composition dynamics between sexes. Proportionate change in body composition was represented by the term %FFML which represents an integrated change in both compartments and not simply a change in FFM (i.e. proportionate fat mass loss (%FML) = 100 - %FFML). Percentage FFML was calculated as the change in FFM during weight loss divided by total weight loss (i.e. (ΔFFM/Δweight)*100) (Chaston, Dixon and O'Brien, 2007; Vink *et al.*, 2016). Percentage FFML values above 80% (n=5) were removed due to this being the greatest reported %FFML which was observed under conditions of semi-starvation in lean individuals (Hall, 2007) therefore were considered erroneous measures. Absolute weight loss was chosen over relative weight loss as the aim was to investigate percentage changes body composition and therefore using absolute weight improves interpretability of body composition changes. Student's t-tests and chi-squared tests were conducted to test baseline differences between sexes for continuous and categorical variables respectively (table 2.6). The associations between baseline body fat and %FFML for both sexes were also examined in line with previous observations (Forbes, 1987; Hall, 2007) which can be found in **figure 2.5**.

Next, Pearson correlations were conducted between predictor, outcome and covariate variables related to initial and changes in body composition and weight. Pearson correlation was chosen based on visual inspection of the distribution of the variables through histogram and Q-Q plots which were deemed to be parametric (Ghasemi and Zahediasl, 2012). Next, univariate linear regressions were conducted to investigate crude associations between predictor and the outcome variables. Beta coefficients were reported as unstandardized estimates and 95% confidence intervals, representing the estimate and confidence of 1-unit change in predictor variable per 1kg change in weight outcomes at 26 weeks. Next, multivariate linear regression models were generated for all individuals and by gender. The models were adjusted for dietary arm and trial centre due to previously observed effects on weight loss maintenance (Larsen *et al.*, 2010; Aller *et al.*, 2014). Further adjustments were made for the amount of weight lost (as strong associations between weight lost and regained has been shown previously; (Turicchi *et al.*, 2019)), as well as initial body weight and body fat, as proportionate changes in body composition are known to be influenced by initial body size (Forbes, 1987; Hall, 2007) and FFM loss may be more pronounced in leaner individuals, with potential effects exerted on energy balance regulation (Dulloo, Jacquet and Girardier, 1997b). Lastly, interaction effects between sex and the primary predictor (%FFML) were tested in these multivariate models. Collinearity and multicollinearity were tested by examining the variance inflation factors of the model variables which are reported in **appendix 2.3** (of which none were deemed to be highly covaried). Scatterplots were produced to visualise main effects.

To test whether differences in the composition of weight loss were associated with changes in appetite measured over the duration of a standardized test meal, total area under the curve (AUC) was calculated using the trapezoid method (Pruessner *et al.*, 2003) consistent with a previous analysis of this data (Andriessen *et al.*, 2018a). Change in total AUC for hunger, fullness, desire to eat and prospective consumption between CID1 and CID2 (i.e. CID2 – CID1) were calculated. Lastly, the association between %FFML and change in appetite perceptions was assessed using Pearson correlation following visual inspection of QQ plots and histograms by which they were deemed parametric. In a final step, the effect of appetitive changes in the available group of weight change at 26 weeks by Pearson correlation was examined. This sub-analysis is documented in **appendix 2.4**. In addition to examining proportionate change in body composition, independent relative change in both

FM and FFM compartments from baseline was calculated and used these variables to predict both (1) weight regain at 26 weeks and (2) changes in appetite perceptions. The specifics of this analysis are expanded in **appendix 2.5.** Since the present study is a post-hoc exploratory analysis, adjustment for the testing of multiple outcomes was not employed (Althouse, 2016). All significance testing, unless otherwise stated, was performed using an alpha level of 0.05. All statistical analyses were conducted in R version 3.5.1 (www.r-project.org).

2.3.3 Results

2.3.3.1 Participant Characteristics

Baseline characteristics are reported in **table 2.6**. A total of 209 participants were included in the primary analysis, of which 132 were females. There was no difference in age between sexes. Males were heavier and had greater FFM than females at baseline, and females had greater FM than males. Males lost greater amounts of absolute (13.0 (4.0) vs 10.1 (2.7) kg, p<0.001) and relative (12 (3.3) vs 10.7 (2.4) %, p=0.002) weight than females, of which a greater proportion was FFM (35.3 (16.3) vs 27.5 (15.8) %, p<0.001). Lastly, males regained more weight during the 26-week follow up period than females (2.9 (4.7) vs 0.8 (4.7) kg, p=0.001).

Table 2.6. Subject Characteristics

	Total (n=209)	Male (n=77)	Female (n=132)	p-value
	209	77	132	
Age (years)	42.4 (5.7)	42.3 (5.8)	42.5 (5.6)	0.804
Country (%)				0.283
Denmark	95 (45.5)	38 (49.4)	57 (43.2)	
UK	51 (24.2)	13 (16.9)	38 (28.8)	
Germany	63 (30.1)	26 (33.8)	37 (28.0)	
Diet Arm (%)				0.544
LPLGI	39 (18.7)	13 (16.9)	26 (19.7)	
LPHGI	34 (16.3)	10 (13.0)	24 (18.2)	
HPLGI	51 (24.4)	23 (29.9)	28 (21.2)	

HPHGI	42 (20.1)	17 (22.1)	25 (18.9)	
CTR	43 (20.6)	14 (18.2)	29 (22.0)	
Baseline weight (kg)	99.58 (16.25)	108.78 (14.84)	94.21 (14.58)	<0.001
Baseline FM (kg)	40.07 (10.25)	36.12 (9.49)	42.37 (10.00)	<0.001
Baseline FFM (kg)	59.05 (12.40)	72.26 (8.03)	51.34 (6.64)	<0.001
Baseline bodyfat (%)	40.26 (7.60)	32.84 (5.18)	44.59 (4.99)	<0.001
Baseline FFM (%)	59.74 (9.21)	67.16 (4.12)	55.41 (3.11)	<0.001
Weight loss (kg)	-11.17 (3.52)	-13.04 (3.96)	-10.08 (2.71)	<0.001
Weight loss (%)	-11.19 (2.84)	-11.99 (3.30)	-10.72 (2.43)	0.002
FFML (%)	30.37 (16.38)	35.31 (16.29)	27.49 (15.79)	<0.001
Weight change at 26 weeks (kg)	1.57 (4.78)	2.94 (4.71)	0.77 (4.65)	0.001

Table 2.6. *Baseline characteristics collected at clinical investigation day 1. Mean (SD) are reported for absolute values or percentages where stated. Weight loss was calculated as the difference before and after the dietary intervention, and relative weight loss was this value as a percentage of baseline weight. Percentage fat-free mass loss (%FFML) was calculated as the fraction of weight lost as FFM (i.e. (ΔFFM/Δweight)*100) during the dietary intervention. Abbreviations: control (CTR); fat-free mass (FFM), fat mass (FM); high-protein, low glycemic index (HPLGI), high-protein, high-glycemic index (HPHGI); low-protein, low-glycemic index (LPLGI), low-protein high-glycemic index (LPHGI); percentage fat-free mass loss (%FFML). P-values denote results of students t-tests for continuous variables and chi-squared tests for categorical variables between males and females.*

2.3.3.2 Weight change at 26 weeks

Univariate regression results predicting weight change at 26 weeks are provided in **table 2.7**. In the total group, the amount of weight lost (β=0.267 (0.086, 0.448) kg, R^2=3.3%) significantly predicted weight change, and the fraction of weight lost as FFM tended towards a significant association (β=0.038 (-0.001, 0.078) %, R^2=1.8%). In males, the amount of weight (β=0.401 (0.148, 0.654) kg, R^2=11.4%) and %FFM (β=0.070 (0.006, 0.134) %, R^2=4.6%) lost during weight loss were significantly associated with subsequent weight change. In females, weight loss (β=0.544 (0.264, 0.824) kg, R^2=10.0%) but not %FFM (β=0.002 (-0.049, 0.052) %, R^2=0.1%) lost was associated with subsequent weight regain. The association between initial body fat and %FFML is shown in **figure 2.5** and the

relationship between %FFML and subsequent weight change at 26 weeks is shown in **figure 2.6**.

Table 2.7 Univariate regression analyses predicting weight regain at 26 weeks

	All (n=209)			Males (n=77)			Females (n=132)		
Predictor	β Coefficient (95% CI)	P-value	R^2	β Coefficient (95% CI)	P-value	R^2	β Coefficient (95% CI)	P-value	R^2
Age (years)	0.091 (-0.023, 0.204)	0.119	1.2%	0.043 (-0.14, 0.226)	0.747	0.3%	0.126 (-0.014, 0.266)	0.081	2.3%
Baseline weight (kg)	0.020 (-0.020, 0.060)	0.326	0.5%	0.031 (-0.041, 0.102)	0.263	1.6%	-0.034 (-0.088, 0.021)	0.224	1.1%
Baseline FFM (kg)	0.085 (0.034, 0.136)	0.002	4.8%	0.107 (-0.024, 0.237)	0.080	3.3%	-0.003 (-0.124, 0.117)	0.959	0%
Baseline FM (kg)	-0.075 (-0.138, -0.012)	0.020	2.6%	-0.009 (-0.122, 0.103)	0.968	0%	-0.070 (-0.149, 0.009)	0.082	2.2%
Baseline body fat (%)	-0.160 (-0.243, -0.077)	<0.001	6.5%	-0.133 (-0.337, 0.071)	0.205	2.1%	-0.126 (-0.285, 0.033)	0.122	1.8%
Weight loss during LCD (kg)	0.267 (0.086, 0.448)	<0.001	3.3%	0.401 (0.148, 0.654)	<0.001	11.4%	0.544 (0.264, 0.824)	<0.001	10.0%
FFML (%)	0.038 (-0.001, 0.078)	0.059	1.8%	0.070 (0.006, 0.134)	0.039	4.6%	0.002 (-0.049, 0.052)	0.949	0.1%

Table 2.7 *Univariate linear regression analyses predicting weight change at 26 months in 209 individuals following weight loss. Each unstandardised beta-coefficient represents 1kg weight change at 26 weeks per unit of the predictor. For example, a beta value of 0.27 (0.09, 0.45) kg for weight loss means that*

*for every 1kg of weight regained, an average of 0.27 kg (ranging from 0.09 – 0.45kg of weight was lost). For categorical variables these represent difference from the reference group.Weight loss was calculated as the difference before and after the dietary intervention, and relative weight loss was this value as a percentage of baseline weight. Percentage fat-free mass loss (%FFML) was calculated as the fraction of weight lost as FFM (i.e. (ΔFFM/Δweight)*100) during the dietary intervention. Abbreviations; fat-free mass (FFM), fat mass (FM), fat-free mass loss (FFML), LCD (low-calorie diet*)

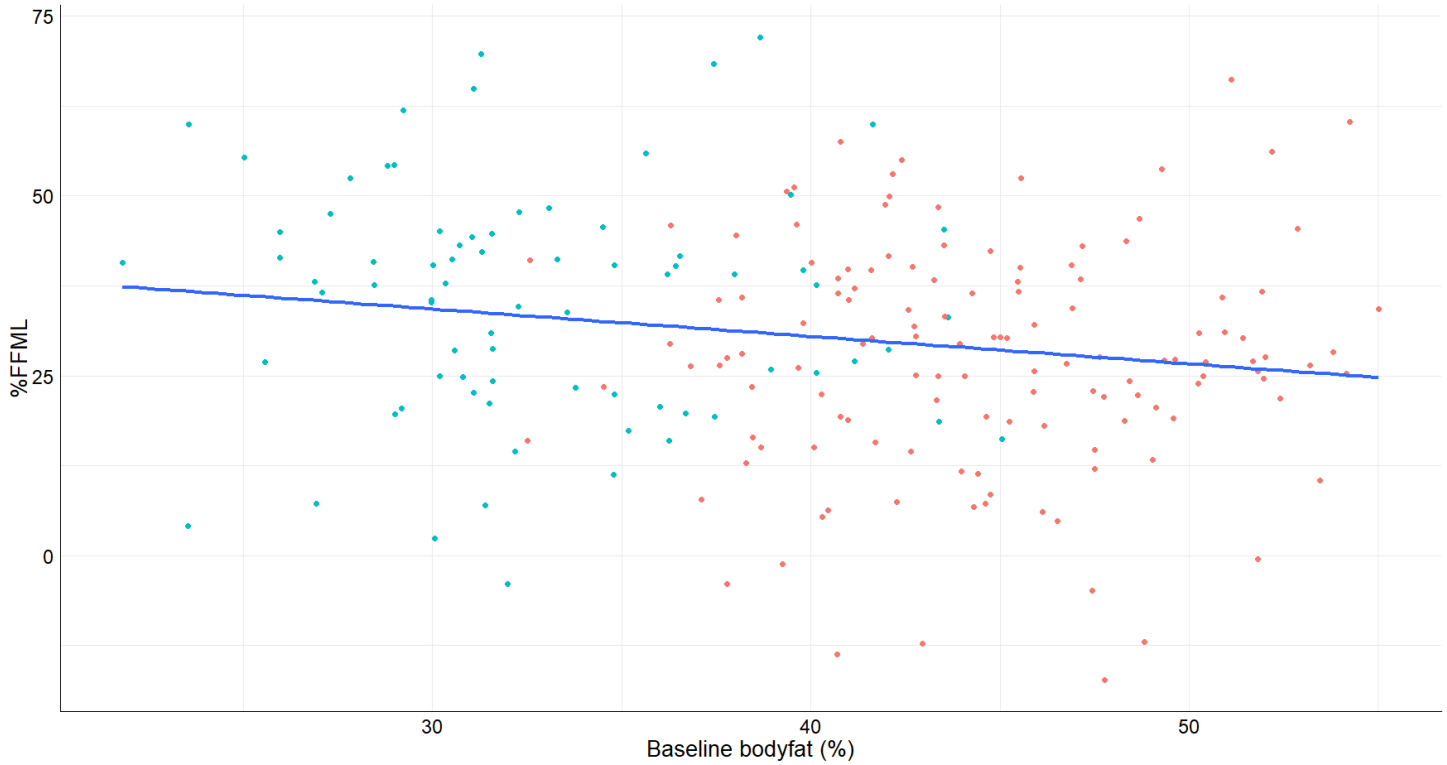


Figure 2.5. Associations between baseline body fat percentage and proportion of weight lost as fat-free mass (%FFML) as measured by dual x-ray absorptiometry in 209 individuals (men (n=77) given in blue circles; women (n=132) given in red circles) during an 8-week low calorie diet. A basic Pearson correlation resulted in a significant association of r= -0.18 (p=0.011). The unadjusted linear relationship is represented by the blue line.

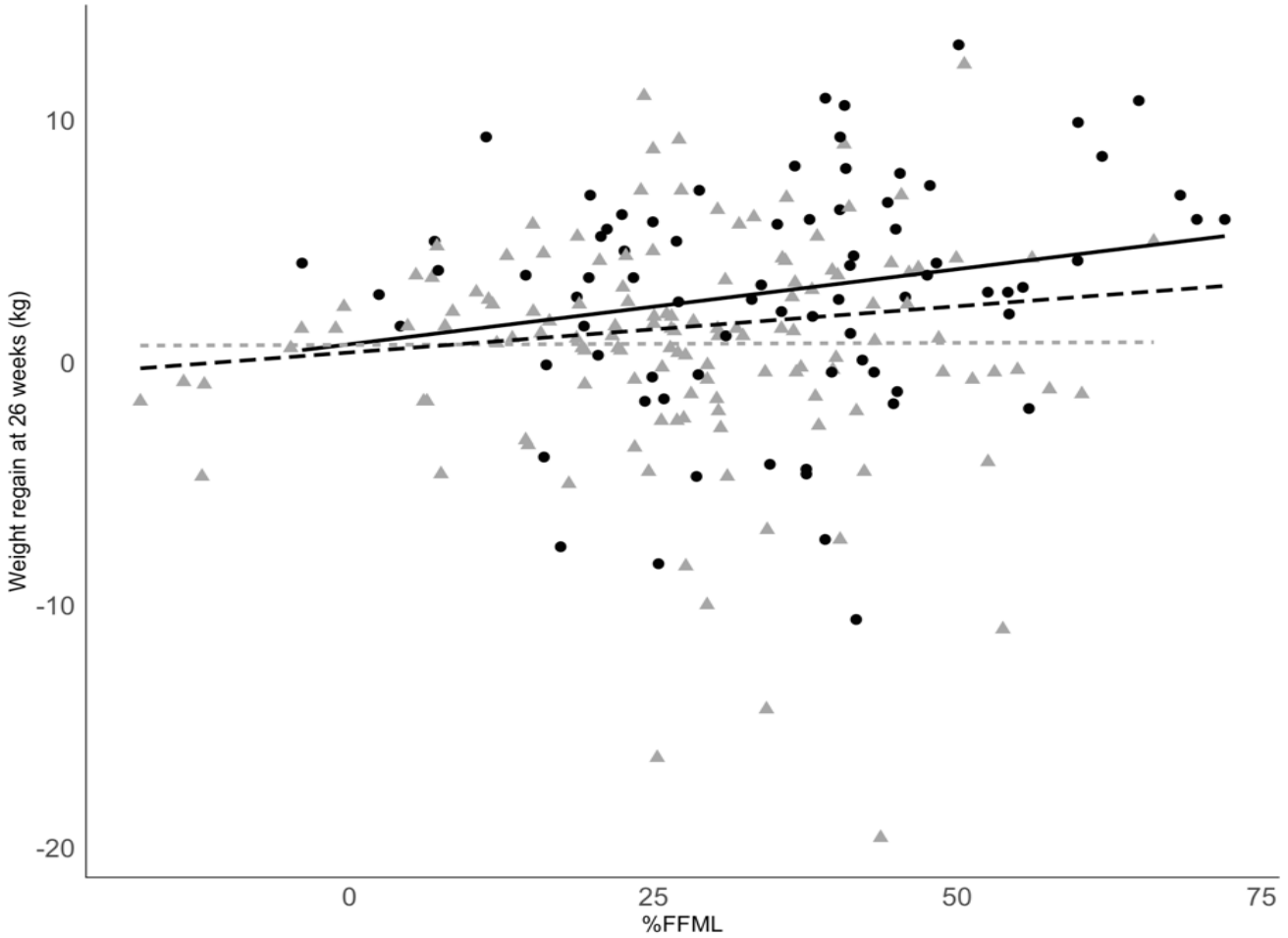


Figure 2.6. *Scatterplot and unadjusted linear trendlines showing associations between the proportion of weight lost as fat-free mass (as measured by dual-energy x-ray absorptiometry (DXA) before and after an 8-week low calorie diet(LCD)) and subsequent weight change at 26 weeks follow up in all participants (dashed black line), males (black circles; solid black line) and females (grey triangles; dotted grey line). Abbreviations; percentage fat-free mass loss (%FFML)*

2.3.3.3 Changes in appetite

Changes in subjective appetite in response to a standardised test meal before and after weight loss are reported in **table 2.8** which were indicative of an overall decrease in appetite. Associations between changes in appetite and %FFML during weight loss are illustrated in **figure 2.7**. In the total group, there was evidence of a weak positive association with %FFML and change in hunger (r=0.28, p=0.07) and a weak negative association with change in fullness (r=-0.30, p=0.054). Associations between %FFML and desire to eat (r=0.20, p=0.20) or prospective consumption (r=0.09, p=0.71) were non-significant. In males, there was a significant positive association between %FFML and change in hunger (r=0.69, p=0.002) and desire to eat (r=0.61, p=0.009) and a weaker association with change in prospective consumption (r=0.34, p=0.17). Lastly in males, a strong negative association with change in fullness (r=-0.55, p=0.02) was observed. In females, non-significant associations between %FFML and change in hunger (r=0.25, p=0.24) and fullness (r=-0.25, p=0.26) were observed. No significant associations between %FFML and change in desire to eat (r=0.18, p=0.39) or prospective consumption (r=0.02, p=0.94) were observed in females.

2.3.4 Discussion

In the current study a positive but modest association between %FFML and subsequent weight change at 26 weeks was observed which was more pronounced in males than females (who did not show a significant effect). Initial weight loss more strongly predicted the magnitude of weight regain. Furthermore, positive associations between %FFML and changes appetite collected during a test meal before and after weight loss were observed, although these were inconsistent and more pronounced in males.

2.3.4.1 Weight Loss and Weight Regain

Consistent with the results of the meta-regression (Turicchi *et al.*, 2019), greater initial weight loss predicted subsequent weight regain, and this was the strongest predictor variable associated with the primary outcome. In the meta-regression in which there was extremely high levels of between-study heterogeneity in study design factors such as weight loss duration, follow-up period, intervention type and sample characteristics, weight loss

Table 2.8 Self-reported appetite perceptions measured by visual analogue scale in response to a fixed test meal

	All (n=40)				Males (n=17)				Females (n=23)			
	CID1	CID2	Change	p-value	CID1	CID2	Change	p-value	CID1	CID2	Change	p-value
Hunger	6144 (3884)	4626 (3004)	-1518 (3068)	0.051	7926 (3737)	6102 (2890)	-1825 (2644)	0.123	4876 (3615)	3670 (2695)	-1207 (3417)	0.231
Fullness	10876 (4106)	12497 (3115)	1620 (3695)	0.048	9719 (3950)	11320 (3008)	1601 (3653)	0.191	11651 (4182)	13217 (2986)	1566 (3874)	0.150
Desire	6725 (3947)	4837 (2818)	-1888 (3381)	0.015	8435 (3671)	5940 (2762)	-2495 (2864)	0.034	5531 (3829)	4126 (2677)	-1405 (3776)	0.151
Prospective	7071 (3718)	4929 (2853)	-2144 (3351)	0.004	9044 (3286)	6407 (2488)	-2637 (2878)	0.014	5640 (3481)	3970 (2681)	-1671 (3699)	0.070

Table 2.8. *Visual analogue scale ratings for hunger, fullness, desire to eat and prospective consumption given as mean (SD) calculated as the total area under the curve by trapezoid method summating 8 repeated measures beginning 15 minutes before and ending 180 minutes after a fixed pasta-based test meal. P-values denote significant differences between clinical investigation days 1 and 2 in each group as tested by students t-test. Abbreviations; clinical investigation day 1 (CID1) (before dietary intervention); clinical investigation date 2 (CID2) (after dietary intervention)*

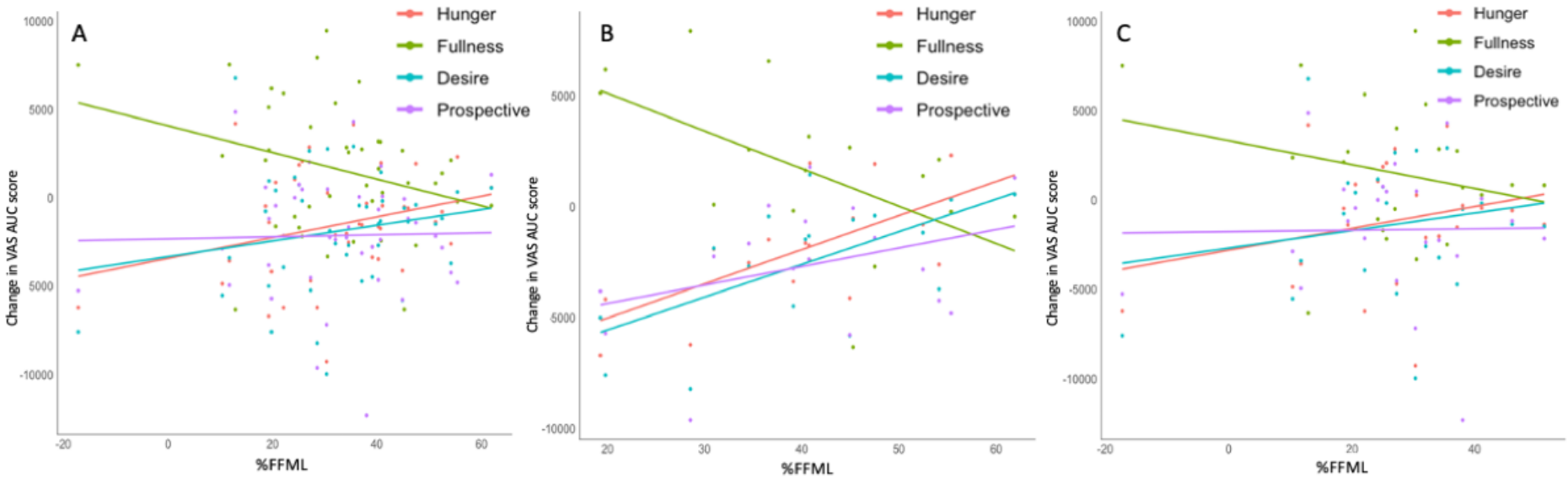


Figure 2.7. *Scatterplots and unadjusted linear trendlines showing associations between the proportion of weight lost as fat-free mass during an 8-week low calorie diet (LCD) and changes in appetite during the 8 weeks. Results are reported for hunger (red), fullness (green), desire to eat (blue) and prospective consumption (purple). Figure (A) represented results in the total group (n=40); (B) represents the results in males (n=17) and (C) represents the results in females (n=23). Scores were calculated as the total difference in area under of curve from 8 repeated measures around a fixed test meal, and change scores were calculated as the difference between clinical investigation day 1 and 2. Abbreviations; area under curve (AUC), percentage fat-free mass loss (%FFML);.visual analogue scale (VAS*)

explained ~29% of the weight subsequently regained, however in the present study this was reduced to 11.4% and 10% in men and women respectively. It is possible that this difference was driven by the fact that (a) the variability of weight loss responses was constrained by the intervention (i.e. 8-week LCD) with a minimum of 8% weight loss for inclusion and (b) mean weight change at 26 weeks was minimum (1.6kg (SD 4.78) %). Together, these lower the variability in outcome and predictor which can result in modest effect sizes. Nonetheless, this evidence is again inconsistent with the suggestion that greater weight loss during an intervention is associated with better weight loss maintenance (Elfhag and Rossner, 2005; Wadden *et al.*, 2011). Conversely, it may be explained by the physiological defence (set point) theory – that physiological resistance develops to defends a set point or settling point in body weight (Speakman *et al.*, 2011). This model relies on the assumption that body weight is regulated, largely by leptin and additionally insulin, and that reductions in these anorexigenic hormones which accompany reduced body fatness are key determinants in the physiological resistance predisposing weight regain. This theory has been challenged (Müller, Geisler, Heymsfield, *et al.*, 2018), particularly for its failure to account for the asymmetry in any regulation system shown by the body's defence against weight loss but not weight gain, which has been demonstrated primarily as a function of leptin's operation in animal models (Leibel, 2008).

2.3.4.2 Fat Free Mass Loss and Weight Regain

Importantly, the concept of the asymmetrical 'homeostatic' system has traditionally relied on adipocentric mechanisms. The inference of an adipocentric supposition is that when weight is lost, greater reductions in FM would be associated with greater weight regain. The inverse hypothesis was tested, originally suggested by Dulloo and colleagues, who provided that greater amounts of FFML during weight loss were associated with greater subsequent regain driven by hyperphagic responses of FFML (Dulloo, Jacquet and Girardier, 1997b) although this original observation was under extreme conditions of starvation in initially lean individuals. A direct association between %FFML and weight regain was present in males (explaining up to 6.5% of the variance in weight regain) but not for females. Importantly, this was observed not under extreme conditions, but under

therapeutic conditions in individuals initially with overweight and obesity. The gender difference observed has two potential explanations: (1) the existence of gender differences in the function role of changing in FM and FFM proportions during weight loss or (2) the fact that in females, there was significantly less FFML and variability in FFML, as well as less weight regain and variability weight regain both resulting in a constrained ability to observe associations. It is likely that the latter is a more likely explanation for gender differences in the effect size yet may not fully explain this observation and indeed further research is required on the role of proportionate changes in body composition on subsequent energy balance and body weight.

Only one study has examined the role of %FFML in weight regain, reporting a significant direct association in 57 individuals losing a mean 8.6kg (Vink *et al.*, 2016), thought their analysis was limited to unadjusted correlations. In the present study, the variance explained by %FFML in addition to weight loss was considered. Additionally, adjustments were made for initial body size, given that knowledge that (a) proportionate changes in FM differ as a function of initial body composition (Forbes, 1987); (b) functional effects of changes in body composition (such as increased appetite) are suggested to be more pronounced in leaner individuals (Dulloo *et al.*, 2015). Together, these provide a more robust and comprehensive testing of the hypothesis.

In response to debate with a journal reviewer, an additional analysis was conducted which considered the independent reduction in each compartment (FM and FFM) from their baseline values (described in full in appendix 2.5). This was based on the potential for a signal to be influencing behaviour or weight regain which arose from a single compartment, rather than the integrated proportionate change in body composition. Following adjustment for total weight loss, reductions in FM (ΔFM) from baseline values did not predict weight regain, though there was a non-significant tendency for greater reduction in FFM (ΔFFM) to predict increased weight regain ($p=0.065$) in males. Although partially consistent with the primary analysis, these results are again weak and reveal unexplained gender differences.

2.3.4.3 Fat Free Mass Loss and Changes in Appetite

The mechanism by which %FFML may be associated with weight regain is unclear. Greater loss of protein tissues (e.g. muscle and organs) causes greater reductions in EE, but the effect of these changes on appetite and EI are less understood. Increased appetite

following weight loss is observed in most (Doucet *et al.*, 2000; Sumithran *et al.*, 2011; Polidori *et al.*, 2016), but not all studies (Iepsen *et al.*, 2016; Andriessen *et al.*, 2018b). In a previous analysis of the test meal VAS data collected during the DiOGenes trial, post-prandial appetite in response to the test meal was decreased in response to weight loss (Andriessen *et al.*, 2018b). This is counterintuitive and possible explanations for this response included: (a) participants were still in a negative energy balance at the time of the second measure; (b) reductions in gastrointestinal transit time following the 8-week LCD; (c) psychological habituation to smaller portion sizes, resulting in greater satiety from the test-meal following the LCD.

Similar to Andreissen et al., an overall decrease in appetite during weight loss in our sub-sample was observed. Sex differences in the relationship between %FFML and appetite were evident, with stronger correlations in males and weak-to-no correlations in females, again potentially driven by the greater %FFML observed in male participants or the smaller overall change in appetite between visits in females. To our knowledge only one study has considered the effect of FFML on change in EI during extreme weight loss in lean individuals(Dulloo, Jacquet and Girardier, 1997b). The current study suggests that the effect of %FFML on subsequent appetite is evident (albeit relatively weak) in individuals with overweight and obesity undergoing therapeutic weight loss. It has been suggested that signals released from protein tissue such as organ and skeletal muscle (referred to as proteinstats) during weight and FFM loss may act on higher centres to produce this effect (Dulloo *et al.*, 2015). In a supplementary analysis (appendix 2.4), association between change in appetite and weight change at 26 weeks was examined. All correlations were generally in a direction representative of increased weight change in response to greater increases in appetite in both males and females, however, most were non-significant, potentially due to the small sample sizes available (n=17).

2.3.4.4 Changes in Body Composition

The fraction of weight lost as FFM is known to be affected by the magnitude of the energy deficit, with diets such as VLCDs producing proportionately larger reductions in FFM than less severe caloric restrictions (Chaston, Dixon and O'Brien, 2007). The mean %FFML in the present study (30.4%) was comparable to that reported by several other studies (31-37%) in which weight reduction was achieved by severe caloric restriction (LCD or VLCD) in

similar populations with similar weight losses (Eston *et al.*, 1992; Hoie, Bruusgaard and Thom, 1993; Janssen and Ross, 1999; Bérubé-Parent *et al.*, 2001). In the present study, large variability in %FFML was observed, with many individuals losing over 50% of their weight as FFM, and some gaining FFM during weight loss (a phenomenon also observed by Vink et al. (2016)). Individuals with %FFML > 80% (n=5) were removed due to this cut-off being similar to the greatest recorded %FFML (Hall, 2007) occurring during weight loss in extreme conditions. It was assumed measurement error or substantial water flux might explain these observations. Removing these outliers decreased apparent effects of the relationships between %FFML and weight regain reported here but was preferred as a more plausible and conservative approach. There was a negative association between %FFML and weight loss. This can be explained by the rapid losses of FFM in the initial phase of weight loss which slows over time, as described previously (Krotkiewski, 2001; Heymsfield *et al.*, 2011). However, adjustments were made for both changes in body composition and total weight loss this association does not confound the observed effect.

It is hypothesised that the functional effect of FFM on EI is activated by a threat to the structure of organ and skeletal muscle tissue (i.e. protein) by prolonged negative energy balance. Early work by Dulloo was based on FFM measurements which were adjusted for hydration and relative bone mass (Dulloo, Jacquet and Girardier, 1997b). However, 2-compartment models of body composition fail to differentiate between protein, water, mineral, carbohydrate and other components of FFM. In the first few weeks of weight loss, changes in total body water are likely to contribute disproportionately to FFML (Heymsfield *et al.*, 2011). Therefore, it is difficult to relate changes in 2-compartment models to the functional properties of specific components of these compartments. To further understand the functional role of body composition in various states of energy balance, higher resolution body composition models should be used to estimate the fractional contribution of water and protein to FFML and estimate change in individual organ weights and mineral mass (Müller, Geisler, Hübers, *et al.*, 2018). Such models, longitudinally aligned with repeated measurements of appetite, EI or EE, may allow cause-effect relationships between changes in body structure and components of energy balance that resist weight loss or promote weight regain to be determined.

2.3.4.5 Limitations

The study population was limited to individuals with overweight and obesity. It is likely that a similar percentage of weight loss in a sample with healthy weight would have led to a greater %FFML, which may have had a more pronounced impact on appetite and weight regain. Further, repeated VAS scores during a fixed test meal were used to assess appetite, however, further research using *ad libitum* EI may provide greater mechanistic insight. Limitations in sample size for the analysis relating to appetite which was therefore constrained to simple bivariate correlations meant it was not possible to examine whether changes in appetite perceptions mediated the relationship between %FFML and weight change. Models may have been better informed by inclusion of physical activity measurements during the weight loss and maintenance phases due to interactions between activity, weight and body composition, though no accurate and consistent measure was available. Information on loss to follow-up and withdrawal were unavailable in this specific sub-sample and may have affected observed outcomes. A range of unmeasured physiological, cognitive and behavioural factors will have also affected the observed outcomes although the data was not available to adjust for these in our models. Lastly, a 2-compartment model to assess longitudinal changes in body composition used change in FFM as a proxy for change in skeletal muscle and organ weights which are hypothesised to be the functional components of FFM, such that the hyperphagic response aims to preserve these tissues. Yet, most of FFM change is known to be non-energy related components (e.g. water, glycogen and gut weight) (Bhutani *et al.*, 2017b) but we were not able to differentiate between these compartments.

2.3.4.6 Conclusion

These data suggest that the composition of weight loss may help to explain physiological resistance to weight loss via appetitive responses, but under the conditions of this study the effect was small and variable. In the whole population as well as in males and females separately, the amount of weight loss was a predictor of weight regain. Functional effects of %FFML on subsequent appetite and weight regain were evident in males, but not in females. These data are partially consistent with Dulloo's model of an active drive from %FFML elevating appetite. Relationships between functional changes in body composition

(measured using more advanced methods and models) and energy balance behaviours warrant further investigation.

2.3 General Conclusions

Instability in body weight occurs at both the micro level (such as between day or week fluctuations) and the macro level, which can represent individuals losing and gaining weight over months and years. The latter might more formally be referred to as weight cycling. Importantly, longitudinal and detailed data looking at acute weight instability is generally unavailable. This is because in traditional research pertaining to body weight change, measurement of body weight occurs at remote time points (e.g. at 6-month follow-ups). In the present chapter, this traditional longitudinal framework was employed as a proxy model of longer-term weight instability by examining weight loss and regain (or a single weight cycle). This allowed us to investigate the factors impacting a weight cycle by looking at how the characteristics of weight loss (amount, rate and composition) affect weight regain, and exploring a potential mechanism (through changes in appetite). Of course, the underlying assumption is not that this cycle occurs in a vacuum, but instead is one instance in a series of weight loss and relapse episodes, as is known to occur frequently in the general population (Lahti-Koski *et al.*, 2005).

Both studies were consistent in showing that during a period of weight reduction, the magnitude of weight loss was directly associated with the amount of weight subsequently regained. Importantly, these results were consistent in spite of considerable differences in the study designs which have been discussed previously. The implication is that there is resistance to weight loss occurring in response to changes in physiology, and that this resistance increases with as weight loss progresses. The physiological resistance referred to functions to modify both energy intake and expenditure, and these responses were discussed in full earlier (see section 1.3). This does not necessarily imply that the body is regulated in reference to a set point or settling point as suggested by some (originally (KENNEDY, 1953)) but, in combination with evidence that weight gain is not strongly defended against (Müller, Enderle and Bosy-Westphal, 2016), implies that there is asymmetry in the homeostatic system which predisposes weight regain.

Given that weight loss is a product of reductions in FM and FFM, this physiological resistance must be a response to one or (more likely) both of these compartments. The results of our meta-regression provided that reduction in FM, but less so FFM (attenuated after adjusted for reduction in FM) predicted greater weight regain. This initially sounds inconsistent with the second study in which %FFML was directly associated with weight regain. However, the way that change in body composition was defined differed: in the meta-regression analysis, FFML was used as an absolute value (kg) and therefore was closely associated with weight loss (given that ~80% of weight loss was FM) and FFML was minor (<2kg). In the DiOGenes reanalysis, %FFML was considered as a proportion of weight loss, and as such is the inverse of %FML. This means that an integrated response in body composition is being used, rather than an absolute reduction from baseline (which is more representative of change in body weight). This study also benefitted from (a) use of individual-level data rather than group data (as used in the meta-analysis) and (b) consistency in the measurement of body composition used, which was a major limitation of the meta-analysis. Furthermore, the meta-analysis was limited by the minor amounts of FFML observed (1.9kg), however this value was greater in the second study (4.6kg in men and 2.7kg in women) and may have allowed for the functional effects of FFML to be observed (particularly in men who's FFML was substantial).

The %FFML was shown to predict increases in appetite in response to a test meal, evidencing one mechanism linking the physiological changes to a psychological outcome which potentially impacts behaviour, though ideally a measure of ad libitum energy intake would be available. Importantly, it had originally been hypothesised that %FFML drives appetite in initially lean individuals as they have little fat to lose and are at greater risk of adverse structural changes (e.g. organ deterioration) (Dulloo *et al.*, 2015). However, this effect (though modest) was observed in an overweight and obese sample for the first time.

2.4 Progressing to Weight Variability

Together, these results function to improve the understanding of the aetiology of weight regain, and this can be used to partially understand longer weight instability, such that over longer periods of time, the magnitude and rate of reductions in weight, as well as the composition, relate to weight regain. This is important given that previous evidence has

related instability in body weight to later weight gain (Lowe, Benson and Singh, 2020) and cardiometabolic disease (Kodama *et al.*, 2017). Nonetheless, the infrequent measurement of body weight is a consistent and unavoidable issue when relating body weight dynamics to any outcome. To illustrate this problem, see **figure 2.8** below shows true data collected from 2 individuals as part of the NoHoW trial (described in chapter 4).

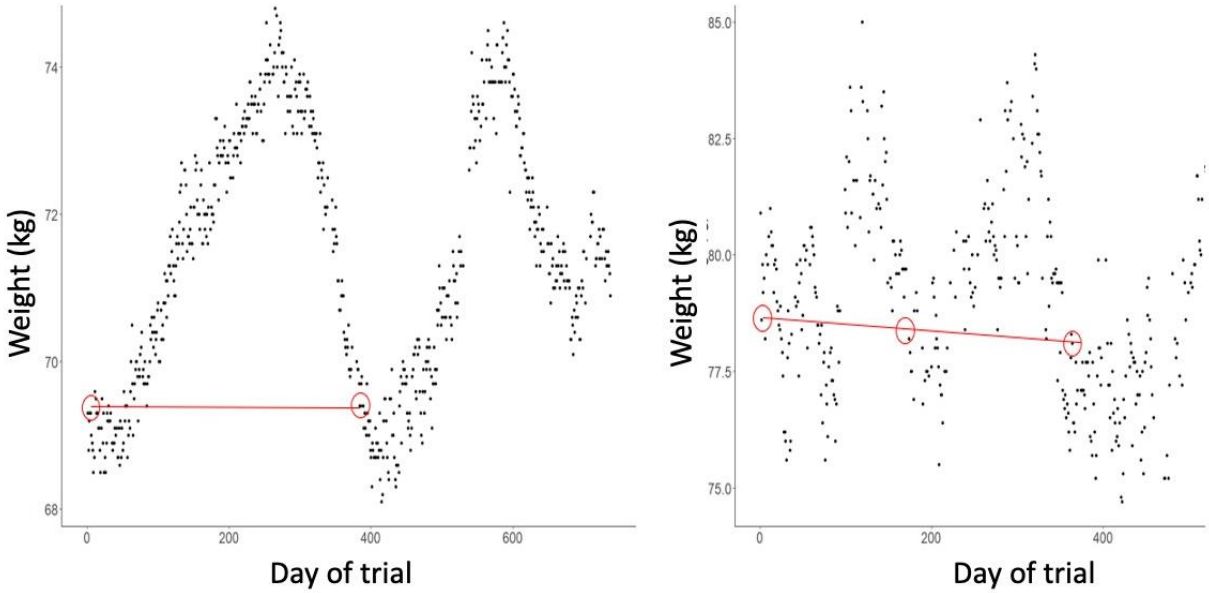


Figure 2.8. *Example data from 2 individuals participating in the NoHoW trial. Data was collected using WiFi connected smart scales (see section 4.1 for full method*)

If body weight measurements were made every 12 months (left), or 6 months (right), then approximate weight stability is assumed. However, if weight is tracked frequently, the data exposes significant variability with weight cycles in the region of 5-10% occurring which would go unmeasured in traditional environments. Until recently, the ability to track body weight frequently has been limited, as daily or weekly site visits can be burdensome to participants and researchers, and self-reported data may be prone to biases. In the past few years, WiFi-connected smart scales which link to a user account which can be accessed by a network device, allowing data to visualise their weight dynamics over time has become commonplace, and with it comes considerable new potential for research concerned with body weight change. In the following this chapters, I move forward from investigations relating to the traditional study of weight change (using a single weight cycle) by examining

how variability in frequently-tracked body weight (shown in the above figure) relates to physiological and psychological health using novel strategies and technologies.

Chapter 3. A Review of the Literature on the Operationalisation of Body Weight Instability and Its Health Consequences

The evidence presented in the previous chapters suggests that (a) weight loss attempts are common in the general population and (b) weight regain occurs following most weight loss attempts. As such, it is likely that individual-level instability in body weight is common and may be represented by cycles of weight loss and regain (i.e. weight cycling), though many other patterns are possible, such as more acute variability in body weight occurring at lower magnitudes. This body weight instability has been related to several negative health consequences in a literature spanning over 30 years, originating in the animal models of Brownell (Brownell *et al.*, 1986) and medical studies of Lissner (Lissner *et al.*, 1989, 1990; Stevens and Lissner, 1990) and has been a particular focus of research attention in the past few years as a risk factor for noncommunicable disease and mortality. Nonetheless, substantial heterogeneity and limitations of the methods used to examine the phenomenon may detract from the conclusions reached. A comprehensive synthesis of the health consequences of body weight instability with a focus on a critical evaluation of the literature has not been conducted previously and forms the basis of this chapter.

In the following section, a comprehensive literature review describes and evaluates the existing research relating to (a) the methodological approaches to quantifying body weight instability; (b) the impact of body weight instability on risk of disease and mortality; (c) associations between body weight instability and changes in health markers and (d) the associations between body weight instability and weight changes. The review takes a systematic approach by attempting to examine all available literature but given the width of topics covered and numerous searches required, it does not adhere to a strict systematic review protocol (such as PICOS which applies to searching, screening, data extraction etc) such as that provided by Cochrane. A critical commentary is provided throughout.

3.1 Definitions of Weight Instability

In order to review the literature on body weight instability, an explanation of the definition and use of the term is required. Within, the term body weight instability is used as a blanket term to refer to what authors may refer to as weight cycling, body weight

variability (BWV) or weight fluctuation amongst other terms. These terms have been, at times, used interchangeably in research, though do reflect discrete body weight patterns and discrete methods used to quantify them. For this reason, it is difficult to disentangle research relating to each of these. The following section will focus primarily on the differentiation between BWV and weight cycling and how their measurement helps to discern the two.

3.1.1 Weight cycling

Much of the early literature on body weight instability during the 1990s focused on weight cycling, which is a non-specific term given to the pattern of weight loss and subsequent regain. Currently, no existing set of criteria exist with which to define a "weight cycler" from a "non-weight cycler" or provide consistent categorisation of weight cycling. Indeed, this is because weight cycling has numerous dimensions giving it almost limitless possible definitions. These dimensions include the cycle amplitude (i.e. amount of weight lost and gained), cycle frequency (i.e. how many times did the cycle occur) and cycle duration (i.e. over how long did the weight loss and weight regain period occur). No attempt has previously been made to review the extent of the heterogeneity in the measurement of weight cycling, though it is a problem often alluded to by authors (Mackie, Samocha-Bonet and Tam, 2017). Accordingly, definitions were extracted from a systematic search of the literature and exclude all measures of calculated BWV which are discussed in a later section.

The definitions of weight cycling are reported in **table 3.1**. Overall, 67 studies were found which defined weight cycling in an arbitrary manner. Of these, there were approximately 37 different definitions of weight cycling used, although this number may vary dependent on differences in specific wording between definitions which is common. The most commonly used definitions included "number of times lost 4.5kg (or 10lbs) over the lifetime", "number of times lost and regained 10kg (including 20lbs and 9.1kg)" and "number of times lost and regained: 5-9, 10-19, 20-49, 50-99, >100lbs" derived from the Brownell weight cycling questionnaire. Twenty-six studies attributed a binary value (i.e. weight cycler or non-weight cycler), whereas 36 studies defined individuals by categorical variable. The most commonly used categories were "mild weight cyclers" and "severe weight cyclers" which were used 6 times. Many studies focused only on weight lost and made the assumption that since individuals were overweight or obese at the point of recall,

the weight lost was regained. A common approach used was to quantify the amounts of weight lost and the number of times the weight was lost and create a cumulative total for overall weight loss and then assume it was regained.

Table 3.1. Definitions of Weight Cycling

Study name	Prospective/ retrospective	Definition of weight cycling	Primary outcomes
Djoeke van Dale & Saris, 1989	Retrospective	>=2 times lost and regained >=10kg in past 5 years	RMR, substrate oxidation
Kramer et al., 1989	Retrospective	At least one cycle of 20% body weight	Weight
Peggy Ham et al., 1989	Retrospective	At least one cycle of 10% body weight	Coronary death
Melby et al., 1990	Retrospective	>=10 cycles of 4.5kg	RMR
Jeffery et al., 1992	Retrospective	Number of times lost 4.5-9, 9.1-22, 23-35, 36-45 or >45kg (BWCQ)	BP, LDL, HDL, TAG, glucose, WHR
Blaire et al., 1993	Retrospective	Loss and gain or gain and loss of 5%	All-cause and cause specific mortality
Brunner et al., 1994	Retrospective	Number of times lost and regained: 5-9, 10-19, 20-49, 50-99, >100lbs (BWCQ)	Binge eating, body image
Haus et al., 1994	Retrospective	Number of 5% body weight cycles	Physical activity, fat intake
Kuehnel et al., 1994	Retrospective	Number of times lost >= 4.5kg	BDI, DAS, ATQ, BHS, EDI-2, TFEQ
Yanovski et al., 1994	Retrospective	Number of times lost and regained >10kg	Binge eating
Carmody et al., 1995	Retrospective	Number of times lost and regained: 5-9, 10-19, 20-49, 50-99, >100lbs (BWCQ)	TFEQ, NAS
Hanson et al., 1995	Retrospective	Low cycler: <2kg lost and regained; middle cycler: 2-4kg lost and regained; high cycler: >4kg lost and regained	T2D incidence
Ferguson et al., 1995	Retrospective	At least one cycle of 4.5kg	BED
Foreyt et al., 1995	Retrospective	Answering "yes" to "are you a yo-yo dieter?" (BWCQ)	GWB, CESD, ESES, LCE
Jeffery et al., 1996	Retrospective	At least one cycle of 10% body weight	All-cause and cause specific mortality
Bartlett et al., 1996	Retrospective	Number of weight cycles of >4.5kg	POMS, MMPI, PSES, BES, QEWP
Dalle Grave et al., 1996	Retrospective	Number of times lost >5kg	SCL-90, EDI, TFEQ
Folsom et al., 1996	Retrospective	Smaller cycler: loss and regain of 5%; large cycler: loss and regain of 10%	All-cause mortality, CVD mortality

Timmerman et al., 1996	Retrospective	Number of times lost >9.1kg (20lbs) and regained >=50% of weight lost	Binge eating
Venditti et al., 1996	Retrospective	Number of weight cycles of >=10kg	SCL-90-R, EDI, BES, BDI, PSS, SF-36
Toray et ak., 1997	Retrospective	One cycle of 15lbs	EDI, SAM, WSDQ
Kensinger et al., 1998	Retrospective	>=2 cycles of 10% body weight	BDI, RSES, BES, TFEQ, ESES, WCCL-R, SCL-90-R
Simkin-Silverman et al., 1998	Retrospective	Number of times lost >4.5kg	BDI, PSS, STAS, TAS
Coakley et al., 1998	Retrospective	Number of times lost >4.5kg	Physical acivity, eating behaviours, TV-watching behaviours
Carmody et al., 1999	Retrospective	Number of times lost and regained: 5-9, 10-19, 20-49, 50-99, >100lbs (BWCQ)	BDHI, GSI, SCL-90-R, TFEQ, NAS
Field et al., 1999	Retrospective	Mild: 1-2 cycles of 4.5kg; severe: 3 or more cycles of 4.5kg	Hypertension
Guagano et al., 2000	Retrospective	>=5 times lost >=4.5kg	Hypertension
Olson et al., 2000	Retrospective	>=3 times lost >=4.5kg	HDL
Benini et al., 2001	Retrospective	Number of previous diet episodes, cumulative weight lost, cumulative weight regained	Leptin
Kroke et al., 2002	Retrospective	One cycle of >5kg in past 2 years	Incident T2D
Ackard et al., 2002	Retrospective	Lifetime dieting frequency	EDI-2, DES-D, RSES, Physical activity
Borges et al., 2002	Retrospective	>=3 times lost and regained 9kg (20lbs)	BED
Wakui et al., 2002	Retrospective	Number of times lost and regained 10% body weight	Range of serum proteins and lipids
Wannamethee et al., 2002	Retrospective	Loss and gain of >=4% or gain and loss of >=4%	All-cause mortality and CVD mortality
Field et al., 2004	Retrospective	Mild: 1-2 times lost >=4.5kg; severe: >=3 times lost >=4.5kg	BE, physical activity, weight change, eating patterns
Guisti et al., 2004	Retrospective	>=3 weight reductions of >=5kg and subsequent regain of >=50% of weight lost.	Binge eating
Lowe et al., 2004	Retrospective	Number of times lost: 0–4, 5–9, 10–14, 15–19, and 20+ lbs (total weight lost by calculating times by weight lost)	Restraint
Marchesini et al., 2004	Retrospective	Number of times lost <5, 5-10, 10-20, 20-30, >30kg (total weight lost by calculating times by weight lost)	BES, TFEQ, SCL-90

Wallner et al., 2004	Retrospective	>=3 times lost and regained 4kg	Regional fat distribution
Hart and Warriner, 2005	Retrospective	Number of weight loss programmes attended in past 5 years	Weight loss
Lahti-Koski et al., 2005	Retrospective	Mild: 1-2 times lost and regained >=5kg; Severe: >=3 times lost and regained >=5kg in past 10 years	Medical history, medication use
Schulz et al., 2005	Retrospective	Loss and regain of >=5kg in past 2 years	Hypertension
Nguygen et al., 2007	Prospective	One cycle of 3% body weight	All-cause mortality
Petroni et al., 2007	Retrospective	Index of: number of dieting attempts/year, BMI change since age 20 and cumulative BMI loss providing a score of 1-3	Psychological distress
Rzehak et al., 2007	Prospective	One cycle of 3% body weight	All-cause mortality
Elder et al., 2008	Retrospective	One cycle of 3.49 BMI units	EDE, LOC
Field et al., 2009	Retrospective	Mild: 1-2 cycles of 4.5kg; severe: 3 or more cycles of 4.5kg	All-cause mortality, CVD mortality
Roehrig et al., 2009	Retrospective	Lifetime dieting frequency	EDE, BDI, TFEQ, BSQ, RSES, HDL, LDL
Strychar et al., 2009	Retrospective	Number of times lost >=10kg	RMR, body composition, leptin, ghrelin, PSS, SES, BES, TFEQ
Anastasiou et al., 2010	Retrospective	Number of times lost 1-2.5, 3-5, >6kg in lifetime	Body composition, insulin, glucose, HOMA
Arnold et al., 2010	Prospective	Number of times lost and regained 5%	All-cause mortality
Hooper et al., 2010	Retrospective	Number of times lost between 10-19, 20-49 and >50lbs	Glucose, insulin, HOMA, leptin, ghrelin, sex hormones
Lee et al., 2010	Prospective	Loss and regain of >=3% over a 2 year period	Body composition
Taing et al., 2010	Retrospective	Gain and loss of 5% body weight	All-cause mortality
Yoo et al., 2010	Prospective	Weight change >5% of initial body weight within the previous 2 years	Body composition
Cereda et al., 2011	Retrospective	>=5 times lost and regained >=5kg	Regional fat distribution
Osborn et al., 2011	Retrospective	>=1 time(s) lost >= 9.1kg (20lbs)	BP, SSES, BDI, BAI, TBQ, EDI-2
Stevens et al., 2012	Retrospective	Number of tmes lost and regained 10lbs (4.5kg)	Endometrial cancer

Mason et al., 2013	Retrospective	Mild >=3 losses of 4.5kg; Severe: >=3 losses of 9.1kg	Weight loss and metabolic improvement
Delahanty et al., 2014	Prospective	Number of times lost and regained 5lbs (2.25kg)	T2D incidence
Messier et al., 2014	Retrospective	Mild: 1-3 times lost >= 10kg; Severe >=4 times lost >=10kg	Depressive symptoms
Murphy et al., 2014	Prospective	One cycle of 5% body weight	All-cause mortality
de Zwaan et al., 2015	Retrospective	>= 3 times lost >=10kg	Reward sensitivity, self-regulatory abilities, depression
Aucott et al., 2016	Prospective	Some WC: 2.5% lost and regained; Moderate WC: 5% lost and regained; Large WC: >10% lost and regained	All-cause mortality and CVD events
Yokomichi et al., 2017	Prospective	Loss and gain of >=4% or gain and loss of >=4%	T2D incidence

Table 3.1 *Definitions of weight cycling identified in the literature including whether it was prospectively or retrospectively measured in addition to the outcomes they were compared to*

Existing definitions are currently not sensitive to differences in the interaction between cycle dimensions (frequency, duration and amplitude). For example, many definitions cannot differentiate between an individual who has lost and regained 50kg compared to one who has lost and regained 5kg ten times. Of course, the metabolic, psychological and behavioural impact of these weight patterns may be differ considerably. Moreover, the assumption that weight lost can be considered regained is unsubstantiated and prone to error. For example, someone may have lost 5kg ten times and ended up 20kg above their starting weight, whereas another individual may end up 20kg below their starting weight. Furthermore, the duration of a cycle is not addressed. One individual may lose 10kg in 2 months and regain it over 2 years, whereas another individual may lose 10kg in 2 years and then regain it over 2 months. These differences in these cycle qualities are very likely to impact any outcomes of interest. Measures of weight cycling were almost entirely collected by self-report making the results susceptible to biases such as memory bias (given that questionnaires often refer to the entire adult lifespan) and social desirability bias.

Together, these results provide evidence that the measurement of weight cycling is extremely heterogenous and thus caution should be taking when comparing results of studies relating to these measures.

3.1.2 Body Weight Variability

In order to overcome many of the limitations associated with measuring weight cycling, approaches aiming to estimate the variability around an overall change in body weight using more mathematical methods have been developed. In a research context, these variables are more commonly referred to as BWV or weight fluctuation and are often employed in cohort studies investigating health outcomes. Their use was introduced in a range of studies by Lissner (Lissner *et al.*, 1989, 1990; Stevens and Lissner, 1990) to consider the effect of BWV on outcomes such as all-cause mortality, cardiovascular mortality and coronary events. In these and similar early studies into BWV, the co-efficient of variation was typically used to estimate BWV which is defined as the standard deviation divided by the mean and often corrected for the mean weight/BMI or weight/BMI change (in some but not all studies).

A more commonly used method in more recent studies is the root mean square error (RMSE) method. RMSE calculates the variability (i.e. error) around the linear regression between weight and time, by taking the RMSE of the residuals. The method is described in full, with illustrated examples in section 4.2.3. Briefly, a linear regression is fit to the participants weight data and the residuals are extracted which give an index of the variability around the linear trend. These residuals are then summarized by taking the root mean square error.

The RMSE method has some limitations which have been discussed previously (Wing, 1992; Vergnaud *et al.*, 2008). A key limitation is the assumption of linearity in individual body weight trends over time. This limitation is illustrated in **figure 3.1** which shows real body weight data from two participants of the NoHoW trial (for full info on data collection, see section 4.1). The participant on the top panel shows a nonlinear weight trend and in the bottom panel a more linear weight trend is illustrated. The nonlinear weight trajectory produces residuals with a range of around 30 (**figure 3.1B**), whereas the linear trajectory this is ~4. Resultantly, the nonlinear trend provides massively inflated RMSE values, yet, if two linear trajectories were fitted to the loss and regain sections separately these values would be massive reduced given the V-shaped appearance of the trend.

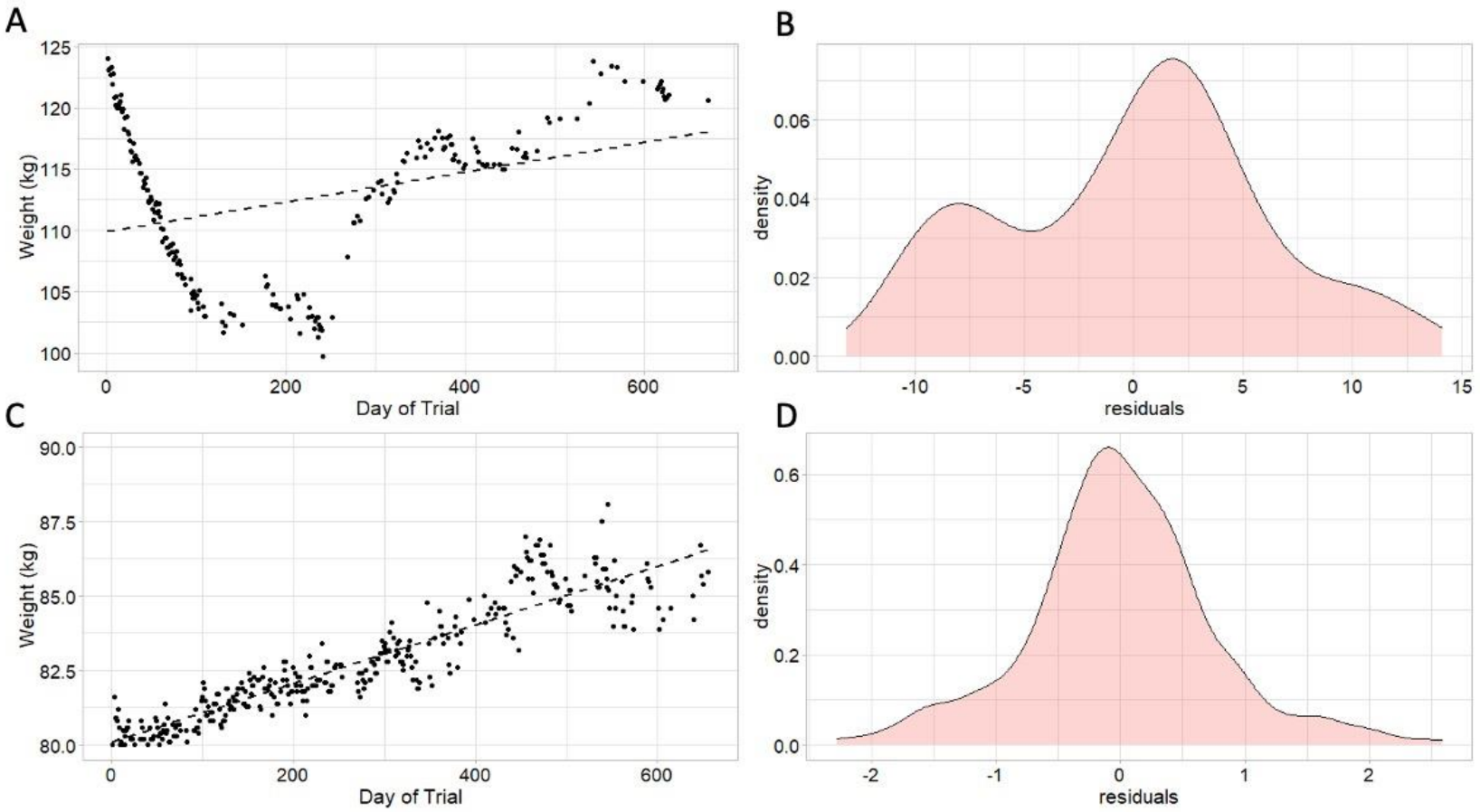


Figure 3.1. *Comparison of body weight data from two individuals from the NoHoW trial. The individual shown in the top chart has a nonlinear weight pattern and the bottom participant has a linear weight pattern. A linear trendline has been fitted to the body weight data as shown by the dashed line. On the right is the distribution of the residuals from the linear regression*

The comparability of BWV estimates by RMSE between individuals with linear and non-linear weight trajectories is very limited, though this issue is not addressed in the research at present. The method has been criticised as it is sensitive to large changes around the linear trend in body weight of weight change rather than many small changes which may be more realistically indicative of weight cycling (Wing, 1992). Furthermore, the residuals to calculate RMSE are commonly in absolute terms (i.e. kg) and given that heavier individuals have more weight to fluctuate, RMSE estimates can become positively associated with body weight, an issue which may confound further analyses. The use of nonlinear regression techniques and calculation of relative (%) residuals may help overcome these limitation (see section 4.2 for an expansion of these topics).

Comparability between BWV estimates in different studies is further reduced by heterogeneity in (a) the number of weight measures used to define BWV (e.g. the use of 3 (Brancati et al., 1999) to 12 (Bangalore et al., 2017) body weights); (b) the duration between each body weight measure (often every 6 or 12 months) which may vary both within and between subjects within a study, as well as between studies; (c) whether weight is recorded retrospectively or prospectively; (d) whether weight is self-reported or objectively measured and (e) the duration of the follow-up period which has ranged from 2 years (Delahanty et al., 2014) to 32 years (Lissner et al., 1999). Together, inconsistency in each of these factors limit the ability to draw consistent conclusions on BWV.

Together these factors highlight the importance of caution when comparing and synthesising results in relation to weight cycling and BWV. Many authors choose to employ the use of the terms weight cycling and weight variability or fluctuation interchangeably although these terms are unlikely to be measuring identical constructs. One key discrepancy is that in the definition of weight cycling the intentionality of weight loss in implicit, whereas in epidemiological studies prospectively measuring BWV, intentionality of weight changes are unknown and thus may confound results given that weight loss often coincides with the pre-mortal stage or serious cardiometabolic disease. To tackle this, some studies have used both weight cycling and BWV measures within a single study (Folsom et al., 1996; French et al., 1997; Arnold et al. 2010). In some cases, these different definitions have led to statistically different results even while assessing the same cohort and outcomes (Folsom et

al., 1996), further highlighting the need for increased understanding and synchronization of these definitions

3.2 Associations Between Weight Instability and Health Risk

There is strong evidence to suggest that BMI is closely associated with risk of mortality (De Gonzalez *et al.*, 2010; Di Angelantonio *et al.*, 2016) and comorbities such as CVD (Khan *et al.*, 2018) and T2D (Ganz *et al.*, 2014). Weight loss of around 5% has been shown to produce a clinically significant reduction in risk factors for these diseases (Diabetes Prevention Program Research Group, 2002; Rena R Wing *et al.*, 2011a). These topics have been discussed in greater detail in section 1.1.2. However, weight change (i.e. loss or gain) is also associated with variability around the trend. This variability occurs both acute (e.g. within week) and longer (e.g. between years) periods.

In the literature there is now substantial evidence to suggest that this variability is an independent risk factor for mortality and disease, even after adjustment for overall weight change. However, these results are often inconsistent and dependent on methodological limitations and lack of consistency in their use. If it is the cases that BWV negatively impacts health, then weight loss attempts (which probablistically result in subsequent weight regain) should be considered carefully and potentially avoided in some individuals (Cologne *et al.*, 2019) and indeed, this would be an extremely controversial statement to make.

Previous reviews have attempted to explore the effects of body weight instability on health, concluding that there is no effect (Mehta *et al.*, 2014) or some (Mackie, Samocha-Bonet and Tam, 2017) to significant (Rhee, 2017) evidence of detrimental effects. However, each of these reviews fail to consider the entirety of relevant literature and have resulted in incongruent conclusions. In response, the following section provides a comprehensive review of the evidence relating body weight instability to health. The term body weight instability is used to group both BWV and weight cycling studies as the literature on both of these metrics is overlapping. Firstly, the epidemiological evidence exploring relationships between body weight instability and risk of mortality or disease is reviewed, and limitations are discussed. Second, mechanistic evidence linking body weight instability and disease using evidence from (a) human studies and (b) animal models is reported and discussed.

Table 3.2. Longitudinal studies investigating the effect of weight instability on CVD, T2D and mortality

Study	Participant characteristics	Follow-up Duration	M/R	Weight measures	Method of determining weight variability	Outcomes (Cases)	Results
Arnold 2010	n= 3,278 (61% W) BMI= NA Age= 72.8±5.6	7	M	7	1) CV of weight 2) WC defined as >5% lost and gained over lifetime	All-cause mortality (1,072)	Compared to weight stability: 1) HR for all-cause mortality: 1.13 (1.07, 1.20) 2) HR for all-cause mortality: 1.20 (1.04, 1.39)
Aucott 2016	n= 29,316 (45% W) BMI= 33.2±6 Age= 58.4±12 Diabetics	5.2	M	4	WC categories: Little (<2.5%), Some (2.5 to <5%), Moderate (5 to <10%) and Large (10%+) loss and regain	All-cause mortality (743) Myocardial infarction (MI) (616) Congestive heart failure (CHF) (425) Peripheral Vascular disease (PVD) (300) Cerebrovascular disease (CD) (360)	Compared to weight stability for little, some, moderate and large weight cycling categories respectively: Mortality HR: 1, 1.14 (0.94, 1.38), p=0.182; 1.77 (1.41, 2.23), p <0.001; 2.49 (1.68, 3.68), p <0.001. MI HR: 1, 1.15 (0.94, 1.41), p= 0.189; 1.57 (1.21, 2.03), p<0.001; 0.99 (0.54, 1.84), p=0.976. CHF HR: 1, 1.68 (1.30, 2.15), p <0.001; 2.00 (1.46, 2.75) <0.001; 2.23 (1.26, 3.96), p=0.006. PVD HR: 1, 1.21 (0.90, 1.63), p=0.208; 1.55 (1.07, 2.24), p=0.021; 2.08 (1.06, 4.08), p=0.034. CD HR: 1, 1.23 (0.94, 1.60) p=0.131; 1.36 (0.96, 1.92), p=0.085; 1.11 (0.51, 2.42) p=0.792
Bangalore 2017	n= 9,509 (19% W) BMI = NA Age= 61.8 CAD patients	4.9	M	12	CV of weight (1 SD = 1.5.1.9kg)	All-cause mortality (185) Coronary events (884) All cardiovascular events (1149) Myocardial Infarction (198) Stroke (101) T2D incidence (222)	HR for highest vs lowest quintile of WV: Any coronary event 1.64 (1.41, 1.90), p<0.001 Any cardiovascular event 1.85 (1.62, 2.11), p<0.001 All-cause mortality 2.24 (1.74, 2.89), p<0.001 Myocardial infarction 2.17 (1.59, 2.97), p<0.001 Stroke 2.36 (1.56, 3.58), p<0.001 T2D incidence 1.78 (1.32, 2.40), p<0.001

Blair 1993	n= 10,529 (0% W) BMI= 27.7 Age= 46.3 Upper 10-15% risk for CHD	3.8	M	7.2	1) CV of weight 2) WC categories: (a) loss and gain of >5% (b) gain and loss of >5%	All-cause Mortality (380) CVD Mortality (228)	For all-cause mortality: 1) Regression coefficient for the number of weight cycles = 0.304, p=0.005 2a) Cycle, lose at end RR: 1.76 (1.23 to 2.50) 2b) Cycle, gain at end RR: 1.53 (1.13 to 2.07) For CVD mortality: 1) Coefficient for the number of weight change cycles r = 0.379, p=0.006 2a) RR: 1.73 (1.08, 2.79) 2b) RR: 1.89 (1.29, 2.78)
Brancati 1999	n= 916 (0% W) BMI= 23.2±2.4 Age= 22.7±1.8	15.6	R	3	CV of BMI	T2D Incidence (35)	Highest vs lowest weight stability: RR: 2.1 (1.0, 4.6)
Delahanty 2014	n= 1,000 (68% W) BMI= 33.7±6.56 Age= 51±11	2	M	5	WC defined as loss and regain of >5lbs (2.25kg)	T2D Incidence (99)	HR for T2D: 1.22 (1.02, 1.48), p = 0.03
Diaz 2005	n= 8,479 (48.8%W) BMI= 24.0±2.8 Age= 44.7±22.1	21	R	5	CV of BMI (WF defined as a sum of deviations > 5.04 BMI units)	All-cause mortality (979) CVD mortality	Highest vs lowest weight fluctuation group: All-cause mortality RR: 1.83 (1.25, 2.69) CVD Mortality RR: 1.86 (1.10, 3.15)
Dyer 2000	n= 1,281 (0% W) BMI= 25.8±3.1 Age=55.3±4.3	25	M	5	CV of BMI	All-cause mortality (686) CVD Mortality (356)	Highest vs lowest quintile of WV: RR for mortality: 1.11 (1.04, 1.19) CVD mortality RR for highest vs lowest quintile of WV: 1.20 (1.1, 1.31)
Field 2004	n= 46,634 (100% W) BMI= 25.6±5.2 Age= 39.3±4.4	6	M	?	WC Categories: (a) Mild weight cycler: losing >4.5kg three or more times (b) Severe weight cycler: losing >9.1kg three or more times	T2D Incidence (418)	(a) Mild cycler RR: 1.11 (0.89, 1.37) vs non-cyclers (b) Severe cycler RR: 1.39 (0.9, 2.13) vs non-cyclers

Field 2009	n= 44,876 (100%W) BMI= 26.3 Age= 57.1±6.9	20	R	10	WC Categories: (a) Mild weight cycler: losing >4.5kg three or more times (b) Severe weight cycler: losing >9.1kg three or more times	All-cause mortality (2,882) CVD mortality (424)	1a) All-cause mortality RR 0.84 (0.75, 0.93) CVD mortality RR 0.90 (0.67, 1.19) 1b) All-cause mortality RR 0.90 (0.77, 1.04) CVD mortality RR 1.10 (0.76, 1.58)
Folsom 1996	n= 33,760 (100% W) BMI= NA Age= 62.0	5	R	5	1) RMSE of weight divided into quartiles 2) WC categories: (a) small weight cycler: loss and regain of >5% bodyweight (b) large weight cycler: loss and regain of >10% bodyweight	All-cause mortality (702) CVD mortality (195)	1) All-cause mortality RR for RMSE quartiles: Q1 RR: 1; Q2 RR: 1.17; Q3 RR: 1.45; Q4 RR: 1.82 (p<0.001 for trend) CVD mortality RR for RMSE quartiles: Q1 RR: 1; Q2 RR: 1.12; Q3 RR: 1.15; Q4 RR 1.16 (p=0.2 for trend) 2a) All cause mortality RR: 1.05 (0.6, 1.8) CVD mortality RR: 1.4 (0.6, 3.2) 2b) All cause mortality RR: 1.32 (0.8, 2.1) CVD mortality RR: 1.68 (0.8, 3.6)
French 1997	n= 33,834 (100% W) BMI= NA Age= 55-69	6	R	5	1) RMSE of weight divided into quartiles 2) WC categories: (a) small weight cycler: loss and regain of >5% bodyweight (b) large weight cycler: loss and regain of >10% bodyweight	Stroke (457) Myocardial Infarction (562) T2D Incidence (914)	1) Stroke RR for RMSE quartiles: Q1 RR: 1; Q2 RR: 0.91 (0.69, 1.21); Q3 RR: 1.04 (0.79, 1.37); Q4 RR: 1.14 (0.86, 1.51) (p=0.22 for trend) MI RR for RMSE quartiles: Q1 RR: 1; Q2 RR: 1.11(0.85,1.44); Q3 RR: 1.08(0.83,1.40); Q4 RR: 1.51(1.16,1.95), (p=0.008 for trend) T2D RR for RMSE quartiles: Q1 RR: 1, Q2 RR: 0.84(0.66,1.05); Q3 RR: 1.22(0.99,1.51) Q4 RR: 1.29(1.04,1.60) (p<0.001 for trend)
Hanson 1995	n= 584 (66% W) BMI= 31.7 Age= 38.8 Pima Indians	24	M	5	RMSE of weight divided into three tertiles: (a) low (<2kg cycled) (b) middle (2-4kg cycled) (c) high (>4kg cycled)	T2D Incidence (162 cases)	2 data RR of T2D Incidence in high vs low RMSE teriles: 1.03 (0.85, 1.25)

Hanson 1996 Cohort A	n= 572 (0% W) BMI= 32.0 Age= 39 Non-diabetic Pima Indians	9.1	M	4	RMSE of weight seperated into two groups: (a) low RMSE (<3.2kg cycled) (b) high RMSE (>3.2kg cycled)	All-cause mortality (75) CVD mortality (22)	For high vs low RMSE: All-cause mortality RR: 1.5 (1, 2.1) CVD mortality RR: 1.1 (0.5, 2.3)
Hanson 1996 Cohort B	n= 766 (0% W) BMI= 29.8 Age= 52 Diabetic Pima Indians	9.1	M	4	RMSE of weight seperated into two groups: (a) low RMSE (<2.8kg cycled) (b) high RMSE (>2.8kg cycled)	All-cause mortality (115) CVD mortality (19)	For high vs low RMSE of weight: All-cause mortality RR: 1 (0.8, 1.3) CVD mortality RR: 0.9 (0.4, 1.7)
Iribarren 1995	n= 6,537 (0%W) BMI= 23.9±3.0 Age= 54.0±5.5	14.5	M	3	RMSE of weight divided into quintiles	All-cause mortality (1217) CVD mortality (355)	All-cause mortality RR for quintiles of RMSE (Q1-Q5) 1; 1.14 (0.95, 1.37); 1.07 (0.89, 1.29); 1.01 (0.84, 1.21); 1.25 (1.05, 1.48), p=0.27 for trend CVD mortality RR for quintiles of RMSE (Q1-Q5) 1; 0.99 (0.69, 1.42); 1.08 (0.77, 1.52); 1.11 (0.79, 1.55); 1.41 (1.03–1.93), p=0.6 for trend
Kataja-Tuomola 2010	n= 20,952 (0% W) BMI= 25.9 Age= 56.9	6	M	6	RMSE of weight divided into quintiles	T2D Incidence	RR for T2D incidence in highest vs lowest quintile of WV: 1.36 (1.16, 1.61)
Kim 2018	n=6,748,773	5.5	M	≥3	CV of BMI (reported) Similar results were obtained when modelling the variability using the (1) SD, (2) variability independent of the mean, and (3) average real variability	All-cause mortality (54,785) Stroke (22,498) MI (21,452)	Highest vs lowest quartile HR for all-cause mortality: 1.53 (1.50–1.57) HR for stroke: 1.14 (1.10–1.18) HR for MI: 1.14 (1.09–1.18)

Lissner 1990	n= 3,171 (43% W) BMI= 25.3 Age= 42.8	32	M	10	CV of BMI	All-cause mortality (942) CHD mortality (356)	In men: RR for all-cause mortality 1.65 (1.32-2.06) RR for CHD mortality : 1.93 (1.35-2.77) In women: RR for all-cause mortality 1.27 (1.01-1.67) RR for CHD mortality: 1.55 (1.09-2.21) vs weight stability
Nam 2018	n=125,391 (38%W) BMI=23.6±3.1 Age=45.7±13	7	M	3.2	1) CV of weight 2) CV of BMI	All-cause mortality CVD mortality	1) HR for all-cause mortality (weight) Overall loss: 1.19 (1.05, 1.35) Overall gain: 1.41 (1.24, 1.60) HR for CVD mortality Overall loss: 1.04 (0.78- 1.40) Overall gain: 1.37 (1.03, 1.83) 2) HR for all-cause mortality (BMI) Overall loss: 1.26 (1.11, 1.43) Overall gain: 1.38 (1.21, 1.57) HR for CVD mortality Overall loss: 1.13 (0.85, 1.50) Overall gain: 1.33 (0.99, 1.79)
Neamat-Allah 2015	n= 53,088 (57% W) BMI= 27.3 Age= 50.0	2.5	R	4	1) FPCA 2) WC categories (a) Mild WC: >0.75kg cycled between measures (b) Strong WC: >1.5kg cycled between measures	T2D incidence (643)	1) HR for T2D incidence by a-priori defined patterns of weight change: 1.36 (1.09, 1.68) 2a) HR for T2D incidence: 1.20 (0.98, 1.48) 2b) HR for T2D incidence: 1.34 (1.03, 1.73)
Nguygen 2007	n= 1,703 (62% W) BMI= 26.0±4 Age= 70.0	13	M	4	WC defined as 3% weight cycled	All-cause mortality (547)	In men, HR for all-cause mortality: 1.5 (1.1, 2) In women, HR for all-cause mortality 1.3 (1, 1.7)
Morris 1992	n= 8,232 (100% W) BMI= NA Age= 42.2±2.9	9	R	6	RMSE of weight	T2D Incidence (355)	OR for T2D incidence: 1.10 (1.07, 1.14)

Murphy 2014	n= 1,975 (53% W) BMI= 27.4±5.4 Age= 78.2±2.8	8	M	6	WC defined as 5% weight cycled	All-cause mortality (145)	HR for all-cause mortality in men: 1.45 (1.04, 2.03) HR for all-cause mortality in women: 1.61 (1.14, 2.28)
Peters 1995	n= 6,441 (0% W) BMI= NA Age= NA	15	M	3	CV of weight	All-cause mortality CHD MI	RR for all-cause mortality: 1.2 (1.0, 1.4) RR for CHD: 1.5 (1.0, 1.9) RR for MI 1.5 (1.0, 2.2) vs weight stability
Rhee 2018	N=4,818 (22% W) BMI=24.1±2.9 Age=42.9 ± 4.0	4	M	5	Average successive variability of weight (ASVW) divided into 3 tertiles of weight variability	T2D Incidence	OR for T2D: 1.86; 95% CI 1.13–3.06 for highest vs lowest category of weight variability
Rzehak 2007	n= 1160 (0% W) BMI= 26.9 Age= 63.2±5.3	30	M	4	WC defined by >3.49 BMI units cycled	All-cause mortality (183)	All-cause mortality HR: 1.86 (1.31, 2.66)
Saito 2017	n= 11,281 (51% W) BMI= 22.5±3.5 Age= 51.3±11.0	4	M	3	RMSE of bodyfat (%) divided into quartiles	T2D Incidence (425)	OR for T2D incidence for quartiles of RMSE of body fat (Q1-Q4) 1; 0.86 (0.62, 1.17); 0.74 (0.54, 1.00); 0.79 (0.58, 1.08)
Taing 2011	n= 47,473 (0% W) BMI= 30.6±5.1 Age= 63.4±7.3	7	R	4	WC defined as >5% weight cycled	All-cause mortality (3,192)	HR for all-cause mortality: 1.08 (0.79–1.48)
Wannameth ee 2002	n= 5,609 (0% W) BMI= 25.5 Age= NA	8	R	3	WC categories: (a) loss-gain of >4% weight (b) gain-loss of >4% weight	All-cause mortality (477) CVD mortality (186)	1a) RR for all-cause mortality: 1.40 (1.06, 1.85) RR for CVD mortality: 1.45 (0.98, 2.15) 1b) RR for all-cause mortality: 1.31 (1.02,

							1.68) RR for CVD mortality: 1.44 (1.02, 2.04)
Waring 2010	n= 1,476 (57% W) BMI= NA Age= 40.0	10	M	11	FPCA	T2D Incidence (217)	HR for weight cycling: 1.1 (0.8, 1.5)
Yokomichi 2017 Urban participants	20,708 (51% W) BMI= 22.3 Age= 48.9	7.4	M	4.9	WC categories: (a) loss-gain of >4% weight (b) gain-loss of >4% weight	T2D incidence (413)	1a) OR for T2D incidence = 0.63 (0.45 to 0.89) 1b) OR for T2D incidence = 0.51 (0.32 to 0.82)
Yokomichi 2017 Rural participants	n= 9670 (50% W) BMI= 22.6 Age= 52.1	7	M	5	WC categories: (a) loss-gain of >4% weight (b) gain-loss of >4% weight	T2D incidence (66)	1a) OR for T2D incidence = 1.58 (0.78 to 3.17) 1b) OR for T2D incidence = 0.44 (0.15 to 1.29)
Zoppini 2008 Age<65 Type 2 Diabetics	n= 565 (51% W) BMI= 27.7±4.5 Age= 56.6±7.7	10	M	7	CV of BMI	All-cause mortality (438 for both groups)	For highest vs lowest tertiles: HR for all-cause mortality: 1.16 (0.72–1.86)
Zoppini 2008 Age>65 Type 2 Diabetics	n= 754 (63% W) BMI= 27.2±3.8 Age= 72.7±5.3	10	M	7	CV of BMI	All-cause mortality (438 for both groups)	For highest vs lowest tertiles: HR for all-cause mortality: 1.34 (1.03–1.75)

Table 3.2. *Associations between weight instability patterns (i.e. weight variability and weight cycling) and future risk of all-cause mortality, cardiovascular disease and type 2 diabetes. Results are generally reported as a risk, odds or hazard ratio when comparing the least body weight stable group to the most body weight stable group (reference group). The definition of the measure of instability is included and showing the heterogeneity in definitions between studies. Sample sizes are reported as n (% women). Where sample characteristics are described as NA, data was not available on the group mean. Abbreviations: M; measured, R; recorded, CV; coefficient of variation, WC; weight cycling, RMSE; root mean square error, ASVW; average successive weight variability, FPCA; functional principle components analysis, T2D; type 2 diabetes, CVD; cardiovascular disease, CAD; coronary artery disease, CHD, HR; hazard ratio, RR; risk ratio, OR; odds ratio*

3.3.1 All-Cause Mortality

The associations between body weight instability and risk of mortality and disease incidence can be found in **table 3.2**. We found 25 studies which assessed the impact of body weight instability on risk of all-cause mortality. Of these, 19 reported a significant increase in the risk of mortality in the most compared to least weight variable groups (Stevens and Lissner, 1990; Blair *et al.*, 1993a; Peters *et al.*, 1995; Iribarren *et al.*, 1995; Folsom *et al.*, 1996; Dyer, Stamler and Greenland, 2000; Wannamethee, Shaper and Walker, 2002; Diaz, Mainous and Everett, 2005; Nguyen *et al.*, 2007; Rzehak *et al.*, 2007; Arnold *et al.*, 2010; Murphy *et al.*, 2014; Lorna S. Aucott *et al.*, 2016; Bangalore *et al.*, 2017; Nam *et al.*, 2018; Kim *et al.*, 2018; Oh *et al.*, 2019; Yeboah *et al.*, 2019; Cologne *et al.*, 2019). Reported increases in risk ranged from an 11% in 1,281 men recruited to the Chicago Western Electric Company Study (Dyer, Stamler and Greenland, 2000) to a 149% increased risk in 29,316 Scottish diabetic men and women (Lorna S Aucott *et al.*, 2016). Several studies showed evidence of a dose-response relationship between body weight instability and mortality (Folsom *et al.*, 1996; Lorna S Aucott *et al.*, 2016; Bangalore *et al.*, 2017; Kim *et al.*, 2018; Nam *et al.*, 2018; Rhee *et al.*, 2018; Cologne *et al.*, 2019). Only one study from the Nurse's Health Study (n=44,876) reported a significant decrease in risk by 16% in mild weight cyclers who self-reported intentionally losing ≥4.5kg three or more times (Field, Malspeis and Willett, 2009) and in all other studies results were non-significant or inconsistent (Hanson *et al.*, 1996; Zoppini *et al.*, 2008; Taing, Ardern and Kuk, 2012).

3.3.2 Cardiovascular Disease

Sixteen studies investigating associations between weight instability and risk of cardiovascular outcomes were found, including risk of CVD mortality (11 studies) and cardiovascular events (5 studies). Of these, 7 showed increased risk of CVD mortality (Lissner *et al.*, 1990; Blair *et al.*, 1993b; Iribarren *et al.*, 1995; Dyer, Stamler and Greenland, 2000; Diaz, Mainous and Everett, 2005; Kim *et al.*, 2018; Nam *et al.*, 2018) ranging from 20% (Dyer, Stamler and Greenland, 2000) to 89% in a group of 10,529 men from the Multiple Risk Factor Intervention Trial considered already at risk of CVD (Blair *et al.*, 1993b). Again, these risk increases reflect a comparison of the most vs least weight variable groups. In

contrast, three studies showed no significant association (Folsom *et al.*, 1996; Hanson *et al.*, 1996; Field, Malspeis and Willett, 2009) and one studies reported inconsistent results depending on the direction of the cycle or overall weight change (Wannamethee, Shaper and Walker, 2002). Five studies measured the effect of weight instability on risk of myocardial infarction, of which four showed a significant increase in risk (Peters *et al.*, 1995; French *et al.*, 1997; Bangalore *et al.*, 2017; Kim *et al.*, 2018) ranging from 14% (Kim *et al.*, 2018) to 117% (Bangalore *et al.*, 2017), and one showed no effect (Lorna S Aucott *et al.*, 2016). Three studies investigated the risk of stroke, of which two reported an increase in risk (Bangalore *et al.*, 2017; Kim *et al.*, 2018) ranging from 14% (Kim *et al.*, 2018) to 136% (Bangalore *et al.*, 2017) and one showed no effect (French *et al.*, 1997). Both studies which measured coronary heart disease reported an increased risk in the least weight stable group, ranging from 50% (Peters *et al.*, 1995) to 93% (Lissner *et al.*, 1990). Other cardiovascular events were occasionally investigated. Aucott and colleagues (2016) observed an increased risk in congestive heart failure and peripheral vascular disease but not cerebrovascular disease in the group with the greatest BWV. Cologne and colleagues (2019) observed increased risk of ischemic heart disease (by 149%) but not cerebrovascular disease. Yeboah and colleagues (2018) found increased risks of congestive heart failure (by 59%) and microvascular events (by 18%).

3.3.3 Type 2 Diabetes

A total of 15 studies investigated the effect of weight instability on risk of T2D incidence. Of these, 8 studies reported a significant increase in the risk of developing T2D in individuals showing the greatest weight instability in comparison to the least (Morris and Rimm, 1992; French *et al.*, 1997; Brancati *et al.*, 1999; Kataja-Tuomola *et al.*, 2010; Delahanty *et al.*, 2014; Bangalore *et al.*, 2017; Rhee *et al.*, 2018; Park *et al.*, 2019) ranging from a 10% (Park *et al.*, 2019) in almost 4 million citizens registered in to the Japanese National Health Insurance System to 110% (Brancati *et al.*, 1999) in 500 middle aged men. Only one study showed a significant decrease in risk of T2D associated with BWV in 20,708 urban Japanese residents although no association was found in 9,670 rural Japanese residents in the same study (Yokomichi *et al.*, 2017). Five studies reported no significant association (Hanson *et al.*, 1995; Alison E. Field *et al.*, 2004; Waring *et al.*, 2010; Saito *et al.*, 2017; Zhang *et al.*, 2017) and one study showed inconsistent associations dependent on the

magnitude of the cycle, with only larger weight cycles showing increased risk (Neamat-Allah *et al.*, 2015).

3.3.4 Discussion

Overall, the weight of the evidence points towards a potentially detrimental effect of body weight instability on risk of mortality, CVD and (to a lesser extent) T2D. However, inconsistency in results and substantial heterogeneity in study design functions to limit confidence in the evidence. Notably, the magnitude of the effect sizes vary greatly. In some studies these are modest (in the region of 10% increased risk) and in others they are substantial (in the region of 100-200% increased risk). Between-study variability in the method used to quantify body weight instability may provide some explanation. Indeed, in a recent meta-analysis examining the effect of body weight instability on T2D risk, authors reported that although they found a significantly increased risk, their analysis was limited by heterogeneity in the methods used to define body weight instability, and as such synthesising results is likely to be highly susceptible to misclassification bias (Kodama *et al.*, 2017). This limitation can be observed between studies, but also within a single study. For example, in one study, when body weight instability was analysed using RMSE around the linear trend and quintiled of severity, authors reported a dose-response relationship between RMSE and mortality, however, when defined by weight cycling categories of 5% or 10% loss and regain, no effect was observed (Folsom *et al.*, 1996). In contrast, in one of the largest investigations into BWV to date, Kim and colleagues (2018) observed a significant increase in risk of mortality, stroke and myocardial infarction using data from collected by the Korean National Health Insurance System (n=6,748,773) and these associations remained similar while using 4 independent methods of defining BWV.

The direction of the most recent weight change may also be of importance. For example, in one study the risk of CVD mortality was increased in those who experienced a gain-loss cycle of ≥4% body weight, but not for with a loss-gain cycle of similar magnitude (Wannamethee, Shaper and Walker, 2002). It is possible that recent weight loss is attributable to poor health causing this effect. Another factor which remains inconsistent between studies is the metric upon which variability is calculated, such as weight or BMI, or, as in one study, body fat (%) (Saito *et al.*, 2017). In a recent study, Nam and colleagues (2019) used the co-efficient of variation to quantify variability in both BMI and in body

weight in relation to risk of CVD mortality and all-cause mortality (Nam *et al.*, 2019). While most results were similar, a significantly increased risk of CVD mortality was observed when weight variability was used in one instance, although this was non-significant when BMI variability was used. Indeed, the use of BMI adjusts for variability in height between individuals and therefore may be advantageous to use in comparison to body weight.

Intentionality of weight change is difficult to assess, particularly in very large cohort studies. The confounding effect of intentionality in relation to body weight instability has been discussed previously in relation to health outcomes (Mehta *et al.*, 2014; Kodama *et al.*, 2017; Mackie, Samocha-Bonet and Tam, 2017). In the studies reported, only a small minority provided information on intentionality of weight loss. Deliberate weight loss is typically associated with decreased risk of mortality and disease (Kritchevsky *et al.*, 2015), whereas unintentional weight loss may be a sign of underlying health conditions such as malignant disease and thus may increase the risk of mortality (Bosch *et al.*, 2017). Unintentional weight loss may also be attributable to gastrointestinal disorders (e.g. gluten intolerance), psychological disorders (e.g. depression (Lankisch *et al.*, 2001)) and socioeconomic factors (Xiao *et al.*, 2017). Indeed, cancer and other potentially terminal illnesses have been reported to only account for a small fraction of cases of involuntary weight loss (Baicus *et al.*, 2014) and are less probable in the non-elderly (Gaddey and Holder, 2014). Therefore, excluding all studies where intentionality has not been assessed, as done in previous reviews (Mehta *et al.*, 2014; Mackie, Samocha-Bonet and Tam, 2017), assumes that the large majority of existing evidence is confounded by underlying disease, even though this is unlikely to be the case. In these reviews excluding a large amount of the literature, instability in body weight was concluded to have no (Mehta *et al.*, 2014) or potentially some (Mackie, Samocha-Bonet and Tam, 2017) negative impact on health. By including all evidence investigating body weight instability, our conclusions are inconsistent with these reviews and instead show evidence of a potentially detrimental health effect of body weight instability, which, in some studies showed large increases in health risks.

3.3. Mechanisms Linking Weight Instability to Health Risks

While there is extensive evidence relating body weight instability to disease and mortality, few studies discuss the potential physiological mechanisms through which these

epidemiological relationships operate. Two simplified ways to explain these observations are possible: (a) that body weight instability acts as an independent risk factor for disease or (b) that body weight instability produces metabolic adaptations (e.g. increased blood pressure (Zeigler *et al.*, 2018)), which in turn increase the risk of disease. To test the latter, longitudinal measures of body weight aligned with cardiometabolic health measurements allow associations between body weight instability and changes in health markers to be drawn. However, body weight data which is both frequent and long-term is lacking in research environments. Instead, much of the evidence examining the associations between instability in body weight and health markers is reliant on retrospective questionnaires.

To overcome issues associated with measuring body weight instability in humans, many research groups have opted to apply animal models, specifically mice models, to the study of body weight instability. The following section reviews mechanistic evidence linking body weight instability and health coming from (a) human studies and (b) animal models.

3.3.1 Evidence from Human Studies

The mechanisms linking body weight instability to increased risk of disease are unclear. Several studies have made attempts to quantify the impact of body weight instability measures (i.e. weight cycling or BWV) on physiological factors, including glucose and insulin metabolism, blood lipids, EE and body composition among others. A discussion of the potential physiological effects of body weight instability is provided. The evidence relating to each outcome is summarized briefly in **table 3.3** and studies are divided into cross-sectional and prospective designs.

3.3.1.1 Blood Pressure

Weight loss is known to produce reductions in blood pressure in a dose-response manner though any influence of body weight instability on blood pressure is unknown. We found 14 studies in which the association between body weight instability and blood pressure was examined, of which 7 showed significant, positive associations (Guagnano *et al.*, 1999, 2000; Kajioka *et al.*, 2002; Zhang *et al.*, 2005; Vergnaud *et al.*, 2008; Saito *et al.*, 2017; Zeigler *et al.*, 2018) and 7 showed no effect (Wing, Jeffery and Hellerstedt, 1995; Field *et al.*, 1999; Olson *et al.*, 2000; Graci *et al.*, 2004; Li *et al.*, 2007; Strychar *et al.*, 2009; Cereda *et al.*, 2011) with no studies showing an inverse association. These included a variety of

study designs including retrospective, prospective and cross-sectional studies. Slightly more prospective studies showed a positive effect than no effect (4 vs 3 respectively); whereas slightly more cross-sectional studies (which relied on self-reported retrospective weight

Table 3.3. Influence of Weight Instability on Markers of Health in Humans

Metabolic Effect	Positive Association	C/P	Negative (-)/no association	C/P
Increased blood pressure	Zeigler 2018	C	Strychar 2009	C
	Guagano 2000	C	Graci 2004	C
	Guagano 1999	C	Cereda 2011	C
	Saito 2015	P	Field 1999	P
	Vergnaud 2008	P	Wing 1995	P
	Kajioka 2002	P	Li 2007	P
	Zhang 2005	C	Olson 2000	C
Increased LDL	Beavers 2013	P	Strychar 2009	C
			Graci 2004	C
			Wing 1995	P
			Li 2007	P
			Kajioka 2002	P
			Olson 2000	C
Decreased HDL	Vergnaud 2008	P	Kajioka 2002	P
	Olson 2000	C	Wing 1995	P
	Zhang 2005	C	Beavers 2013	P
Decreased leptin	Benini 2001	C	Strychar 2009	C
			Forthergill 2016	P
Increased insulin	Beavers 2013	P	Strychar 2009	C
			Graci 2004	C
Decreased insulin sensitivity	Beavers 2013	P		
Increased glucose	Zhang 2005	P	Strychar 2009	C
			Graci 2004	C

			Vergnaud 2008	P
			Olson 2000	C
Energy expenditure				
Decreased RMR (per kg FFM)	Strychar 2009	C	Bosy-Westphal 2013	P
	Kajioka 2002	P		
	Forthergill 2016	P		
Body composition				
Increased body fat (%)	Dulloo 1996	P	Wing 1995	P
	Lee 2009	P	Prentice 1992	P
	Beavers 2011	P	Fothergill 2016	P
	Chmelo 2016	P		
Increased WHR			Wing 1995	P
			Olson 2000	C
Increased visceral/abdominal fat	Zeigler 2018	C	Bosy-Westphal 2013	P
	Banasik 2013	P	Van Der Kooy 1993	P
Decreased bone mineral density	Beavers 2011	P		

Table 3.3. *Influence of weight instability on markers of health. Evidence is broken into positive and negative associations with each outcome which has been previously studied. Studies are dividing into cross-sectional evidence (C) and prospective evidence (L). Proposed effects are split into metabolic effects, effects on energy expenditure and effects on body composition. Abbreviations: LDL; low-density lipoproteins, HDL; high-density lipoproteins, RMR; resting metabolic rate, FFM; fat free mass, WHR; waist-to-hip ratio*

history questionnaires) showed no effect than a positive effect (4 vs 3 respectively). One study found a positive association between body weight instability and systolic blood pressure, and reported that this effect was mediated by changes in visceral fat (Zeigler *et al.*, 2018), which is consistent with the hypothesis that changes in body composition mediate the relationship between body weight instability and cardiometabolic health

(Montani, Schutz and Dulloo, 2015a). However, this is the only study to examine this (or any) pathway to date. Overall, the association between BWV and blood pressure or changes in blood pressure is unclear based on current evidence.

3.3.1.2 Cholesterol

Several studies have examined the influence of body weight instability on low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) concentrations. We found 8 studies which examined associations with LDL-C, of which seven found no associations (Strychar et al. 2009; Graci et al. 2004; Cereda et al. 2011; Wing, Jeffery, and Hellerstedt 1995; Z. Li et al. 2007; Kajioka et al. 2002; Olson et al. 2000) and one reported an increase in a study examining changes in cardiometabolic factors over a single weight cycle in elderly women (Beavers et al. 2013). Again, these were a mix of cross-sectional and prospective analyses, three of which examined cardiometabolic changes over a single weight cycle (Beavers et al. 2013; Kajioka et al. 2002; Wing, Jeffery, and Hellerstedt 1995) and results were inconsistent. Of these, no study attempted to propose a potential mechanistic link between body weight instability and LDL-C. Six studies which examined associations between body weight instability and HDL-C were identified, of which 3 showed no effect (Kajioka et al. 2002; Wing, Jeffery, and Hellerstedt 1995; Beavers et al. 2013) and 3 showed a negative association (Vergnaud et al. 2008; Olson et al. 2000; Zhang et al. 2005), bearing in mind that reductions in HDL-C is a detrimental health effect. The three studies which showed no effect all examined single cycles of loss and regain whereas studies showing a significant negative associations were either cross-sectional, or, in one case, a long-term prospective study (Vergnaud *et al.*, 2008).

3.3.1.3 Insulin and Glucose

Three studies reported associations between insulin and body weight instability. One study examining changes in cardiometabolic risk in response to a single weight cycle reported increased fasting insulin as well as decreased insulin sensitivity following weight regain in 80 older women with overweight or obesity (Beavers *et al.*, 2013). In contrast, two cross-sectional studies showed no association between weight cycling history and current insulin concentrations (Graci *et al.*, 2004; Strychar *et al.*, 2009). Five studies examined associations between glucose concentrations and body weight instability, of which only 1 reported a positive association (Zhang *et al.*, 2005) in a retrospective cohort analysis of

weight fluctuation in Japanese men. Four studies showed no effect (Olson *et al.*, 2000; Graci *et al.*, 2004; Vergnaud *et al.*, 2008; Strychar *et al.*, 2009) of which 3 were cross-sectional and questionnaire-based (Olson *et al.*, 2000; Graci *et al.*, 2004; Strychar *et al.*, 2009). No studies showed a negative association. The weight of the current evidence suggests there is no association between insulin or glucose and body weight instability in humans. Interestingly, these results are somewhat inconsistent with reported metabolic responses to weight cycling in animal models (see section 3.4.2.1 below).

3.3.1.4 Leptin

Two cross-sectional studies have investigated associations between body weight instability and leptin concentrations, of which one reported a negative association (Strychar *et al.*, 2009) and the other a positive association (Benini *et al.*, 2001). The latter study focused entirely of the contribution of weight cycling to leptin concentrations in 183 individuals with obesity – they found that the association of weight cycling and leptin was largely confounded by the positive association between weight cycling and percentage body fat, which is known to be correlated with leptin. One longitudinal study reported information on a single (but extreme) weight cycle in 14 participants of "The Biggest Loser" study (Fothergill, Guo, Howard, Jennifer C Kerns, *et al.*, 2016). They found that following 58.3kg weight reduction and 41kg weight regain, leptin concentrations were still less than half recovered towards baseline, potentially suggesting large weight loss and regain may incrementally decrease leptin. However, these weight losses are extreme, and no further evidence is available to further examine this effect under these conditions.

3.3.1.5 Energy Expenditure

Four studies reported on the associations between weight cycling and RMR per kg of FFM. One cross-sectional study showed an association between greater historical weight cycling and decreased energy expenditure (Strychar *et al.*, 2009). Three studies investigated the effects of single weight cycle, of which two showed significantly decreased RMR (per kg of FFM) following weight regain (Kajioka *et al.*, 2002; Fothergill, Guo, Howard, Jennifer C Kerns, *et al.*, 2016). Importantly, in these studies weight loss was either extreme (Fothergill, Guo, Howard, Jennifer C Kerns, *et al.*, 2016), or in initially lean subjects (Kajioka *et al.*, 2002). Such an effect is in favour of the concept of adaptive thermogenesis, which suggests that the body become increasingly energy efficient (beyond that predicted by changes in body

composition) as weight loss proceeds (Müller and Bosy-Westphal, 2013), and that this effect may persist following weight regain, making it harder to lose weight after multiple cycles, as hypothesised in early weight cycling literature by Brownell (Brownell *et al.*, 1986; Blackburn *et al.*, 1989). One study reported no effect of weight loss and regain on relative RMR.

3.3.1.6 Body Composition

While body composition itself may not be an independent risk factor for disease risk, greater body fatness (Mushengezi and Chillo, 2014), waist-to-hip ratio (White, Pereira and Garner, 1986) or visceral fat storage (J. J. Lee *et al.*, 2016) are each associated with detrimental cardiometabolic health effects such as increased blood pressure, higher cholesterol concentrations or lower insulin sensitivity. The role of weight cycling on body composition has received significant attention after Dulloo's re-analysis of the Minnesota Starvation study (Keys *et al.*, 1950) suggested that weight cycling functions to repartition mass from FFM to FM due to differences in the p-ratio (the proportion of protein to fat added to or withdrawn from a system during weight gain or loss respectively) of weight loss and weight regain (Dulloo, Jacquet and Girardier, 1996).

In the systematic review and meta-analysis (Turicchi *et al.*, 2019) detailed in section 2.2 which described changes in body composition during clinically significant (>5%) weight loss and subsequent weight regain in 2,379 individuals from 52 weight loss intervention groups, an average of 19.6% of the weight lost was from FFM whereas during weight regain, 21.6% was regained as FFM. This is inconsistent with the hypothesis presented by Dulloo, although two important differences are notable: (a) Dulloo's hypothesis was generated in relation to results observed in initially lean individuals, whose FFM loss during weight loss is known to be greater than heavier individuals (Forbes, 1987; Hall, 2007) and (b) weight loss in the Minnesota study was substantial (~20% reduction), whereas the mean weight reduction in described in section 2.2 was closer to half of this. Furthermore, availability in the body composition measurements used made it difficult to compare FFM and FM changes. Only one other study to my knowledge has examined weight cycling effects on body composition in initially lean individuals, reporting that there was a greater proportion of weight regained as body fat (Kajioka *et al.*, 2002). Weight loss was even more substantial in "The Greatest Loser" study, however, individuals had a baseline BMI of 49.5kg/m^2. In this group, there was preferential gain of FFM rather than FM upon weight recovery, however

the large initial BMI and fact that individuals were involved in vigorous exercise is likely to have limited FFM reductions during weight loss.

In addition, two studies examined relationships between weight cycling and WHR but found no associations. Four prospective studies have examined fat distribution. Two studies showed that weight loss and regain led to increased visceral/abdominal fat deposition (Banasik *et al.*, 2013; Zeigler *et al.*, 2018), which was referred to as 'rebound visceral adiposity', whereas two studies showed no effect (van der Kooy *et al.*, 1993; Bosy-Westphal *et al.*, 2013). Given that visceral fat storage is involved in the development of T2D (Jung, Ha and Kim, 2016), further research should focus on the impact of weight loss and regain on proportionate changes in adipose storage locations. Lastly, one study showed that weight loss and regain decreased BMD in elderly individuals (Beavers *et al.*, 2011), suggesting that BMD is not regained at the rate it is lost in older adults, and that care should be taken in this group to avoid unnecessary weight cycling. It has also been shown that weight variability measured over 12-years predicted increased risk of hip fractures in middle aged adults (Meyer, Tverdal and Selmer, 1998).

3.4.2 Evidence from Animal Models

Animal models offer novel advantages to the study of body weight instability. Most animal models studies examine weight cycling specifically because it is simple to accurately manipulate body weight through periods of weight loss and gain, without any substantial variability associated with complex human behaviours. Like most human disease research, the mouse model has been favoured in weight cycling research. The use of animal models to investigate weight cycling was initially popular in the late 1980s to early 1990s, however, in 1993 a narrative review by Reed and Hill which examined 24 publications relating to the physical effects of weight cycling in animals, concluded that no clear evidence of a detrimental effect existed in the literature (Reed and Hill, 1993). However, in the past 8 or so years, driven by advances in experimental animal model techniques (Justice and Dhillon, 2016), an increase in weight cycling studies using animal models has provided new mechanistic insights. In this section, recent animal model studies of weight cycling following the 1993 review paper are considered. In the interests of clarity, effects have been grouped into those related to metabolic processes, inflammation, body composition, behaviour and long-term outcomes and a summary of the results can be found in **table 3.4**.

Table 3.4. Influence of Weight Instability on Markers of Health in Mice Models

Metabolic effects	Positive association	Negative (-)/no association
Increased fasting glucose	Schofield et al., 2017 Anderson et al., 2013	Palm et al., 2017 (-) McMillen et al., 2013 Dankel et al., 2014 Caria et al., 2017
Decreased glucose tolerance	Anderson et al., 2013 Dankel et al., 2014 Li et al., 2018 Barbosa-da-Silva et al., 2012 McMillen et al., 2013 Simonds et al., 2018	Fischer et al., 2018
Increased circulating insulin	Zamarron et al., 2017 Barbosa-da-Silva et al., 2012 Anderson et al., 2013 Schoenfield et al., 2017 Caria et al., 2017	McMillen et al., 2013 Dankel et al., 2014 Fischer et al., 2017 Simonds et al., 2018
Decreased insulin sensitivity	Li et al., 2018	
Decreased total energy expenditure	Simonds et al., 2018	Palm et al., 2017 Caria et al., 2017
Increased food efficiency	Dankel et al., 2014	Barbosa-da-Silva et al., 2012
Inflammatory responses		
Pro-inflammatory responses (including T-cell accumulation)	Kyung et al., 2018 Li et al., 2018 Zamarron et al.,2017	Caria et al., 2017

	Anderson et al., 2013	
	Barbosa-da-Silva et al., 2012	
	Fischer et al., 2018	
Body composition		
Increased fat mass	Dankel et al., 2014	Smith et al., 2018 (-)
	Schofield et al., 2017	
		Caria et al., 2017
		Fischer et al., 2017
Increased internal fat deposition	Schofield et al., 2017	Chikamoto et al., 2016 (in epididymal but not liver fat)
Hepatic steatosis	Zamarron et al., 2017	
	Barbosa-da-Silva et al., 2012	
	Fischer et al., 2017	
Behavioural		
Increased appetite	Simonds et al., 2018	
	Schofield et al., 2017	
Longevity		Smith et al., 2018 (-)
Decreased lifespan		List et al., 2013 (-)

Table 3.4. *Influence of weight cycling on markers of health in mice studies. Evidence is broken into positive and negative associations with each outcome which has been previously studied. Proposed effects are split into metabolic effects, inflammatory and immune responses, body composition, behaviour and longevity. Abbreviations: LDL; low-density lipoproteins, HDL; high-density lipoproteins, RMR; resting metabolic rate, FFM; fat free mass, WHR; waist-to-hip ratio*

3.4.2.1 Insulin and Glucose Metabolism

Nine recent studies were identified that investigated the effect of weight cycling on glucose and insulin metabolism in mice. Of these, two studies reported that weight cycling increased fasting glucose concentrations (Anderson *et al.*, 2013; Schofield *et al.*, 2017), one study found glucose levels to be improved (Palm *et al.*, 2017) and in three studies found no effect on fasting glucose was observed (McMillen, Minami and Leboeuf, 2013; Dankel *et al.*, 2014; Caria *et al.*, 2017). Six studies found that glucose tolerance was decreased following weight cycling (Barbosa-da-Silva *et al.*, 2012; Anderson *et al.*, 2013; McMillen, Minami and

Leboeuf, 2013; Dankel *et al.*, 2014; Kyung *et al.*, 2018; Simonds, Pryor and Cowley, 2018a) and one study found no effect (Fischer *et al.*, 2018). In relation to insulin metabolism, five studies found significantly increased circulating insulin levels in response to weight cycling (Barbosa-da-Silva *et al.*, 2012; Anderson *et al.*, 2013; Caria *et al.*, 2017; Schofield *et al.*, 2017; Zamarron, 2017), whereas four studies reported no effects on insulin (McMillen, Minami and Leboeuf, 2013; Dankel *et al.*, 2014; Simonds, Pryor and Cowley, 2018a). Lastly, in the only study which measured insulin sensitivity, a decrease was observed following cycling (Li *et al.*, 2018). The present evidence suggests a potential link between glucose and insulin metabolism and weight cycling in mice and provides rationale for further research into this association in humans as a potential mechanism underlying the observed association between BWV and T2D incidence (Kodama *et al.*, 2017) amongst other health effects.

3.4.2.2 Energy Expenditure

Early weight cycling research in animal models suggested that weight loss becomes harder to achieve with each successive cycle (Brownell *et al.*, 1986), thought to be through metabolic adaptation to decrease energy expenditure or increase food efficiency. This again brings forth the question of whether dieting is a proxy or a cause of future weight gain (Lowe, 2015). Only one study was found in which weight cycling reduced total energy expenditure (Simonds, Pryor and Cowley, 2018a) and in two studies there was no effect (Caria *et al.*, 2017; Palm *et al.*, 2017). Two studies examined effects on food efficiency of which one showed a significant increase (Dankel *et al.*, 2014), and the other showed no effect in response to weight cycling (Barbosa-da-Silva *et al.*, 2012). Presently, evidence is weighted towards no effects of body weight instability on metabolic adaptations affecting energy expenditure or food efficiency in mice.

3.4.2.3 Inflammation and Immune Responses

Associations between inflammatory and immune responses and weight cycling in mice have been well studied. Six studies have reported increased inflammatory responses following exposure to weight cycling (Barbosa-da-Silva *et al.*, 2012; Anderson *et al.*, 2013; Zamarron, 2017; Fischer *et al.*, 2018; Li *et al.*, 2018), and one study found no effect (Caria *et al.*, 2017). The nature of the inflammatory responses measured differed between studies. For example, inflammation of adipocytes was most commonly observed in all studies which found a significant effect and liver inflammation was also observed (Zamarron, 2017; Fischer

et al., 2018). These responses can be detected by changes in molecular markers of inflammation such as IL-6 and TNF-α (Li *et al.*, 2018) and immune markers such as CD4+ and CD8+ T-cells (Anderson *et al.*, 2013). Furthermore, changes to gene expression predisposing increased inflammation has been observed in response to weight cycling (Kyung *et al.*, 2018). Three studies measured hepatic steatosis in which increases were observed in all studies (Barbosa-da-Silva *et al.*, 2012; Zamarron, 2017; Fischer *et al.*, 2018). Hepatic steatosis is associated with insulin resistance and glucose intolerance in humans (Matsuzaka and Shimano, 2011) and accordingly this may provide another mechanism for the epidemiological link between BWV and risk of T2D. The current evidence suggests inflammation in adipose and liver tissue may be related to weight cycling and may influence future risk of disease, and further research in humans is warranted.

3.4.2.4 Body Composition

Five studies were found in which changes in body composition in response to weight cycling was examined. Of these, two studies found a detrimental effect on body composition (e.g. increased %body fat) (Dankel *et al.*, 2014; Schofield *et al.*, 2017), one study showed an improved body composition (Smith *et al.*, 2018) and two studies found no effect on body composition after exposure to weight cycling (Caria *et al.*, 2017; Fischer *et al.*, 2018). Two studies measured changes in internal fat deposition, of which one study reported that weight cycled mice had a higher percentage of internal and subcutaneous fat after return to baseline weight (Schofield *et al.*, 2017), whereas in another study epididymal fat deposition increased but liver fat did not after exposure to weight cycling (Chikamoto *et al.*, 2016). Similar to evidence in human studies, there is not convincing evidence that weight cycling causes redistribution of fat-free mass to fat mass in mice, although there may be some evidence of internal fat deposition which is a risk factor for cardiometabolic disease.

3.4.2.5 Appetite

In two studies, an increase in appetite in weight cycled mice was observed (Schofield *et al.*, 2017; Simonds, Pryor and Cowley, 2018a) shown by a marked increase in ad libitum food intake following loss and regain in one study (Simonds, Pryor and Cowley, 2018a) – reminiscent of the observations by Dulloo and colleagues in the Minnesota Starvation study (Dulloo, Jacquet and Girardier, 1996) - and by increased expression of NPY neurons of the

ARC nucleus, a neurophysiological adaptation associated with increased appetite, following a single weight cycle in comparison to weight stable mice (Schofield *et al.*, 2017). Indeed, obese-reversed mice have previously been shown to exhibit sustained expression of AgRP and NPY neurons associated with increased appetite (Yu, Deng and Huang, 2009). Schofield and colleagues proposed that weight cycling may moderate appetite by producing a "reward deficit" which occurs during energy restriction.

3.4.2.6 Lifespan

Lastly, only two studies investigated the effect of weight cycling on longevity (List *et al.*, 2013; Smith *et al.*, 2018). In both, weight cycling was found to increase the lifespan of the mice. This is contradictory to the previously discussed research in which cardiometabolic changes associated with increased risk of disease and mortality were observed and highlights the need for further research under more standardised methods.

3.4.3 Discussion

3.4.3.1 Human Studies

There was some evidence to suggest that blood pressure, but not cholesterol, glucose or insulin metabolism was affected by instability in body weight in humans. Not enough evidence existed to comment on changes in leptin or energy expenditure, though results from "The Biggest Loser" study did seem to suggest that extreme weight cycling (in the region of 40-50kg) may substantially lower leptin and energy expenditure even after most of the weight is regained (Fothergill, Guo, Howard, Jennifer C. Kerns, *et al.*, 2016b). With regards to body composition, it seems that while weight cycling may potentially cause increased proportions of FM in initially lean individuals (with this data coming from limited studies), this is unlikely to be the case in individuals with overweight and obesity, as evidenced from our analysis of 52 study samples of weight loss and regain which showed a slight preferential regain of FFM on average (Turicchi *et al.*, 2019).

Significant heterogeneity in study designs limited the ability for consistent conclusions to be reached in relation to the influence of body weight instability on any of the health outcomes examined. Many studies assessed weight cycling by use of retrospective questionnaire while others calculated BWV from retrospective or prospective body weight measurements and some studies examined the effects of a single cycle of loss

and regain. The direct comparison of such discrete studies should be taken with considerable caution as each of these designs have independent as well as overlapping limitations. Both the limitations and sources of heterogeneity in the measurement of body weight instability has been discussed extensively (see section 3.1). No systematic bias was observed between study designs which may have suggested that the method of measurement or study design was potentially confounding these observations.

The lack of any clear mechanisms linking body weight instability to increased risk of disease is somewhat inconsistent with the weight of evidence suggesting that risk of disease incidence or mortality is increased over long periods, and even following this review the mechanisms for this association remain unclear. Some studies (such as those examining a single weight loss and regain cycle) may be limited by their short duration, with the possibility that body weight instability affects health only over long periods (several years or decades). Nonetheless, many studies retrospectively measured weight cycling or BWV over the entire adult life using retrospective questionnaires. Yet, these questionnaires are limited substantially by recall bias, and prospectively measured body weight is preferable. In order to fully elucidate any association between body weight instability and detrimental health effects, prospectively and preferably frequent tracked body weights coinciding with longitudinal measures of health markers are required.

3.4.3.2 Animal Studies

Similar to evidence provided by human studies, there was unclear evidence on the health effects of weight cycling in animal studies, though some more consistent evidence was found in relation to some outcomes. The weight of the evidence was in favour of detrimental effects on glucose and insulin metabolism which is worthy of more detailed study in humans. Furthermore, reported changes in immunity and inflammation seemed to show degredation of immune systems and increased inflammation after exposure to weight cycling in most studies. Importantly, immunity and inflammation have not been studied in relation to any measure of body weight instability in humans, despite relatively consistent evidence in mice, and this potential effect warrants further study. The hypothesis that weight cycling reduces energy expenditure with each cycle (Brownell *et al.*, 1986) was not supported, nor was there evidence of increased body fatness, however, similar to human studies there was some evidence to suggest that body weight instability may potentially

increase internal/visceral fat deposition, though further more controlled studies are required in humans. Surprisingly, despite some evidence of negative health effects in other studies, two studies measuring lifespan found that weight cycled mice lived longer. This is inconsistent with the conclusion that body weight instability in humans increases risk of mortality in humans. Again, there were inconsistencies between the study designs, such as the amount of weight cycled, or times cycled. For example, some studies examined a single cycle (Anderson *et al.*, 2013; Caria *et al.*, 2017; Li *et al.*, 2018) compared to multiple cycles (Barbosa-da-Silva *et al.*, 2012; Dankel *et al.*, 2014; Palm *et al.*, 2017; Simonds, Pryor and Cowley, 2018a).

Of course, evidence provided by animal models is not directly comparable to human studies due to differences in physiology. Moreover, the exposure to weight cycling in animals is typically more severe and rapid than the weight cycling reported in human studies (i.e. greater fractions of body weight are lost and regained in short periods of time). For example, one study in mice manipulated multiple consecutive body weight cycles up to 23% body weight (Palm *et al.*, 2017) over the space of only 3 months. Similar relative weight changes would be extreme in human examples. The duration of the lifespan which these cycles occur over also vary greatly between mice and humans. The method by which weight loss and regain is achieved may be another confounding factor. In mice, rapid weight gain is often achieved by a very high-fat diets, and weight loss is achieved via a low-fat diet. Excessive fat content of a diet may predispose metabolic disturbance, such as insulin resistance (Jornayvaz *et al.*, 2010), independent of weight change alone and therefore may confound results relating purely to weight change in mice. Nonetheless, the mouse model has the advantages of being able to (a) begin from any start point (i.e. initially lean) and (b) accurately manipulate body weight. In humans studies; (a) is limited by the lack of evidence on weight loss and regain in lean individuals (and lack of therapeutic interest in providing weight loss in this group) and (b) is limited by the inability to experimentally manipulate weight regain in individuals who have recently lost weight. Without these issues being resolved, studying the effect of weight cycling on human health may continue to be limited.

3.4 Associations Between Weight Instability and Weight Management

As mentioned, body weight seems to be highly stable at population level though, at individual level, there is considerable acute variability. One hypothesis presented by Lowe and colleagues (initially (Lowe *et al.*, 2015)) is that instability in body weight (specifically they refer to measured BWV in their research rather than weight cycling) signals an acute dysregulation of energy balance which may predict longer-term dysregulation (and thus weight gain). The implication is that BWV can be measured in the short term (such as a 6-26 weeks) and used to predict weight change in the longer term (e.g. 1-3 years). The evidence relating to this effect comes from a small selection of studies. In the following section these studies are briefly reviewed.

Three studies were found in which short-term BWV predicted increased weight over longer periods (Lowe *et al.*, 2015; Feig and Lowe, 2017; Benson *et al.*, 2020), and one study reported positive associations between BWV and weight change over the same time period (Winter *et al.*, 2017). All studies came from the same research group. The first study to report this effect (Lowe *et al.*, 2015) found that greater BWV measured over the first 6-months of an observational study in 171 women without obesity predicted increased weight at 24 months (R^2=6%). BWV was estimated from 3 body weights (at baseline, 6 weeks and 6 months) using the RMSE from a linear trendline. The BWV estimates were not relative (i.e. converted to percentage error), and the primary analysis presented was univariate, meaning that (given heavier individuals are more likely to have greater BWV), body size may have confounded the observed effects.

Next, the group examined the influence of 6 and 12-week BWV on weight changes at 6, 12 and 24 months in a group of 183 individuals with obesity who were enrolled in a 12-month behavioural weight loss intervention (Feig and Lowe, 2017). BWV was measured using a single weekly body weight over the exposure period. Greater 6-week BWV predicted increased weight at 12 and 24-months (R^2=3% for both) but not 6 months and 12-week BWV predicted increased weight at 12 and 24 months (R^2= 7% and 6% in univariate models, reducing to 4% and 3% in adjusted models, respectively). In this study they additionally reported positive associations between baseline self-reported eating behaviour constructs (power of food, preoccupation with food and emotional craving) and 6 to 12-week BWV. In the most recent study, they examined the associations between 12-week BWV measured

using WiFi connected smart scales in 24,009 American users who reported currently trying to lose weight, and weight outcomes at 48, 72 and 96 weeks. The study was entirely digital, and no intervention or user interaction took place. They reported that greater BWV predicted increased weight at 48, 72 and 96 weeks, with effect sizes increasing with increased follow up duration, reaching R^2=3.6% at 96 weeks.

Together, these studies implicate a potential role of short-term BWV to predict subsequent weight gain. The observed effect sizes are modest, which is not discussed in any of the papers. Nonetheless, the magnitude and direction of these observations remain similar for all analyses. The ability to identify earlier indicators of treatment success in a weight loss or weight loss maintenance intervention could be of significant scientific value. However, some questions remain unanswered. Firstly, what is the optimal period to measure BWV? Ideally, shorter durations are preferable, though Feig et al 2017 found similar effect sizes when measuring 6 and 12-week BWV. Secondly, what is the mechanism linking BWV to increased weight gain? Some evidence suggests associations between baseline uncontrolled eating factors and subsequent BWV which may indicate a pathway to weight gain, though further research is required. Thirdly, how can this evidence be applied to limit weight gain? Some data has shown that inconsistency in energy intake is associated with (a) increased absolute energy intake and (b) increased weight (Rosenbaum *et al.*, 2016), and as such perhaps promoting adherence to a consistent energy intake or diet may function to reduce BWV and weight gain. Lastly, no studies have examined the influence of BWV on weight outcomes following recent weight loss, or in individuals engaged in a weight loss maintenance intervention, and further research is required in these contexts.

3.5 Overall Conclusions

A comprehensive review of existing research relating to body weight instability was conducted. Firstly, it was important to differentiate between self-reported weight cycling and measured BWV, which both indicate instability in body weight but the former relies on arbitrary definitions of the magnitudes of loss and regain required to contribute to a cycle, whereas the latter calculates the variability around the trend in body weight. In a review of the definitions of weight cycling, their use was found to be extremely heterogenous, limiting comparison between studies. Furthermore, their reliance on historical weight data makes

information collected prone to recall bias. Measures of BWV were also found to be highly heterogenous in relation to (a) the measurement period; (b) the time between measurements; (c) whether body weights were retrospectively or prospectively collected; (d) the metric used to calculate variability (in some cases weight, BMI and body fat variability were used). Furthermore, the infrequent measurement of body weight (i.e. every 6-12 months) means considerable unmeasured weight changes can occur, and the extent to which these single points reflect true BWV is unclear. The weight of the evidence suggested that the risk of mortality, CVD (events of mortality) and T2D was increased with greater BWV, however, methodological inconsistencies in addition to the failure to account for intentionality of weight changes mean that these associations should be interpreted with caution. The mechanisms linking BWV to risk of disease or mortality was unclear – evidence from human studies showed inconsistent associations, with the weight of evidence only being in favour of increased blood pressure. In animal studies there was some evidence of dysregulation insulin and glucose metabolism, as well as decreased immune function and increased inflammation, which may warrant further study in humans. Evidence from a handful of select studies from a single research group suggest that BWV measured over the short-term may weakly predict increases in weight over subsequent longer durations, though several questions remain unanswered and replication is required in different samples under varying conditions (such as in weight loss maintenance).

3.6 Directions for Future Research

Together, this evidence provides sufficient rationale to assume BWV as a potentially important clinical marker. However, significant advances in the measurement of BWV are required in order to fully understand the phenomenon's associations with health. The infrequent measurement of body weight is an important limitation, which has been addressed by only a single study (Benson *et al.*, 2020) which used WiFi connected smart scales to collect body weight data. It is likely that use of similar devices will be critical in the future study of BWV. The statistical methods used to quantify BWV are often too simplistic, and further research is required to develop new methods which overcome existing limitations such as the assumption of linearity in body weight change, or the use of absolute RMSE values which are likely to be confounded by initial body weight. Furthermore,

variability in weight should be aligned with longitudinal measurements of cardiometabolic health and body composition to assess associations between variability and health.

Little information about the determinants of BWV exists. Indeed, weight may vary based on energy balance related factors (i.e. changes in energy intake or physical activity) or non-energy balance related factors (such as fluctuations in water, glycogen and gut tissue). It is likely that acute weight variability is attribute mostly to the latter (Bhutani *et al.*, 2017a). Only with longitudinal, frequent and accurate measurement of body composition is it possible to differentiate between energy and non-energy related weight changes. Nonetheless, future research should focus on the psychological and behavioural determinants of BWV if it is potentially a risk factor for disease and mortality.

Chapter 4: General Methods

4.1 The NoHoW study

The NoHoW study was the context of and provided data for the subsequent investigations into weight instability presented in the following chapters. The NoHoW study was not a-priori designed to investigate body weight variability, however, the data collected lends itself to a unique opportunity to address relevant research questions using novel technologies and analytical approaches. In order to understand the subsequent studies conducted, it is critical to understand the context in which they occurred and the intervention which made the sample unique. In the following chapter, the details of the intervention and methods used are described in detail.

Importantly, I took no part in conceptualisation or design of the NoHoW trial as part of this PhD (which was finalised before the initiation of my PhD), however I did work extensively on data collection, management of the trial conduct at one of the trial centres, data management, data analysis and dissemination through most of the trial's lifespan.

4.1.1 Rationale

Many studies examining weight management have dealt primarily with the goal of weight loss often with insufficient durations for follow up or maintenance. It is suggested that while weight loss is shown to be achievable by most traditional approaches (Franz *et al.*, 2007a), WLM requires continuous clinical attention (Hall and Kahan, 2018). Accordingly, the past decade has seen an increase in studies intervening during the WLM period (Varkevisser *et al.*, 2019), in turn providing a greater understanding of the determinants of weight management following weight loss.

A range of behaviour change strategies have been applied to the study of WLM. One consistent observation arising from this literature is the direct association between self-regulatory processes and successful WLM (Varkevisser *et al.*, 2019). Self-regulation in a weight management context refers to the continuous monitoring of energy balance components, specifically body weight, diet and physical activity. A review of self-regulatory and motivational processes in long-term weight management (Pedro J. Teixeira, Silva, *et al.*, 2012) identified a range of psychological processes and behaviours which were associated

with successful weight management in interventions with a behaviour change component. Authors reported that increased autonomous motivation and self-efficacy, coupled with greater self-regulatory skills (such as self-monitoring but also skills related to planning and coping) were important mediators of success. In particular, self-weighing (Zheng *et al.*, 2015a) and self-monitoring of physical activity and diet (Burke, Wang and Sevick, 2011) are central self-regulatory behaviours in successful weight management.

While self-regulation of weight and energy balance behaviours are shown to be important in successful WLM, these behaviours may be undermined by loss of emotional control and negative affect. In the early stages of development of the NoHoW project, a 3-country study questioned 2000 adults from the UK, Portugal and Denmark (the loci of the project) who had recently lost weight on relationships between eating behaviour, emotional control and self-regulation (Sainsbury *et al.*, 2019). They found that individuals who showed greater difficulties regulating emotions regained more weight and used fewer self-regulatory strategies. Indeed, emotional control is consistently associated with improved weight management, often mediated by uncontrolled eating behaviour (Shriver *et al.*, 2019). This model of self-regulation and emotional control relates to the more commonly cited dual-process theory in which there is a balance of competing impulsive and reflective systems, whereby the impulsive system initiates the overconsumption of palatable foods and the reflective system is involved in inhibition of reactive impulses in favour of longer-term rather than immediate reward (Dassen *et al.*, 2018).

Identified as two key (and dependent) mediators of weight management, self-regulation and emotion regulation (or, contextual behavioural approaches to address aspects of reactivity) had not previously been jointly investigated in a WLM intervention. Given the knowledge (a) self-monitoring is a highly consistent predictor of better weight management and that (b) that difficulties controlling emotions and impulsivity may function to undermine self-regulatory processes, an intervention which jointly tested both the behaviour (monitoring) and the underlaying emotional cognitions was conceptualised.

4.1.2 Digital Behaviour Change Interventions

The NoHoW trial was delivered as an online intervention. The method of delivery of a behaviour change intervention is identified as a ‘key active ingredient’ in the intervention’s translation and success (Dombrowski, O’Carroll and Williams, 2016).

Traditionally, behaviour change interventions were delivered either in person, or by telephone. Such approaches, while arguably preferable, are limited by costs, scalability and intervention duration. For an intervention to be distributed on a large scale over long periods, digitization is necessary. Briefly, a digital intervention is one which would deliver intervention content, be that behaviour change or some other component, via a digital device, such as a smartphone, tablet or computer, thus reducing the need for human contact. In the past decade, there has been an increasing number of digital interventions. Several recent reviews have addressed the effectiveness of digital interventions in weight management (Mateo *et al.*, 2015; Beleigoli *et al.*, 2019; Ryan, Dockray and Linehan, 2019). Overall effect sizes in relation to weight loss and maintenance are generally small and variable. Interestingly, no difference in weight outcomes were found between digital and offline interventions in one recent meta-analysis (Beleigoli *et al.*, 2019), inconsistent with the idea that face-to-face interventions are preferable.

A key additional benefit of a digitally delivered intervention is the ability to link intervention components with tracking technologies. Data from activity and body weight trackers can be plugged in to the intervention content, and feedback may even be provided (often in real time) in response to objectively measured data on the participant. Indeed, it is thought that the Internet of Things (a term which refers to network-enabled technologies capable of sensing and actuation in addition to feedback and communication with one another) will become a central component in the future of personalised health (Sheth, Jaimini and Yip, 2018). As such, the move towards complete digitisation of interventions will be a necessary step in this process, at least at scale.

4.1.2 Aims and Hypotheses

The primary aim of the NoHoW trial was to develop and evaluate a digital toolkit delivering an evidence-based intervention to aid successful weight loss maintenance. The primary outcome was body weight at 12-months. Secondary a-priori objectives (Scott *et al.*, 2019) included to:

1. Determine how the intervention affected health markers of disease (eg, levels of glycated haemoglobin (HbA1c), blood lipids) and body composition;
2. Investigate the interventions effects on physical activity, sleep, dietary intake, depression, anxiety, stress, quality of life and well-being;

3. Examine mediators of WLM, such as self-regulation (eg, planning capacity), motivation (eg, autonomous motivation) and emotion regulation processes (eg, self-compassion);
4. Investigate baseline moderators (eg, gender, BMI) of WLM to identify participants who are more responsive to motivational and behavioural self-regulatory or CB-emotion regulatory approaches;
5. Conduct quantitative and qualitative assessment of user-experience, acceptability, engagement and dropout;
6. Examine intervention cost-effectiveness;
7. To determine the efficacy of individualised feedback from data on physical activity self-tracking

With regards to the primary objective, it was hypothesised that:

1. That participants will be more effective at maintaining weight loss in the long-term when receiving a toolkit that combines content for self-regulation and motivation compared to only self-weighing.
2. That participants will be more effective at maintaining weight loss in the long-term when receiving a toolkit that combines content emotion-regulation components compared to only self-weighing.
3. That there is an additive effect of combining self-regulation and emotion regulation at improving maintenance of weight loss compared to only self-weighing.

4.1.3 Study Design

The NoHoW trial was a 2x2 factorial randomised controlled trial testing the efficacy of a digital toolkit for promoting evidence-based behaviour change for weight loss maintenance. It was delivered in three centres located in the United Kingdom (Leeds), Denmark (Copenhagen), and Portugal (Lisbon). Participants were randomised into 4 arms upon entry to the trial ((1) active control, (2) self-regulation and motivation, (3) contextual behavioural emotion regulation and (4) self-regulation, motivation and emotion regulation (i.e. arms 2 and 3 combined)). The ‘active’ component of the intervention spanned the first 6 months, during which participants (in arms 2-4) were provided with weekly theoretically informed, evidenced based behaviour change micro-interventions, based on the arm they

were in. These interventions came in the form of exercises for the participant to do, videos to watch, self-reporting and reflection on certain topics. After 6 months, participants entered a follow-up period for the remaining 12 months. Participants attended trial centres at 0, 6, 12 and 18 months. A summary of the study design can be observed in **figure 4.1** (Scott *et al.*, 2019). The trial was registered at ISRCTN (registration no: 88405328). Funding was acquired from the European Union's Horizon 2020 research and innovation programme (grant agreement no. 643309).

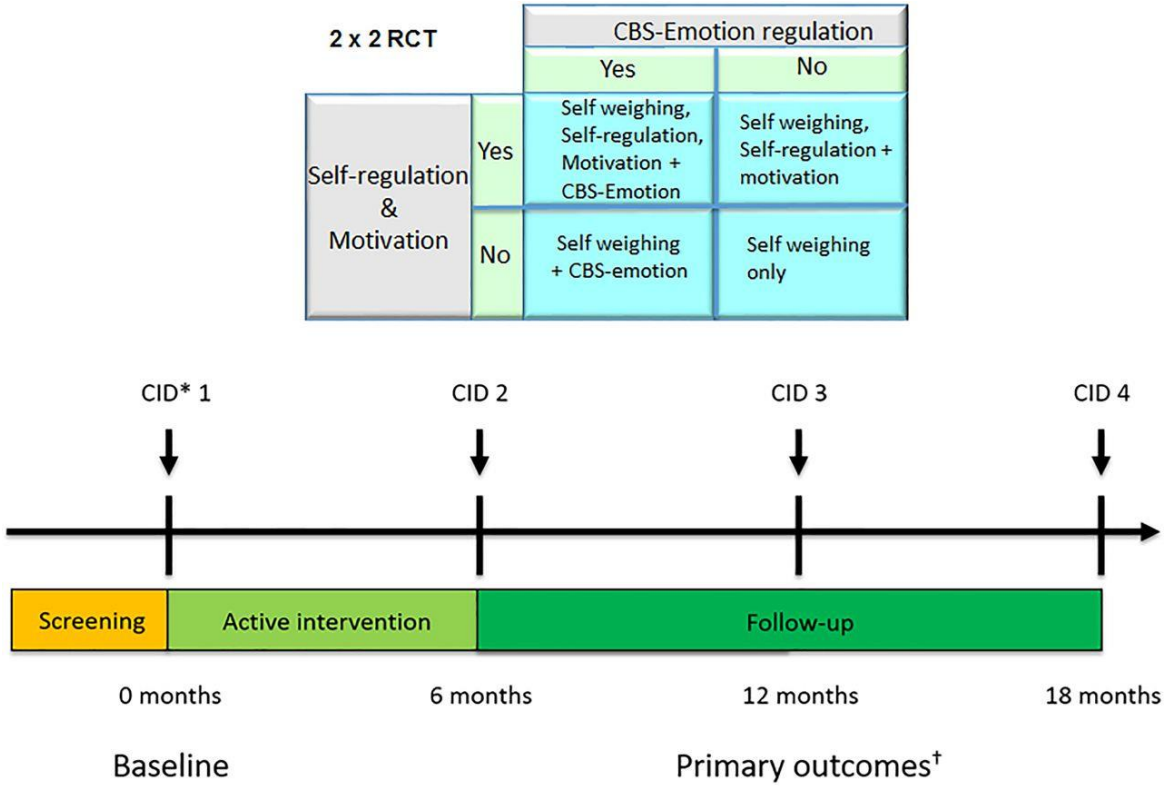


Figure 4.1. *Design of the NoHoW trial. *CID, clinical investigation day. All measures are taken at CID1-4 with the exception of some biomarkers which are only taken at CID1 and CID3. Focus groups are conducted at 6 months*

4.1.4 Participant Recruitment

Recruitment was a rolling process occurring over 12-months (between March 2017 and March 2018), with the aim of recruiting 1,600 participants based on a-priori power calculations for weight and HbA1c outcomes (n=1,627 recruited in total). Recruitment strategies were determined separately at each centre but generally involved recruitment

through commercial weight loss programmes (such as SlimmingWorld and WeightWatchers), government-run weight management programmes, referral from registered dieticians, leisure centres and local media coverage and advertisements. All potential participants were directed to a country-specific recruitment website where they filled out a screening questionnaire to check for eligibility (detailed below). Individuals who met the criteria were contacted via phone call by research staff at each centre. If still deemed eligible, participants were provided with the study information and asked to attend the first CID, where informed consent was collected prior to randomisation.

4.1.4.1 Inclusion and Exclusion Criteria

The following inclusion and exclusion criteria used to determine eligibility for the NoHoW trial. Inclusion criteria were as follows:

- ≥ 18 years old
- BMI of ≥ 25kg/m^2 prior to weight loss
- Verified* weight loss of ≥ 5% in the last 12-months and weight has remained reduced by ≥5%
- Access to a smartphone, tablet or computer and an internet connection
- Ability to use standing scales (cannot weigh over 150kg due to scale limit)

Exclusion criteria were as follows:

- Inability to provide informed consent
- Weight loss was due to surgery or illness
- Currently pregnant or breastfeeding
- Involved in another weight management intervention (not including commercial weight loss programs)
- Unable to read in the language of their centre
- Current diagnosis of an eating disorder
- Any condition which may interfere with mild to moderate physical activity
- Diagnosed with type 1 diabetes
- Planned travel for any more than 4 weeks
- Sharing a household with a previously enrolled participant

* Verification of prior weight loss was provided by a health professional, weight loss counsellor/friend, a weight loss programme record booklet, diary or smartphone app or before/after photographs.
Participants who did not meet any of these criteria were not randomized.

4.1.4.2 Randomization

At the first visit, randomization of participants was conducted via the online administration portal by researchers at each site. An adaptive stratified sampling method using minimisation was used (Altman and Bland, 2005). This minimises differences in previous weight loss at entry, age, gender and BMI. The research team were not blinded due to the need to train participants in arm-specific toolkit versions.

4.1.5 The NoHoW toolkit

The NoHoW toolkit was designed in collaboration with VTT Technical Research Centre of Finland (VTT), a research-based technology development partner. It delivered tasks aimed to nudge psychological and behavioural processes with respect to the trial arm the participant was in. In addition, it synced with Fitbit technologies to incorporate tracking of body weight, physical activity and sleep (further detail below). A layout of the toolkit home screen can be observed in **figure 4.2.** Participants were provided with a 'journey to success' map which delivered micro interventions dependent on which trial arm the participant was in. Details for the complete intervention logic models and behaviour change techniques used are in press. The app also had various qualitative data entry sections. For example, a participant could rate or comment on their mood, or their 'healthy eating' for each day on a 5-star scale. There were also sections were participants could record food diaries, or even keep a general diary, if these approaches aided their weight management.

4.1.6 Tracking technologies

4.1.6.1 The Fitbit Aria Scale

All participants were provided with a commercially available Fitbit Aria scale. In a previous validation study, the Fitbit Aria has shown excellent agreement with a calibrated research grade SECA 704s scale in a group of individuals ranging from underweight to obese (Shaffer *et al.*, 2014) both cross-sectionally and over time. Data collected from the

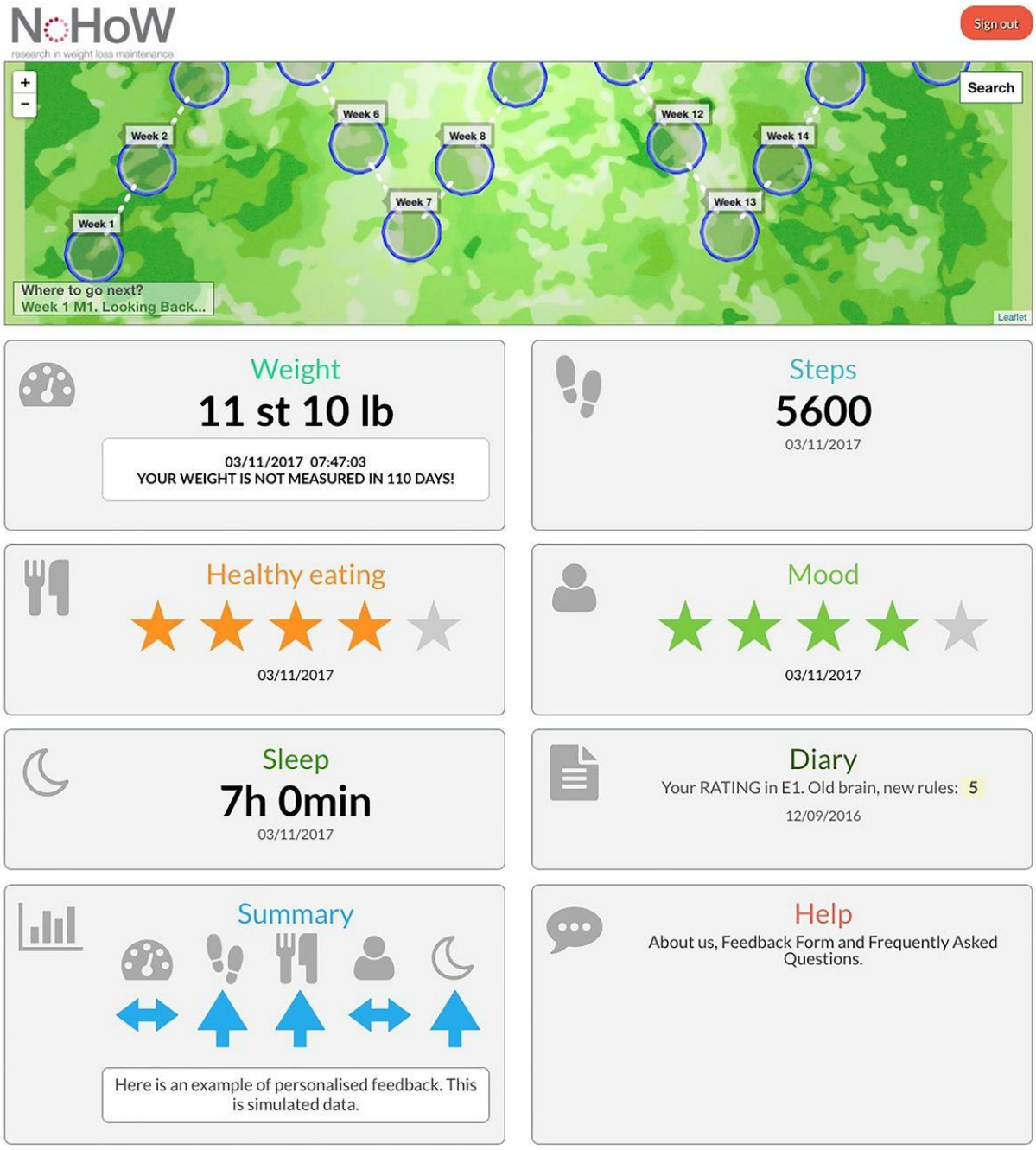


Figure 4.2. *Visual illustration of the NoHoW web app with panels for tracking daily weight, steps, sleep (from Fitbit), healthy eating (self-rated), mood (self-rated)*

device was synchronised to a personal Fitbit account which participants could access on their electronic device and data from each personal account was regularly updated to the NoHoW data hub. Data was collected from the scales for up to 2 years (assuming consent was provided). This data could be viewed by participants on both the Fitbit app and the NoHoW toolkit, though participants were encouraged to use the toolkit. The scales will not associate a body weight with the users account if someone of substantially different

weight steps on the scale (the true difference in this weight has not been reported by Fitbit). If two weight measurements are recorded in a single day, the first measurement is used by default. Given that this is the primary data collection tool in subsequent studies, chapter 5 focuses on processing of this data in detail.

4.1.6.1 The Fitbit Charge 2

The Fitbit Charge 2 is a wrist-worn activity monitor which estimates steps, heart rate, physical activity and sleep metrics based on data obtained from incorporated sensors via proprietary algorithms. The device provides estimates of heart rate, steps, energy expenditure and time spent in activity categories (i.e. light, moderate and intense activity). The device has been reviewed as providing an acceptable estimate of steps but not energy expenditure (Feehan *et al.*, 2018). Our research group recently investigated the validity of the devices in comparison to criterion measures (O'Driscoll *et al.*, 2019), concluding that heart rate, but not energy expenditure (which showed a mean percentage error of 44%), were acceptable outputs of the device.

All data provided by the device were aggregated to the minute-level and synced via the Fitbit mobile application to Fitbit servers and to the NoHoW data hub through an application programming interface. Again, the user could view the data on both the Fitbit app and the NoHoW toolkit but were encouraged to use the latter. The data collected from the Fitbit are dense and complex and an analysis from our research group resulted in the development of a data processing protocol aimed at bias-minimization (R. O'Driscoll *et al.*, 2020).

4.1.7 Physical measurements

At each CID, participants had a series of physical measurements recorded. Some were only conducted at 0 and 12 months, and others at all timepoints (these are detailed below). Participants were instructed to come to each visit fasted and having not yet conducted any exercise on that day. Visits were generally arranged in the morning. Many of these measurements are used in subsequent studies. For each measurement, a standard operating procedure was developed and remained consistent between all 3 centres. Extensive training was provided for each standard operating procedure in each centre to harmonise the data collection at each centre.

4.1.7.1 Body weight and height

Body weight was collected at all timepoints and measured to ±0.1 kg using a validated research grade tool, the SECA 704S instrument (SECA, Germany) in participants wearing light clothing and no shoes. Height was also measured to ±0.1 cm using the SECA 704S, ensuring participants stood straight and level.

4.1.7.2 Body Composition

Body composition was estimated at 0, 6, 12 and 18 months by bio-impedance analysis (BIA) using the ImpediMed SFB7 multifrequency bio-impedance analyser in all three centres following the manufacturer's instructions and by dual-energy X-ray absorptiometry (DXA) at two centres: Portugal (Hologic Explorer-W, Waltham, USA) and Denmark (Norland XR-800, Swissray, USA). Estimates of body composition bio-electrical impedance were transformed using Moissl equations (Moissl *et al.*, 2006) which was deemed more suitable for samples with overweight and obesity. Percent body fat was calculated by dividing fat (kg) by body weight (kg) and multiplying by 100.

4.1.7.3 Waist-to-hip

A tape measure was used to record the hip (at the maximum circumference over the buttocks) and waist (at the thinnest section of the abdomen) circumference to the nearest centimetre. The waist–hip ratio (WHR) was calculated by dividing hip and waist circumference. Three readings were taken, and the average values were used.

4.1.7.4 Blood pressure

Systolic and diastolic BP and resting heart rate (RHR) were recorded every 6 months by a Microlife BP A2 blood pressure monitor after resting in a sitting position for 10 minutes. Three readings were taken, and the average values were used.

4.1.7.5 Cholesterols and HbA1c

Blood lipids (total cholesterol, low-density lipoprotein cholesterol (LDL-C), HDL-C and triglycerides) were measured at 0 and 12 months for participants who opted in to giving a fasting capillary blood sample using an Alere AfinionTM AS100 Analyser. Similarly, fasting blood samples for the analysis of HbA1c were taken at 0 and 12 months and analysed using the Alere AfinionTM AS100 Analyser.

4.1.8 Self-report measurements

4.1.8.1 Self-regulation and motivation

A range of scales were used to collect information on self-regulation and motivation. Self-regulation scales included: The Action Control Scale (ACS-90; (Kuhl, 1994)) and The Action Planning and Coping Planning Scale (Sniehotta, Scholz and Schwarzer, 2005). Scales collecting information on motivational status included: the Basic Psychological Needs and Frustrations Scale (Chen *et al.*, 2015) which assessed autonomy, relatedness and competence and the Goal Content for Weight Loss Maintenance Scale assessed quality of goal contents in relation to weight loss maintenance and was adapted from the goal content for physical activity scale (Sebire, Standage and Vansteenkiste, 2008). Motivations for regulation of exercise were assessed using the Behavioural Regulation in Exercise Questionnaire (BREQ-3) (Markland and Tobin, 2004) with a similar assessment for eating behaviour regulation motivations using the Regulation of Eating Behaviour Scale (REBS) (Kliemann *et al.*, 2016). Lastly, the Regulations for Weight Management Scale was newly adapted from the REBS for the purposes of the NoHoW study.

4.1.8.2 Emotional regulation

The following scales were used in the assessment of emotional regulation: Weight Focused Self-Criticism/Self-Reassurance Scale (Duarte *et al.*, 2019) which measures weight/shape and eating-related self-criticism and self-reassurance; the Weight Focused External Shame Scale (Duarte *et al.*, 2017) which assesses the extent of which individuals believe others judge them based on their weight, body shape and eating; the Compassion Engagement and Actions Scales (Gilbert *et al.*, 2017) which measures compassion for others, compassion from others and self-compassion. Body Image Acceptance and Action Questionnaire (Sandoz *et al.*, 2013) was used to assess psychological flexibility and acceptance in relation to one's body image. Engaged Living Scale (Trompetter *et al.*, 2013) was used to assess valued living and life fulfilment. Mindful Attention Awareness Scale was used to measure the frequency of mindful states in day-to-day life, using both general and situation-specific statements (Carlson and Brown, 2005). Emotional factor was measured using the Difficulties in Emotion Regulation Scale (Gratz and Roemer, 2004). Decentring, defined as the ability to observe one's thoughts and feelings as temporary, was measured

using the Experiences Scales (Fresco *et al.*, 2007). Subjective feels of stress were measured by the Perceived Stress Scale (Cohen, Kamarck and Mermelstein, 1983).

4.1.8.3 Wellbeing and quality of life

Quality of life and well-being were assessed using the 5-level EQ5D (EQ5D-5L) (Herdman *et al.*, 2011) and the Warwick-Edinburgh Well-Being Scale (Tennant *et al.*, 2007), respectively. Anxiety, stress and depression are measured using the Depression & Anxiety Stress Scales (Antony *et al.*, 1998)

4.1.8.4 Eating behaviour

Psychometric measures of eating behaviour included the Three Factor Eating Questionnaire (Stunkard and Messick, 1985) which measures dietary restraint, disinhibition and hunger; the Controllability and Automaticity of Eating Behaviour Scale which was newly developed for the NoHoW project and measures the extent to which certain eating behaviours are regulated or automatic. The Eating in the Absence of Hunger Scale (Arnold *et al.*, 2015) was used to measure eating in the absence of hunger, which is a form of disinhibited eating driven largely by environmental rather than appetitive cues. The Intuitive Eating Scale-2 was used to measure the tendency to follow physical hunger and satiety cues when determining when, what, and how much to eat (Tylka and Kroon Van Diest, 2013) and the Binge Eating Scale was used to measure binge-eating symptoms indicative of an eating disorder (Gormally *et al.*, 1982)

4.1.8.5 Physical activity

Physical activity is measured by the self-reported International Physical Activity Questionnaire (IPAQ) which measures the duration and intensity of physical activities (Craig *et al.*, 2003) and the Activity Choice Index (ACI) which measures preferences for different activity types (Mullen *et al.*, 2016).

4.1.9 Participant demographics

Information on participants such as age, gender, ethnicity, country, marital status, employment and income were collected. In addition, information on smoking, alcohol consumption, prior pregnancies and health conditions were collected.

4.1.10 Weight history

Information on weight history was collected prior to the initial visit. This included previous weight loss strategies used (e.g. dietary, physical activity); use of weight loss programs or counselling; number of attempts at weight loss; number of times successfully losing >5kg; highest weight in the past 12-months and highest lifetime body weight.

4.2 Processing of body weight data

Data collected from WiFi-connected smart scales is dense and complex. Unlike investigations into body weight instability which have typically used lab body weights collected under controlled conditions (usually infrequently such as every 6 or 12 months) to estimate BWV, this data requires significant consideration and preprocessing to ensure that biases are not introduced. Given that the aim of the work in this thesis is to increase scientific understanding of BWV, the first and most crucial step is to ensure appropriate, robust and comprehensive measurement of the phenomenon. In the following section, the steps used to appropriately process the data collected are covered as are the methods used to calculate BWV.

4.2.1 Data cleaning

Data collected by smart scales is pronecircumstances which may produce erroneous weights and therefore function to bias BWV estimates. These include (a) decalibration of electronic scales (this can occur from movement of the scales); (b) inconsistency of weighing conditions (e.g. clothed vs unclothed or morning vs night); (c) weighing of another person of similar weight (which may register as a rapid weight change on the same Fitbit account) and (d) incorrect manual entry of body weight (given that manual entry is an option).

Unfortunately, it is not possible to identify the reasons for erroneous data without any additional information from the user (which was not available). However, inappropriate or excessive removal of data is not advised, and may bias results (Bakker and Wicherts, 2014). Physiological plausibility was deemed to be the most appropriate approach to outlier removal. Data was removed based on evidence detailing physiological limits of plausible weight changes under conditions of rapid weight loss in VLCD (Saris, 2001; Sellahewa *et al.*, 2016) and rapid weight gain in intentional overfeeding conditions (De'riaz, Tremblay and

Bouchard, 1993; Leaf and Antonio, 2017). These boundaries can be viewed in **table 4.1**. Weight changes outside of these limits of physiologically plausibility were considered as outliers and appropriate to remove. However, it is important to note that this is a conservative approach and that erroneous values produced by the reasons listed above may produce errors of a magnitude below these limits, and therefore they would not be excluded.

Table 4.1. Limits of plausible weight change within a given time period

Change in body weight	Duration
± 5%	1 week
± 10%	4 weeks
± 15%	8 weeks
± 20%	12 weeks

Table 4.1. *Limits for maximum weight changes within a given a period which are marked as outliers and removed*

4.3 Calculation of body weight variability

Body weight variability has no validated method of calculation and in the literature addressing the phenomenon, numerous different approaches have been used, in some cases up to 4 methods of calculation within a single study (Nam *et al.*, 2018). The methods commonly used have been discussed previously (section 3.1). In the following section, the statistical approaches used are covered in detail. Given that there is no agreed upon approach, it is logical to test numerous methods and throughout the subsequent works up to 4 different methods are used in a single analysis. The section begins by discussing the calculation of three previously used methods: the coefficient of variation (CV), the mean absolute successive weight variability (MASWV) and the root mean square error (RMSE) method. Upon evaluation of these, a decision to produce a novel method to address some limitations of the most commonly used method (RMSE) was conceived, which was termed the non-linear mean deviation (NLMD) method as is used throughout the subsequent studies in addition to others.

Briefly, it is important to note that given individuals do not self-weigh every day, the data collected is subject to considerable amounts of missing data. The question to impute data or not (especially given that the magnitude of missingness is highly variable both

between and within individuals) was an important consideration point and to address this we ran a comprehensive analysis aiming to minimize bias. This is reported in full in the next section. But for the present section it should be noted that the decision not to impute missing data was taken informed by this analysis to minimize bias.

4.3.1 Coefficient of Variation

The coefficient of variation (CV) is a commonly used metric in statistics to represent the variation (or the dispersion around the mean) in a given set of data. The CV was calculated using the following equation:

$$CV = \frac{\sigma}{\bar{x}} \times 100$$

Where σ represents the standard deviation and $\bar{x}$ represents the mean of body weight.

4.3.2 Mean Absolute Successive Weight Variability

The MASWV is calculated by adding the relative (%) absolute value of each successive weight change and taking the mean of these. It can be represented as the mean (relative) length of the blue line between dots in **figure 4.3** which shows real data from the NoHoW trial of two individuals losing weight though the individual represented in **figure 4.3A** shows much more pronounced BWV than the individual in **figure 4.3B** as measured by MASWV.

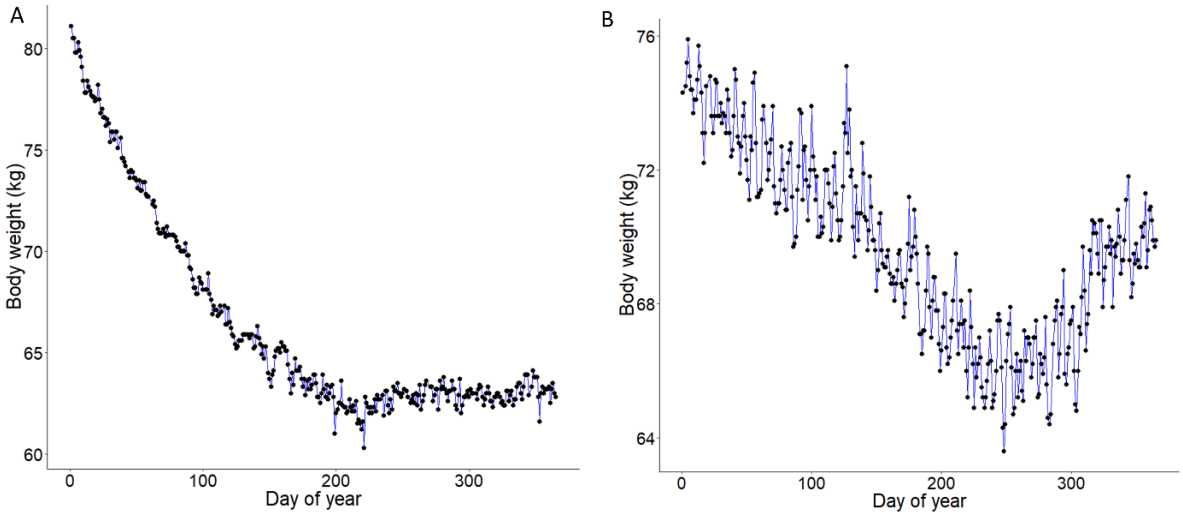


Figure 4.3. *Example data from two NoHoW participants showing (A) low mean average successive weight variability and (B) high mean average successive weight variability*

4.3.3 Root Mean Square Error

Root mean square error is the most commonly used method of estimating BWV in research relating to health or weight management outcomes. Generally, it is can be used to assess the fit of a model for any regression-based analysis. Specific to BWV, RMSE is calculated by fitting a linear regression through a body weight series against time (in days). The values of the regression are then subtracted from the actual weight data, which provides residual values. Illustrated examples can be seen in **figure 4.4** for participants with non-linear (top) and linear (bottom) weight trajectories. **Figures 4.4A** and **C** show the linear regression fitted to the weight data, and **figures 4.4B** and **D** show the distribution of the residuals of the regression. As shown, when a linear regression is fit to a non-linear weight trajectory large residuals are generated.

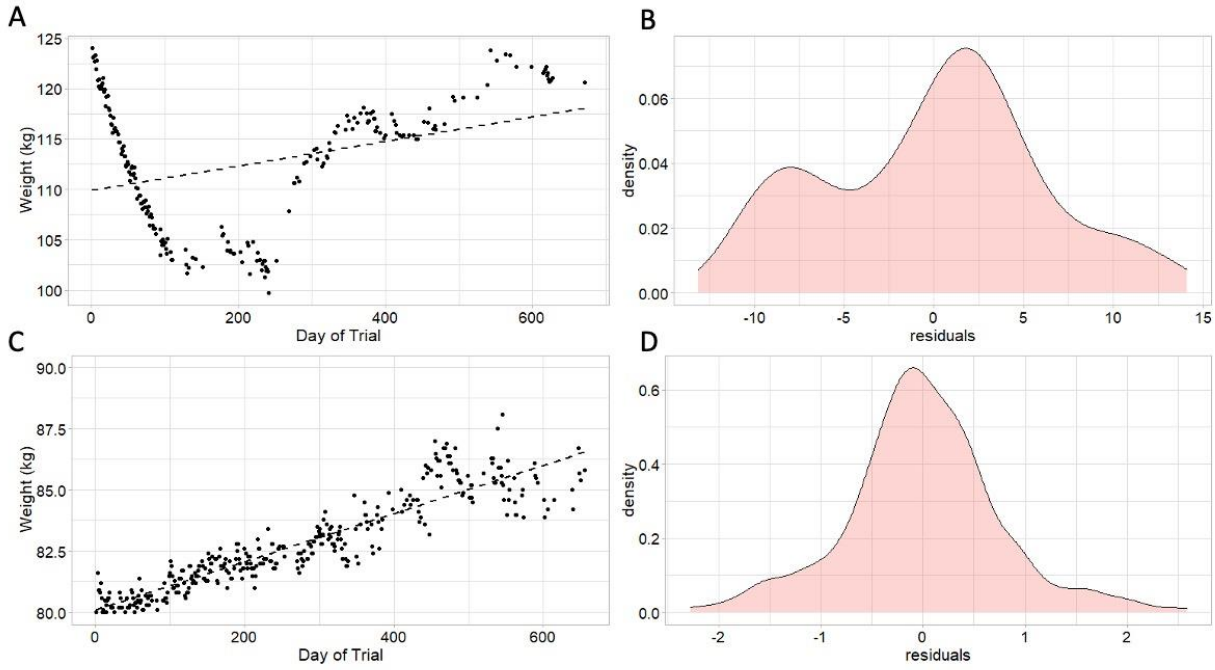


Figure 4.4. *Example data from 2 NoHoW participants with nonlinear (top) and linear (bottom) weight trajectories with a linear trendline fitted to the weight data. Distribution of the residuals from the linear regression are shown on the right graphs*

Importantly, these values were then converted into relative (%) residuals by dividing the residual by the observed data and multiplying by 100. To my knowledge, there is no reference of this step relating to any previous use of the RMSE method in the literature,

however, it is important in bias minimization. If the residuals are left in absolute (kg) then summarised (by mean square error), heavier individuals will naturally have a greater BWV value. This is because large individuals have significantly more mass, in particular fat free mass. Given that fat free mass is comprised of water, glycogen and gut weight which are shown to be the most highly fluctuating compartments of body weight (Bhutani *et al.*, 2017a), these individuals have much more tissue prone to fluctuation. The statistical outcome is that BWV values become correlated with body weight. This collinearity is likely to then confound relationships of interest.

Once the residuals have been converted to percent residuals, a summary value is taken by taking the mean of the residuals, followed by the square root of the mean. The below formula is used for the calculation of RMSE:

$$RMSE = \sqrt{\frac{\sum_{i=1}^{n}(Observed_i - Predicted_i)^2}{n}}$$

Where 'observed' refers to a measured body weight and 'predicted' to the value predicted by the linear regression.

4.3.4 Non-linear Mean Deviation

One limitation of the RMSE method is that it assumes that the trajectory in body weight is linear and calculates the error around the line. However, the limitations of this assumption are highlighted in **figure 4.5B** and **4.5D** which illustrates an individual with a highly non-linear trajectory. To address this, a non-linear regression was fit to the body weight data (see **figure 4.5**). Specifically, a LOESS (locally estimated scatterplot smoothing) regression is fitted to each body weight series. LOESS regression is a non-linear, non-parametric smoothing tool. Due to its non-parametric approach, it does not assume prior specification about the structure of the data, thus allows for visual representation of relationships which do not conform to any structure (Jacoby, 2000). LOESS regressions were fit using the 'stats' package in R (R Core Team, 2019). It employs quadratic polynomial models on a moving collection of data points (termed a "neighbourhood") in a time series (Siangphoe and Wheeler, 2015). The size of the neighbourhood is user-defined and referred to as the "span" of the LOESS model, with greater spans creating more smooth trends because they use a wider collection of surrounding data points, whereas shorter spans result in closer fitting to the data. The span fits data based on the number of available data,

therefore when fitting the loess to data with missingness, the span but be reactive to the number of weight measurements available. In order to address this, we generated a linear relationship between span and number of available data, which results in a similar BWV estimation under varying conditions of missingness. Lastly, a polynomial order of 2 was used in the model based on the non-linearity of body weight data, as suggested previously (Jacoby, 2000).

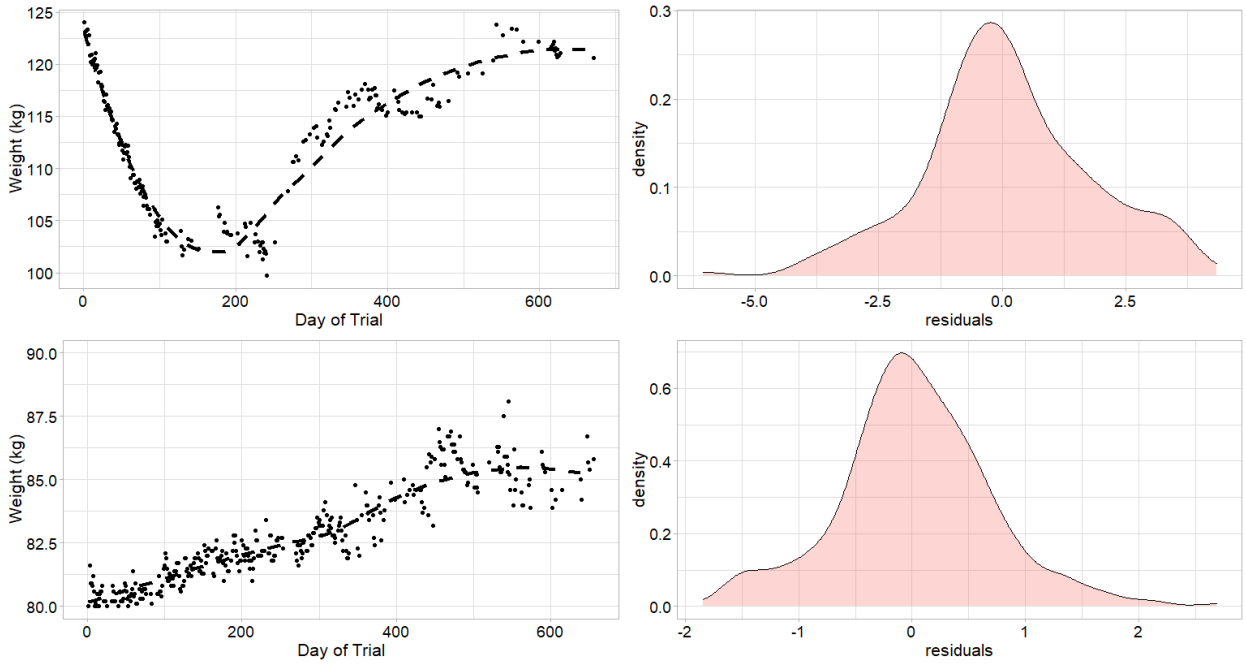


Figure 4.5. *Example data from 2 NoHoW participants with nonlinear (top) and linear (bottom) weight trajectories with a nonlinear trendline fitted to the weight data. Distribution of the residuals from the LOESS regression are shown on the right graphs*

Similar to the RMSE method, the residuals are then calculated by subtracting the observed data from the model predictions and then converted to relative residuals by dividing the residual by the observed data and multiplying by 100. Lastly, a summary value is generated for each participant, by taking the mean of each relative residual. As illustrated in **figure 4.5B**, this generates a substantially different set of residuals in an individual with non-linear trajectory. The result is that RMSE values are more sensitive to larger fluctuations in body weight over longer periods (i.e. weight cycling), where NLMD is more sensitive to smaller day-to-day or week-to-week fluctuations. In the next section, greater detail is provided on the use of and bias associated with each of these methods of BWV in order to fully understand its operationalization before investigating it in rather to other outcomes.

Chapter 5. Estimating Weight Variability Using WiFi-Connected Smart Scales

As highlighted in the previous chapter, traditional estimates of body weight variability (BWV) have been limited by infrequent measurement of weight. Technological advances have recently allowed frequent tracking of body weight but coinciding with these advances are issues relating to data processing and statistical analysis. Indeed, it is of critical importance to minimize biasing estimates of BWV. In particular, researchers may be faced with the questions such as how to remove outliers, whether to impute missing data and the extent to which missing data and imputation of data bias the estimations of BWV. In the following chapter, each of these issues are addressed and guidance is provided. This is done using a comprehensive simulation analysis using thousands of simulated data sets.

The following section is adapted from a manuscript published in the Journal of Medical Internet Research: mHealth and uHealth (Jake Turicchi, O'Driscoll, Finlayson, Duarte, A L Palmeira, *et al.*, 2020). I was solely responsible for the conceptualisation, data analysis and manuscript writing of this publication and adaptation for this chapter. The data used was collected as part of the NoHoW trial (see section 4.1). All other authors on the publication provided minor feedback for manuscript edits.

5.1 Introduction

The impact of weight change on health and other outcomes has been well studied, and dose-response relationships between BMI (or weight change) and health markers have been established (Richard F. Hamman *et al.*, 2006a; Rena R Wing *et al.*, 2011a; Williamson, Bray and Ryan, 2015). This is largely because the study of weight change requires minimal (as little as 2) body weights in order to calculate change. Variability, however, is dependent on several longitudinal body weight measurements and as such, the impact of BWV on health is considerably less well understood. Most studies rely on very infrequent lab measurements (e.g. every 6-12 months) which, as argued previously, is non-representative of true body weight dynamics and therefore is potentially misleading in the study of BWV.

5.1.1 Remote Tracking

Recently, the idea of remote healthcare monitored through a network of internet-connected devices (now termed 'The (Medical) Internet of Things') (Sheth, Jaimini and Yip,

2018; Wu, Wu and Yuce, 2018) has become popularized. In 2020 it is thought that 40% of IoT-related technology is health related, accounting for over $110 billion in market value (Dimitrov, 2016). With this information, precision medicine will become the future of healthcare and frequently tracked body weight data is likely to become a valuable prognostic tool. Already, we have seen incorporation of WiFi-connected smart scales into research environments (Steinberg *et al.*, 2013; Painter *et al.*, 2017; Valle, Deal and Tate, 2017) accompanied by increasing popularity and decreasing costs in the general public. In weight management interventions, 80% and 60% of successful weight loss maintainers report self-weighing weekly or daily respectively (Vanwormer *et al.*, 2008). Regular self-weighing in research environments using tracking technologies will allow for more accurate recognition of body weight patterns which are currently not well understood.

5.1.2 The Problem of Missing Data

The use of data collected via WiFi connected smart scales facilitates collection of data more relevant to the calculation of BWV. However, this data is subject to erroneous values as well as missing data. Erroneous values may arise from inconsistent weighing conditions (e.g. clothed vs unclothed), decalibration of smart scales or other users using the smart scales. Given that self-weighing is a relatively infrequent behaviour (i.e. individuals generally do not self-weigh every day), missing data is common. Generally, missing data is categorized into one of three categories: missing completely at random (MCAR), missing at random (MAR), or not missing at random (NMAR) (Bhaskaran and Smeeth, 2014). Absence of body weight data may have identifiable mechanisms, for example breaks in self-weighing have been shown to be indicative of weight gain (Helander *et al.*, 2014). However, given that these patterns may not be consistent between or within individuals, it is difficult to detect consistent patterns of missing data at group level (i.e. one detectable pattern of missingness in one instance cannot be assumed for all missing data). If there are no clearly identifiable patterns of missingness, data can be described as MAR or MCAR. The difference between MAR and MCAR is that MCAR data has no causes of missingness and is a completely unpredictable process, whereas MAR data is not related to the missing data but may be partially explained by the observed data.

The question of why data is missing is relevant to data imputation. In cases of NMAR where missing data has obvious patterns, these patterns may inform imputation (e.g. if data

is missing during periods of weight gain, this information can be used in the imputation process). In complex behavioural data, it is often hard to detect any reasons for missingness due to differences between and within individuals and the apparent randomness of human behaviour. This makes data imputation less informed.

5.1.3 Data Imputation

Imputation is the process of filling missing data points with values, generally informed by nearby data. It is an approach commonly used in psychological and biological research to maximise data retention, ideally without biasing results. It is crucial to note that both inappropriate removal and inadequate imputation of missing data may bias analyses. Imputation strategies can be grouped by several categories. Firstly, approaches can be univariate or multivariate. In multivariate imputation, relationships between can be drawn between all variables included (e.g. by multiple regression or clustering), and the collinearity between variables helps to inform missing points. For example, in psychology, associations between psychometric variables may be evident in data sets thus information. Assuming there are clear patterns in data, multivariate imputation is generally preferred. Furthermore, it lends itself to more advanced statistical techniques, including machine learning methods such as K-Nearest Neighbours (KNN; (Beretta and Santaniello, 2016)) or random forest (RF; (Tang and Ishwaran, 2017)).

Univariate imputation is often conducted when the single variable is a time series (that is, that each data point represents a consecutive point in time). Univariate time series imputation attempts to differentiate between stochastic and deterministic processes. A purely stochastic process can be described as entirely random, where the previous data do not inform the subsequent data. Conversely, a deterministic process is one in which no randomness is involved in subsequent steps and thus is always entirely predictable by previous data. Of course, almost all time series data are a partially defined by both stochastic and deterministic features.

Body weight data collected by smart scales can be defined as a univariate time series which is largely (but not entirely) stochastic. This makes it particularly difficult to predict missing values or forecast future values. It is possible to consider it a multivariate series by adding additional variables, such as individual characteristics (e.g. age, gender and BMI) or other data relating to time, such as day of the week. However, this relies on these variables

providing information relating to the prediction of missing data values. Recently, research has focused on imputation of time series data collected from physical activity trackers (Borghese *et al.*, 2019; Faust *et al.*, 2019). In our lab, we recently developed an evidence-based protocol for defining minimum data and a data imputation strategy relating to data collected from the Fitbit Aria 2 activity tracker, aimed at minimizing the bias introduced by missingness (R. O'Driscoll *et al.*, 2020). However, no study has considered imputation and bias minimization relating to data collected by WiFi connected smart scales, specifically to the application of BWV.

5.1.4 Objectives

The aims of this section were to:

1. Develop a strategy for removing erroneous data
2. Conduct performance testing on a range of imputation strategies (univariate and multivariate) to inform future imputation of missing data from smart scales;
3. Assess the errors associated with calculation of BWV (by linear and non-linear methods) under conditions of missing data and imputed data.

5.2 Methods

5.2.1 Materials and Subjects

The data was collected as part of the NoHoW trial (detailed in section 4.1). Body weight data was collected using the Fitbit Aria scale (see section 4.1.6.1 for full detail of the measurement tool). To test imputation performance, 50 NoHoW participants with the greatest amount of body weight data in the first 12-months were selected. Selecting those with the greatest fraction of available data allowed for (i) better ability to simulate missingness and impute in the data and (ii) more valid estimation of BWV which can be used to test the agreement with other estimations (in comparison to missing-simulated and complete data). Only 50 individuals were chosen to limit missingness in observed data which increases with sample size. The characteristics of the sample used are shown in **table 5.1**.

Table 1. Participant characteristics

Characteristic	Mean (SD)
Number of participants	50
Gender n (%)	
Male	15 (30.0)
Female	35 (70.0)
Age (years)	49.2 (9.3)
Weight (kg)	81.9 (15.4)
BMI (kg/m^2)	29.3 (6.8)
Weight measurements (n)	336.0 (9.1)

Table 5.1. *Sample characteristics reported as means ad standard deviations*

5.2.2 Analysis overview

All statistical analyses were conducted in R version 3.5.1 (www.r-project.org). All statistical code is uploaded to GitHub (Turicchi, 2020a). A study flow diagram is presented in **figure 5.1.** First, outliers were removed based on limits of physiological plausibility (see section 4.2 for detail). Next, an amputation (data removal) and imputation strategy was used outlined previously (Moritz *et al.*, 2015; Rantou, Karagrigoriou and Vonta, 2017) which involved simulation of missing data by two mechanisms: (1) removal completely at random and (2) removal informed by true patterns of missingness; both followed by imputation using univariate and multivariate methods, and performance testing using root mean square error (RMSE). Next, BWV was calculated in observed (i.e. complete), simulated (i.e. inserted missingness) and imputed data sets. This was done to test the accuracy of BWV estimation under conditions of incrementally missing data, and when missing data was imputed by several methods. Body weight variability was estimated using a linear approach (RMSE) and a non-linear approach (non-linear mean deviation; NLMD). These methods are described in detail in section 4.2. Lastly, the agreement between BWV estimates from observed weight was compared to those generated by simulated and imputed data sets under different amounts of missing data to evaluate bias in BWV estimate under different data conditions.

5.2.3 Data cleaning

Briefly, data cleaning was conducted using a physiological plausibility approach as described in section 4.2.1. This approach is the most conservative method of data cleaning.

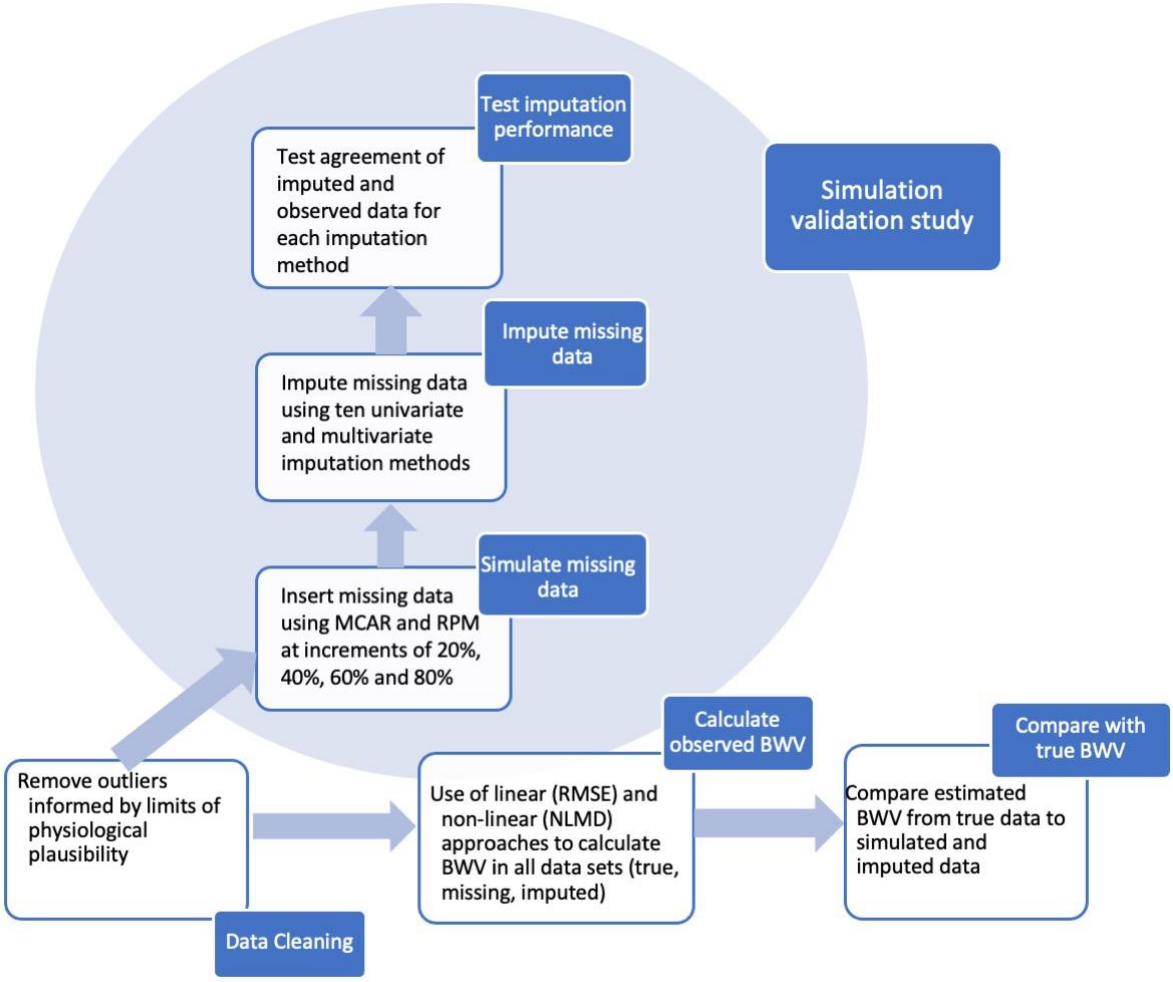


Figure 5.1. *Study flow diagram. Outline of the study detailing the simulation-validation study aimed to test imputation performance and calculating of linear and non-linear body weight variability under conditions of true, missing and imputed data sets with associated comparisons. Abbreviations: NLMD (non-linear mean deviation); RMSE (root mean square error); BWV (body weight variability*

5.2.3 Simulation of Missing Data

In order to test imputation performance, data must first be removed from 'complete' participants. Given that the magnitude of missing data can be drastically different both between and within individuals, data was removed in increments of 20% between 20% and 80%. Firstly, an examination of whether any non-random processes could be identified in the complete NoHoW weight data set using the TestMCARNormality

function from the MissMech package (Jamshidian, Jalal and Jansen, 2014) was conducted. The test returned that, at group level, the missing data was deemed to be MCAR. Indeed, it is likely that there are some mechanisms for missing data but given the inconsistency between and within individuals it is not appropriate to apply these mechanisms to the entire data set.

In the 50-participant sample, data was removed in increments of 20%, 40%, 60% and 80% using an MCAR method in the ImposeMissing function of the simsem package (Terrence Jorgensen, 2018). For each participant, missing data was randomly simulated for each increment 20 times, resulting in 4,000 simulated data (50 participants * 4 levels of missingness * 20 random simulations) sets with varying amounts of missing data. To address the concern that missing body weight data may not be truly MCAR, 20 random participants (for each increment of missingness) were selected from our entire NoHoW study sample of 1,627 individuals with approximately 20%, 40%, 60% and 80% missing data and imposed these missing patterns on our 50-participant sample (with near-complete data), resulting in 4,000 simulated data sets with real patterns of missing (RPM) data. This gave us equal numbers of both random and non-random simulated data sets.

5.2.4 Imputation

Seven univariate and three multivariate imputation algorithms were run on all simulated data sets. Univariate methods included: linear interpolation, cubic spline interpolation, Stine interpolation, exponentially weighted moving average (EWMA), structural modelling with Kalman smoothing (SMKS) and ARIMA state-space representation and Kalman smoothing (ASSRKS) from the impute TimeSeries package (Moritz and Bartz-Beielstein, 2017) and an approach using Friedman's super smoother on non-seasonal data or seasonal decomposition on seasonal data followed by interpolation (TsClean) from the forecast package (Hyndman *et al.*, 2019). Multivariate imputation techniques, namely two machine learning techniques: a K-nearest neighbours method from the DMwR package (Torgo, 2013) and a random forest method from the MissForest package (Stekhoven and Buhlmann, 2012); and a regression-based technique using predictive means matching (PMM) from the Multivariate Imputation by Chained Equations (MICE) package (Buuren, S. van, 2010). All imputation methods are described in **table 5.2**. To maximise the usability of

these methods where further information on participants is not available, only day number and day of the week were used as predictive variables for multivariate imputation.

Table 5.2. Description of time series imputation methods used

Method	Description
Linear interpolation	This method looks for a straight line that passes between two values (X_a and X_b), where the imputed values are bound between X_a and X_b. It has been demonstrated to be efficient when predicting values with constant rate of change [44], however tends to smooth data rather than impute variability.
Spline interpolation	This method fits local polynomial functions which are connected at each end to form a spline, creating a succession of cubic splines over successive intervals of the data [45]. The order of the polynomial is can be defined manually. The approach benefits from its non-linear approach, however its ability to predict oscillations from univariate data is limited [46]
Stine interpolation	This method as an advanced interpolation method where interpolation occurs based on (a) whether values of the ordinates of the specified points change monotonically and (b) the slopes of the line segments joining the specified points change monotonically. It produces a smoothed imputation known to be robust against sporadic outliers and performs better than spline interpolations where abrupt changes are observed [47].
Exponentially weighted moving average (EWMA)	This approach calculates the exponentially weighted moving average (EWMA) by assigning the value of the moving average window, which is user defined, the mean thereafter is calculated from equal number of observations on either side of a central missing value. The weighting factors decrease exponentially the greater distance from the missing value.
Structural modelling with Kalman smoothing (SMKS)	This method aims to identify the structure (trend, seasonality and error) in a time series. Unlike ARIMA state-space approaches where each component is eliminated, these components are used to inform imputation of missing data. Kalman filter and smoothing works in two steps to (1) produce estimates of the current state variables, along with their uncertainties and (2) update estimates using a moving average to give a smoothing effect [48]. The Kalman smoother is given the entire sample and is not locally weighted. The Kalman smoother is robust to disparate observation periods (e.g. when observations are made weekly and monthly in one time series) [49].
ARIMA state-space representation and Kalman smoothing (ASSRKS)	This method converts the time series to an ARIMA model by decomposing the trend, seasonality and error through a differencing protocol, resulting in a stationary time series where means and covariances would remain invariant over time [31]. Next, a Kalman smoother is applied as above.

TsClean [40]	This method first assesses evidence of seasonality. If present, a robust STL decomposition for seasonal series is conducted followed by linear interpolation. If no seasonality is present, Friedman's super smoother [50] is applied followed by linear interpolation.
K Nearest Neighbours (KNN) [41]	For every observation to be imputed, this algorithm locates 'k' closest observations based on the Euclidean distance [51] and computes the weighted average (weighted based on distance) of these 'k' obs.
Random Forest (RF) [42]	This method is an extension of typical classification and regression which generates predictive models that recursively subdivide the data based on values of the predictor variables. It does not rely on parametric assumptions and can accommodate non-linear interactions, though may be prone to overfitting [51].
Predictive means matching (PMM) [43]	For each missing entry, this method generates a small set of candidate donors from all complete cases that have predicted values closest to the predicted value for the missing entry. One donor is randomly drawn from the candidates, and the observed value of the donor is taken to replace the missing value. The assumption is the distribution of the missing cell is the same as the observed data of the candidate donors.

[Table 5.2. *Brief description of all univariate and multivariate imputation algorithm used in the imputation of body weight data collected from smart scales*]

5.2.4 Calculation of Body Weight Variability

Body weight variability was calculated using the RMSE and NLMD methods described in section 4.2. Importantly, BWV was calculated on the true/observed data (this data is near-complete), as well as data sets with simulated missing data and imputed data. This allowed us to examine the errors associated with linear and non-linear BWV estimates under differing conditions of missingness and imputation.

5.3 Results

5.3.1 Imputation Performance

All imputation algorithms were run on every simulated data set, generating 28,000 and 12,000 imputed data sets from MCAR and RPM simulations respectively (4,000 imputed data sets per imputation method). The performance of each imputed data set in comparison

to the observed weight data was evaluated using RMSE which is a commonly used for performance evaluation (Moritz *et al.*, 2015). Results for RMSE is shown in **figures 5.2**.

Errors increased with greater amounts of missing data. SMKS, EWMA, Linear interpolation and Stine interpolation were similar in performance and showed the lowest error respectively. Example of imputation of 80% missing data is illustrated in **figures 5.3A-D** respectively. Machine-learning based methods (RF and KNN) generally performed worse than univariate methods, as did the regression-based multivariate method PMM. The ASSRKS method showed the greatest error, followed by Stine interpolation. Imputation of MCAR-simulated data sets generally showed lower errors than RPM-simulated data sets.

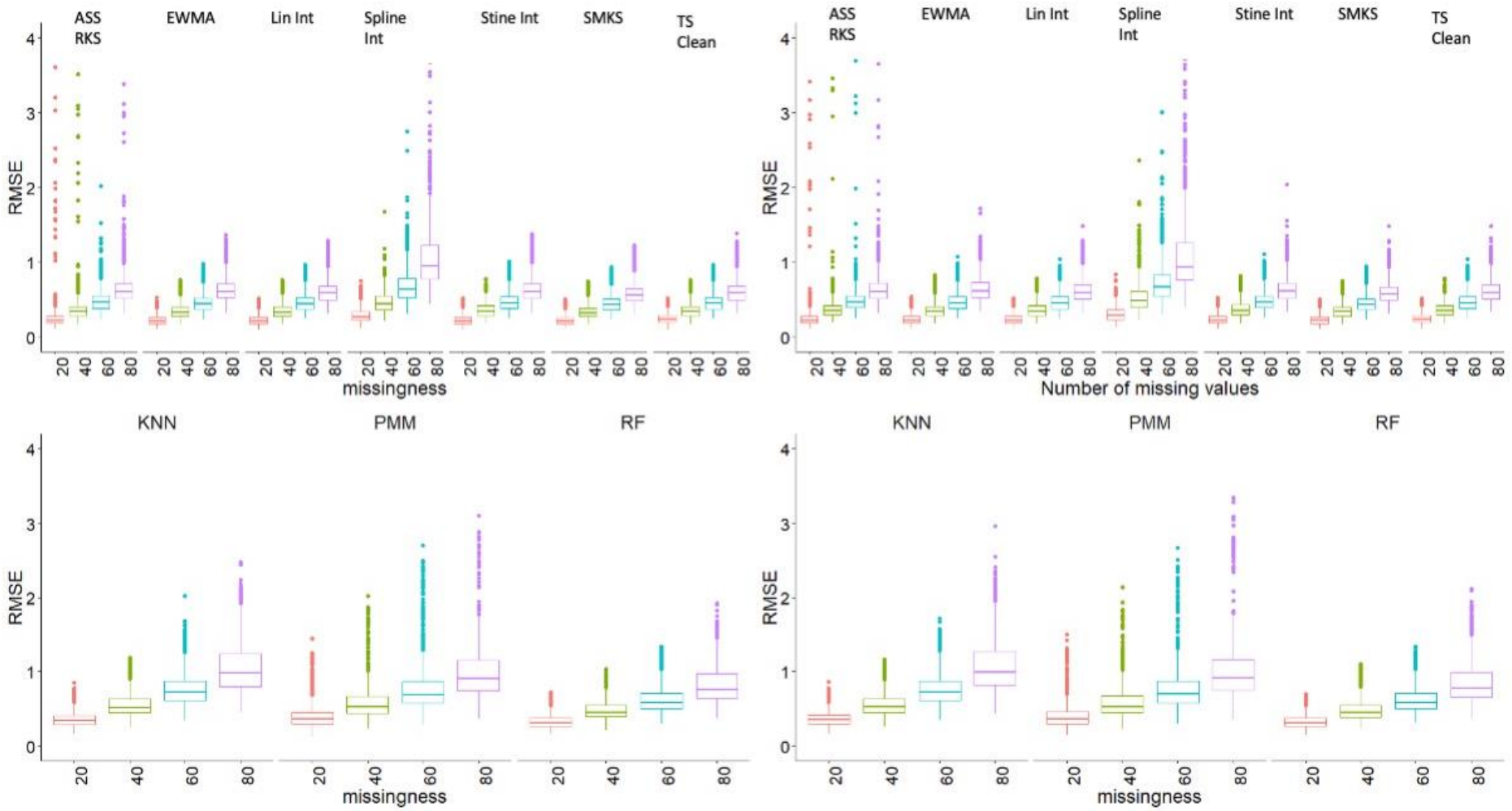
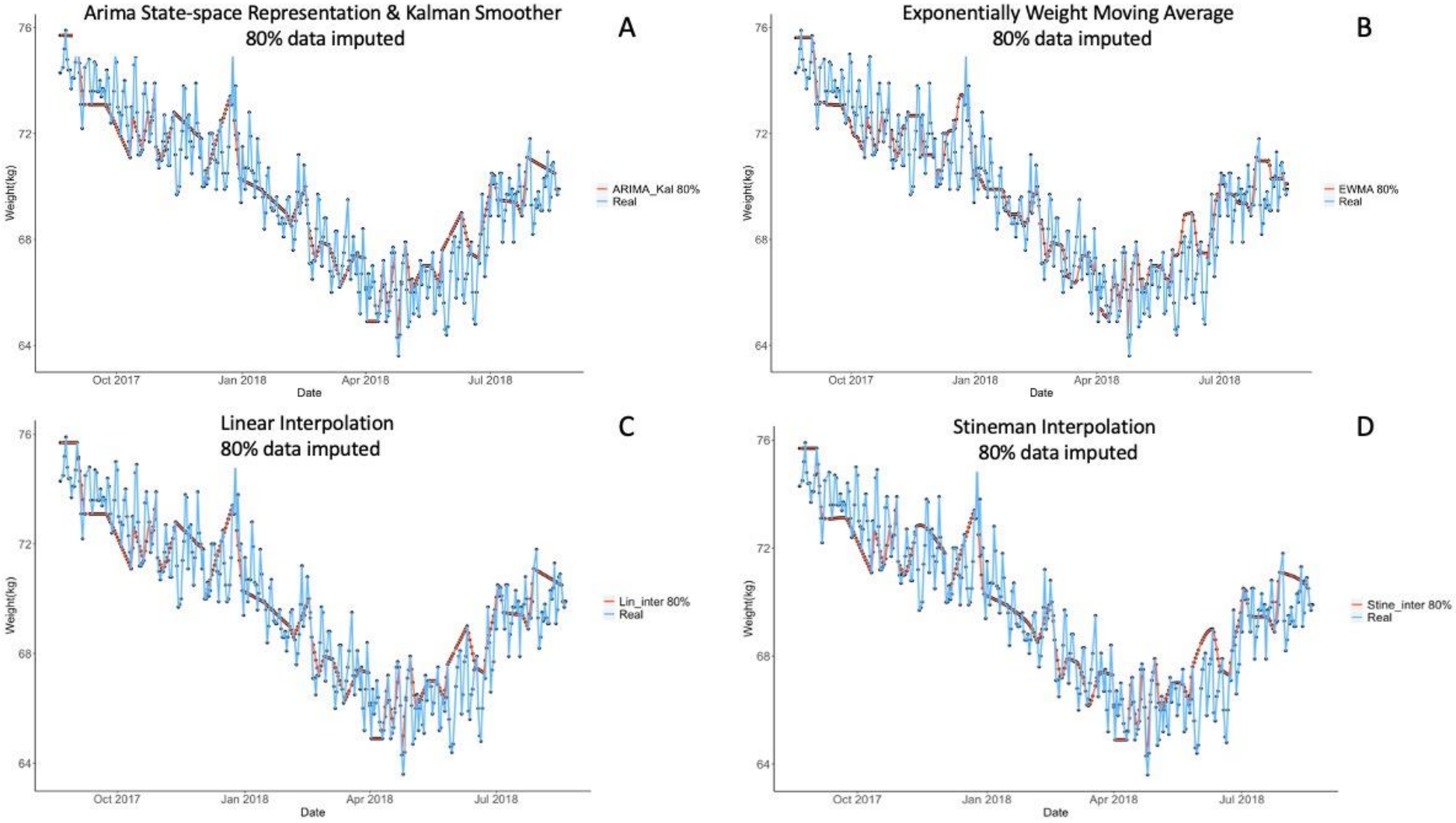


Figure 5.2. *Performance summaries of univariate and multivariate imputation. Caption: Boxplots of the errors associated with imputation of body weight data collected by smart scales. Data was removed by an MCAR (missing completely at random) algorithm (left plots) and also informed by real patterns of*

missingness (right plots) in increments of 20%, 40%, 60% and 80%. Imputation was done by 7 univariate methods (top plots) and 3 multivariate methods (bottom plots). Root mean square error (RMSE) was used as the performance metric. ASSRKS (ARIMA state-space representation and Kalman smoothing); EWMA (Exponentially weighted moving average); Lin Int (linear interpolation); Spline int (Spline interpolation); Stine int (Stine interpolation); KNN (K-Nearest neighbours); PMM (Predictive means matching); RF (random forest); SMKS (Structural modelling with Kalman smoothing); RMSE (Root mean square error)

5.3.2 Errors in Body Weight Variability Estimates

Next, agreement between BWV estimations from observed datasets and simulated/imputed data sets was investigated for each participant. Data sets simulated by MCAR and RPM were collapsed for the present purpose. For simulated data sets, the errors were minimal, averaging 7% and 3.2% disagreement between the true WV estimates and estimates made on 80% missing data for non-linear and linear methods respectively. At 60%, 40% and 20% missing data, errors were 2.3% and 0.6%; 1.3% and 0.4% and 0.4% and 0.2% for non-linear and linear WV estimates respectively, compared to true estimates. Full results can be viewed in **table 5.3**. When data was imputed, imputation introduced substantial errors (summarised in **figure 5.4).** For most methods, imputation resulted in underestimation of BWV, apart from Stine imputation, which overestimated BWV. Biases increased with missingness and were generally greater for NLMD than RMSE. The magnitude of error in imputed data sets was greater than when data was left missing.



[**Figure 5.3.** *Data from 1 random example participant from the NoHoW study. Graphs show examples of imputation of 80% body weight data where blue shows the true data and red shows the imputed data once 80% has been removed and reintroduced*]

Table 5.3: Impact of missing data and data imputation on estimation of body weight variability

		Imputation method (mean % error (se))										
WV	Missing-ness	None	ASSRKS	EWMA	Linear Int	Spline Int	Stine Int	SMKS	TS Clean	KNN	RF	PMM
NLMD	20	-0.4 (0.1)	-5.5 (0.3)	-7.3 (0.1)	-4.1 (0.1)	6.4 (0.2)	-2.8 (0.1)	-9.3 (0.1)	-4.8 (0.1)	-6.9 (0.1)	-12.3 (0.2)	-7.5 (0.2)
RMSE	20	-0.2 (0.1)	-0.5 (0.3)	-2.3 (0.1)	-1.1 (0.1)	4.8 (0.2)	-0.6 (0.1)	-3 (0.1)	-2 (0.1)	-3.4 (0.1)	-6.9 (0.1)	-8.2 (0.1)
NLMD	40	-1.3 (0.1)	-11.2 (0.4)	-12.9 (0.1)	-8.7 (0.1)	8.9 (0.2)	-6.2 (0.1)	-20.3 (0.3)	-9.7 (0.1)	-10.2 (0.2)	-24.8 (0.3)	-14.4 (0.4)
RMSE	40	-0.4 (0.1)	-2.2 (0.4)	-4.3 (0.1)	-2.8 (0.1)	6.4 (0.2)	-1.9 (0.1)	-6.6 (0.2)	-3.9 (0.1)	-6.6 (0.1)	-13.7 (0.2)	-16.8 (0.2)
NLMD	60	-2.3 (0.1)	-16.6 (0.6)	-16.7 (0.2)	-14.6 (0.2)	13.2 (0.2)	-10.2 (0.2)	-37.7 (0.5)	-16 (0.2)	-8.2 (0.3)	-39.1 (0.5)	-22.1 (0.6)
RMSE	60	-0.6 (0.1)	-3.2 (0.5)	-5.5 (0.2)	-4.7 (0.1)	9.1 (0.2)	-3.3 (0.1)	-11.4 (0.3)	-6 (0.2)	-10.2 (0.2)	-22.7 (0.3)	-29.3 (0.4)
NLMD	80	-7 (0.2)	-27.1 (1)	-18.7 (0.3)	-30.3 (0.4)	20.3 (0.4)	-20.6 (0.3)	-84.9 (1.4)	-34.4 (0.5)	1.9 (0.5)	-49.4 (0.8)	-29.5 (0.8)
RMSE	80	-3.2 (0.2)	-3.5 (0.7)	-6.3 (0.2)	-9.6 (0.3)	15.2 (0.4)	-6.7 (0.2)	-23.1 (0.6)	-11.6 (0.3)	-16.9 (0.4)	-38.7 (0.5)	-51.7 (0.6)

Table 5.3. *Mean deviation (%) between true weight variability estimates from observed data and that estimated from simulated and imputed data sets. Performance is reported as root mean square error (standard error). Ten imputation strategies are reported. Abbreviations: NLMD (non-linear mean deviation); RMSE (root mean square error); Int (interpolation); ASSRKS (ARIMA state-space representation and Kalman smoothing); EWMA (Exponentially weighted moving average); KNN (K-Nearest neighbours); PMM (Predictive means matching); RF (random forest); SMKS (Structural modelling with Kalman smoothing); RMSE (Root mean square error).*

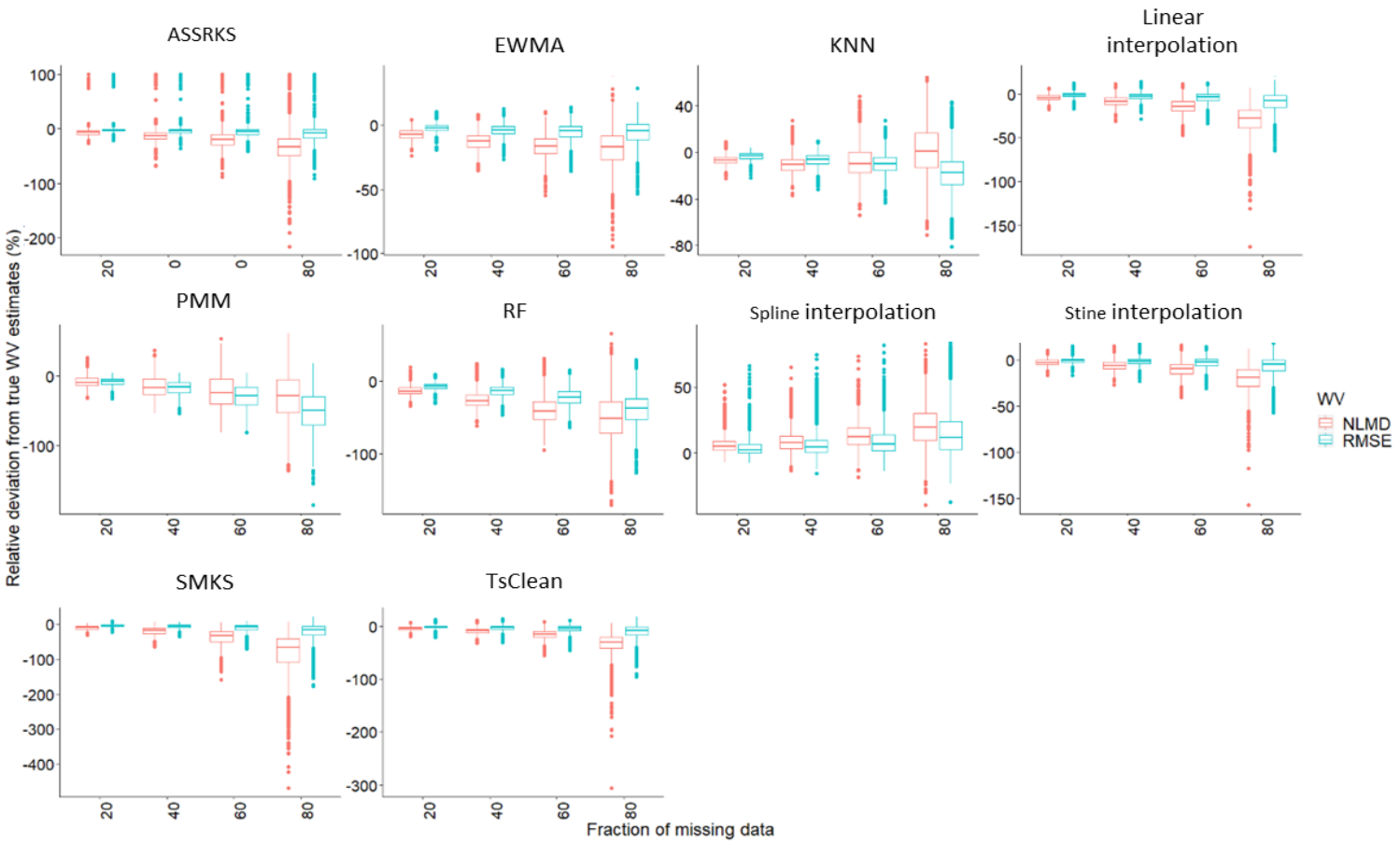


Figure 5.4. *Influence of data imputation on linear and non-linear body weight variability estimates. Caption: Boxplots of the relative errors associated with calculation of body weight variability in body weight data collected by smart scales when using 10 different imputation methods imputing data in increments of 20%, 40%, 60% and 80%. Errors represent the deviation from estimates made from observed data sets. Abbreviations: NLMD (non-linear mean deviation); RMSE (root mean square error), ASSRKS (ARIMA state-space representation and Kalman smoothing); EWMA (Exponentially weighted moving average); KNN (K-Nearest neighbours); PMM (Predictive means matching); RF (random forest); SMKS (Structural modelling with Kalman smoothing*

5.4 Discussion

The present investigation aimed to assess the ability to impute body weight data and examine the biases associated with BWV estimates under conditions of missing data (ranging between 20-80% in increments of 20%) and following data imputation by all methods. Overall, it was found that structural modelling with Kalman smoothing, exponentially weighted moving average and linear interpolation performed imputation best. These methods are available to researchers through many statistical packages (e.g. (Moritz and Bartz-Beielstein, 2017)). For the purposes of estimating BWV, leaving data as missing did not introduce significant bias (only 3-7% error with >80% data missing), whereas calculating BWV on imputed data is prone to significant underestimation and should be avoided.

5.4.1 Imputation Performance

Seven univariate and 3 multivariate approaches to imputation were employed. Since access to further individual-level information (e.g. participant characteristics or behavioural patterns and psychological traits) may be unavailable in many environments, body weight data collected by smart scales is likely to be treated as univariate and as such, use of more advanced approaches to multivariate imputation such as tree-based models, neural networks and KNN methods is limited. Nevertheless, use of multivariate imputation algorithms using a limited number of additional variables (day of trial and day of the week) was conducted to test if machine learning algorithms provided additional advantages. These were chosen as predictive variables as these can be automatically collected in free-living environments without any participant burden. Within-week (e.g. weekday vs weekend) fluctuations in body weight have been shown previously (Racette *et al.*, 2008; Orsama *et al.*, 2014; Helander *et al.*, 2015), characterised by weekend weight gain and weekday weight loss, and therefore day of the week may potentially have predictive value in imputation. However, it was found that these methods, in the current circumstances, did not outperform simple univariate methods such as SMKS or EWMA. Indeed, machine learning methods may perform better when trained on large, complete data sets and then applied to missing data but in the present analysis there was not enough complete data sets to train

machine learning imputation models and the variables used in multivariate imputation was limited to improve accessibility and usability.

Overall, no imputation strategy was able to accurately predict the variability in body weight. It was observed that imputation generally reverts towards the mean trend in a linear fashion (see **figure 5.3** for an illustration). As discussed earlier, it is likely that weight variability is a highly stochastic (unpredictable) process which explains why missing data cannot be well predicted and reversion towards the mean performs best. In contrast, weight change or trend is more determinable (i.e. if an individual has lost weight for the past 4 weeks, the probability is that they will continue losing weight in the next week). As the amount of missing data increases, the more a reversion towards the mean weight is evident (in **figure 5.3**, 80% of data was removed and imputed).

5.4.2 Validation of Body Weight Variability Estimates Under Different Conditions

The implication is that BWV values calculated from imputed data sets show considerable underestimation. When 80% of data was missing, underestimations in NLMD calculation compared to true values ranged from -18.7% to -84.9% for EWMA and SMKS imputation methods respectively, compared to -7% when 80% of the data was left as missing. For RMSE, underestimations generated from 80% imputed data sets were reduced, ranging from -3.5% to -51.7% for ASSRKS and PMM respectively, compared to -3.2% when data was left missing. Only in the case of ASSRKS was the error similar to when data was missing. Importantly, while 80% missing data seems substantial, this would be typical of an individual self-weighing 1-2 times per week. From this analysis, it was deduced that in the subsequent investigations into BWV, imputation would not be conducted in data preprocessing. Importantly, this result may inform future calculations of BWV in studies collecting data using smart scales, which is likely to be the future route forward for these kinds of investigations.

5.4.3 Strengths and Limitations

The present study had several strengths. First, the data processing methods were developed from true, rather than simulated data, thus increasing the validity of the analysis. Our simulation-imputation analysis was comprehensive, including generation 8,000 simulated data sets in total with varying levels of missingness using both random (MCAR)

and real-missingness (RPM) informed simulations which resulted in 80,000 imputed data sets produced using 10 univariate and multivariate algorithms. Next, both linear and non-linear approaches to estimating BWV were described and compared under different conditions of missingness and the errors produced in the common case of missing data were reported, which informs the magnitude of errors expected from missing data estimations in future studies. Some limitations should also be addressed. First, all imputation methods were deterministic, though body weight seems to be a relatively stochastic (i.e. randomly determined) process. The resultant effect is that imputation may reduce the variability by attempting to recognise predictive patterns which are not there. As recommended, consideration should be given as to whether imputation is necessary. In some analyses, including instances which employ machine learning algorithms, complete data is a necessity and therefore imputation is required. Next, there was not entirely complete data by which to test imputation, it was deemed sufficient to use real rather than simulated data for external validity.

5.5 Conclusions

To conclude, based on a comprehensive review of the literature (chapter 3) it was clear that BWV potentially represents i) a significant health risk and ii) a prognostic tool - yet it is currently not well understood nor well measured. In the present study, the ability to impute body weight data was assessed, concluding that the variability component is highly stochastic and unpredictable, and the best performing imputation strategies are therefore those which revert towards the average weight, such as structural modelling with Kalman smoother and linear interpolation methods. The errors associated with BWV estimates under varying levels of missing data were reported, concluding that errors are small when using both linear and non-linear methods even under high proportions of missingness (80%). Calculating BWV following imputation generally resulted in significant underestimations and is strongly not recommended. Together, these results will inform the future study of BWV using data collected from smart scales.

Chapter 6. Weekly, Seasonal and Holiday Body Weight Fluctuations

In the previous chapter, the mostly stochastic nature of variability in body weight was discussed. However, it is likely that there is also a predictable component which relates to temporal factors, such as the day of the week or season of the year, which are termed 'fluctuations'. In the following section, body weight fluctuation patterns are described within a week, a year, and in response to holiday periods, based on previous literature suggesting that energy balance behaviours are modified in response to time and in addition by group according to characteristics and location.

The below chapter is adapted from a publication in PLOS One (Jake Turicchi, Ruairi O'Driscoll, Horgan, Duarte, Antonio L. Palmeira, Larsen, *et al.*, 2020). I was solely responsible for conceptualisation of the present study, data analysis and primary manuscript writing. All other authors of the publication reviewed the manuscript.

6.1 Introduction

6.1.1 Body Weight Stability Over the Long Term

In his 1927 paper, Dubois wrote that "there is no stranger phenomenon than the maintenance of a constant body weight under marked variation in bodily activity and food consumption" (Dubois, 1927). More recently, this phenomenon has been well studied: in humans, energy intake and energy expenditure appears to be extraordinarily well matched over periods of years; evidenced for example by the data from the UK Department of Health providing that average weight gain in the UK was estimated at ~6.7kg at population level over 10 years between 2000 and 2010, corresponding to an average daily caloric surplus of +25kcal/day (Speakman *et al.*, 2011). These and similarly cited figures arising from computational models of body weight which account for the efficiency of energy transformations and the energy expenditure of the deposited tissue (Westerterp *et al.*, 1995; Speakman, Stubbs and Mercer, 2002; Hall, 2010; Speakman *et al.*, 2011) all show a very small discrepancies in energy balance over long periods. The determinants of regulation of body weight have been discussed earlier (see section 1.1.1 for a commentary on body weight regulation and section 1.3 for a commentary on the asymmetry of this regulation).

6.1.2 Body Weight Homeostasis Over the Short Term

In the short term, energy balance (thus body weight) appears to be considerably less stable, and indeed fluctuations in region of 1-3kg over a 2-week period have been reported in free living adults who provided repeated measurements of body composition (Bhutani *et al.*, 2017a). Two reasons contribute to this observation: firstly, of this 1-3kg reported, ~84% was attributed to change in FFM compartments of no energy value (water, glycogen and gut weight) and second, energy intake and expenditure have not been shown to be matched shorter time periods (Chow and Hall, 2014). In data adapted from an exemplary participant of the Belsville dietary intake study (Kim *et al.*, 1984) over one year, Chow and Hall demonstrate the remarkable variability in energy intake at individual level (see **figure 6.1**). Energy expenditure, as shown, tends to be less modifiable, particularly in environments which are not free living. Other mathematical models of human energy balance also expect large day-to-day fluctuations in energy intake which (in the long term) may not necessarily affect weight in the long term (Payne and Dugdale, 1977; Horgan, 2011), though other authors argue that variability in weight or intake may potentially be an early predictor of later weight gain (Rosenbaum *et al.*, 2016; Feig and Lowe, 2017; Benson *et al.*, 2020).

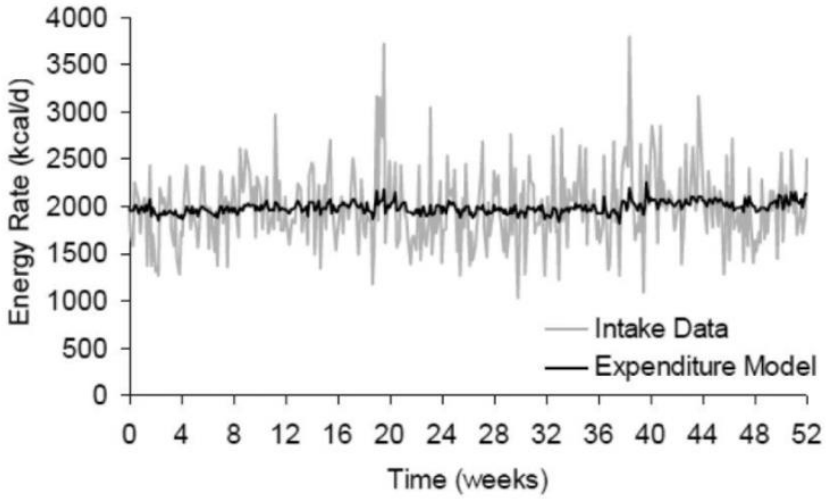


Figure 6.1. *Variability in energy intake and energy expenditure over 1 year in an example participant from the Bellsville dietary intake study, adapted from Chow and Hall 2014*

Importantly, it is likely that these acute (i.e. within week/month) fluctuations occur continuously over long periods. Indeed, this is possible without having a significant effect on long-term weight change. In chapter 3, it was concluded from a comprehensive review of

the evidence that body weight variability (BWV) appears to be a risk factor for disease and mortality. Therefore, understanding the deterministic processes aetiology of BWV is an important step in understanding its role in health.

6.1.3 Temporality, Energy Balance Behaviours and Body Weight

Human behaviour is greatly influence by environmental factors, and this extends to the temporal environment which includes the time of the day, day of the week, time of the month and year. While many of these temporal cycles are essentially a man-made concept, they have considerable impact on the way in which humans live. Considerable epidemiological evidence exists showing within-week pattens of energy intake characterised by increased energy density at the weekend (often driven by increased consumption of processed and fast foods) (An, 2016; Jahns *et al.*, 2017; Czlapka-Matyasik *et al.*, 2018), accompanied by substantial increases in alcohol consumption (Room *et al.*, 2012). The effect of the weekly cycle on physical activity is less consistent, with some studies showing increased (Young *et al.*, 2009; Drenowatz *et al.*, 2016), or decreased (Evenson *et al.*, 2015; Sigmundová *et al.*, 2016) activity at weekends. Weekly fluctuations in body weight have been shown in small samples over short periods, including samples in Europe (Orsama *et al.*, 2014; Helander *et al.*, 2015) and North America (Racette *et al.*, 2008). Nonetheless, these observations are often made using data collected by self-report or lab-based measured and little evidence of body weight fluctuations using home Wi-Fi connected smart scales exists.

Seasonality has also been implicated in modification of energy balance behaviours though the evidence is sparse. Some studies have shown increases in energy intake and decreases in physical activity in winter and autumn months (Ma *et al.*, 2006; Crane *et al.*, 2019). In one study in 156,911 women participating in the Women's Health Initiative, an alternate healthy eating index (calculated using FFQ data) showed that healthy eating was greatest in spring, summer and autumn, though the differences were minimal. In contrast, one study in 9,701 Dutch males and females showed diet quality (a cumulative score assessed as an aggregate of different health and unhealthy food groups collected by FFQ) to be greatest in winter (van der Toorn *et al.*, 2020), and that this increase was greater in those of a higher socio-economic level. Furthermore, there is little evidence on seasonality effects on body weight, but some studies have shown greatest body weight at winter (Fortenberry, 2012; Fahey, Klesges, Kocak, Talcott, *et al.*, 2019a), a pattern that has been shown in both

Northern and Southern hemispheres in a large sample (Mehrang *et al.*, 2016a). Nonetheless, the magnitude of weight reported to fluctuate between seasons is miniscule (usually <1% body weight (Mehrang *et al.*, 2016b; Fahey, Klesges, Kocak, Talcott, *et al.*, 2019a)), and the individuals or groups more prone to these patterns are unexplored.

Another temporal cue for weight change is holiday periods (in particular the Christmas period which will remain the focus from here on). Reported behavioural responses to Christmas include increases in energy and fat intake (Yanovski *et al.*, 2000; Stevenson *et al.*, 2013) in addition to decreases in physical activity and increased sedentary behavior (Phelan *et al.*, 2008). Considerable evidence stemming from reviews (DA, 2014; Díaz-Zavala *et al.*, 2017) of this phenomenon report weight gains in response to the holiday period in the magnitude of 0.2-2.3kg (Yanovski *et al.*, 2000; Díaz-Zavala *et al.*, 2017). Furthermore, this acute weight gain has been implicated in the aetiology of longer-term weight gain and obesity development, as complete compensation for weight gain may never occur (DA, 2014). It is likely that this response varies between populations or different groups of individuals, though this has not yet been explored.

6.1.4 Individual Characteristics and Energy Balance Behaviours

The above evidence is in favor of a behavioural response to temporal cycles. However, the extent to which different individuals are susceptible to this temporal environmemt is unclear. For example, factors such as geographical region may modify responses to weekly, seasonal or holiday cues due to differences in weather/climate, culture or tradition/region. For example, in one study, individuals in Japan showed considerably less weight gain over the Christmas period than those in Germany (and, less so, the United States) (Helander, Wansink and Chieh, 2016). It is suggested that elderly individuals are less prone to binging behaviours than younger groups (Guerdjikova *et al.*, 2012) and therefore may be less likely to experience weekend (or holiday) weight gain which is often due to a change in eating behaviours (specifically, increased energy intake). Individuals with a greater BMI may be more prone to greater weight gain during periods where there is risk of acute weight gain than their lower BMI counterparts, which is consistent with the hypothesis that acute (i.e. holiday) weight gain is partially responsible for longer-term weight gain (DA, 2014). Furthermore, due to differences in eating and activity behaviours between sexes, males and females may potentially have comparatively different behavioural responses to

the temporal environment. Indeed, these differences may be reflected by group differences in weight. Despite the fact it is simple to collect data on these characteristics, no study has examined differences in weekly, seasonal and holiday weight fluctuation patterns between different regions, sexes or age and BMI groups.

6.1.5 Measurement of Weight Fluctuation

Previous studies reporting on body weight fluctuations have been limited in their ability to make frequent measurements of body weight. This often results in (a) using infrequent weight measurements (such as before and after Christmas (Wagner, Larson and Wengreen, 2012; Stevenson *et al.*, 2013) or infrequently across seasons (Fortenberry, 2012)) or (b) use of self-reported weights which may be prone to further biases. Furthermore, most studies fail to account for the overall trend in body weight. For example, if an individual shows an approximate weight gain of 10kg over 40 weeks, then body weight will (on average) be ~0.25kg greater at the end of every week than at the start of the week. This weight change has the potential to confound the appropriate identification of fluctuations independent of the trend in body weight and appropriate time series approaches must be taken to minimize this confound (discussed in section 4.2.2 and later in the methods section). Together, these previous methodological limitations limit our current understanding of body weight fluctuation patterns over different time periods. Given that there is reasonable rationale to study instability in body weight (see chapter 3 for a comprehensive review), greater understanding of these body weight patterns are required.

6.1.5 Objectives

Using data collected as part of the NoHoW project (described in section 4.1), the aims of this section were twofold:

4. To describe temporal fluctuations in body weight within a week, between seasons and over the holiday period
5. Test how these patterns varied between different groups of individuals (based on age, gender, BMI and country)

6.2 Methods

6.2.1 Study Design & Participants

The present study was an exploratory ad hoc analysis using data collected as part of the NoHoW study. The design of the study in relation to the randomized control trial structure and intervention has been described in full in section 4.1.

6.2.2 Participants

For detailed information on the inclusion and exclusion criteria for recruitment to the NoHoW trial, see section 4.1.4.1. Importantly, all participants were adult recent weight losers who had lost ≥5% body weight in the 12-months prior to recruitment, recruited at 3 centres in UK, Denmark and Portugal.

Firstly, for inclusion in all present analyses, participants must have provided at least 20 weight measurements in one year. Additionally, for inclusion in the weekly analysis, at least one weight reading was required on each day of the week. For inclusion in the seasonal analysis, at least 5 weights were required in each season of the year. Seasons were defined as follows: Spring (20th March – 20th June); Summer (21st June – 22nd September), Autumn (23rd September – 20th December) and Winter (21st December – 19th March) based on astronomical dates for solstice and equinox occurrence in year 2019. For inclusion in the Christmas analysis, at least 4 weights were required in the 30 days prior to and after Christmas (defined as the 25th of December). These minimum criteria were designed to improve the accuracy of statistical smoothing as suggested previously (Mehrang *et al.*, 2016b) and also demonstrated previously by our group (Jake Turicchi, O'Driscoll, Finlayson, Duarte, A L Palmeira, *et al.*, 2020). Inclusion in one sample did not affect inclusion in another.

6.2.3 Anthropometrics Measurements

On the initial visit, body weight and height were measured using the SECA 704s combined stadiometer and electronic scale in a fasted state, first thing in the morning, in light clothing. From this, BMI was calculated [BMI=(body weight (kg))/(height $(m)^2$].

6.2.4 Fitbit Aria Scale

The body weight data collected for this analysis was collected from the Fitbit Aria scale. The device is described fully in section 4.1.6.1. The data was collected for up to 2 years (where consent was available).

6.2.5 Statistical Analysis

Three sub-samples were generated based on meeting eligibility criteria (noted above) for each analysis (i.e. for weekly, Christmas and seasonal analyses). Participant characteristics are provided as mean (standard error) or relative percentages (where specified) in **table 6.1** and scale use is described as completeness of data per day of the week and month of the year relative the amount of data possible for the given day or month in **figure 6.2**. Change in scale use per week over 2 years was illustrated as mean (standard error) number of weights per week for each week in all participants from the entire sample. Body weight data was initially screened for outliers based on physiological plausibility of weight change as described in section 4.2.1.

In all analyses, each individual's body weight data was converted to a time-series and decomposed to remove the trend element (i.e. detrended). This process is described in detail in section 4.2.4. Briefly, detrending refers specifically to the process of removing the overall trajectory of the time series thus centering the body weight and leaving the variability component. Detrending of body weight data was conducted to account for the potentially confounding effect of weight change on patterns of variability as suggested previously (Orsama *et al.*, 2014; Mehrang *et al.*, 2016b). For weekly and Christmas analyses, the body weight data was detrended by fitting a locally estimated scatterplot smoothing (LOESS) regression to each participant. LOESS regression was chosen to account for the non-linearity of weight change, allowing recognition of weekly and Christmas patterns independent of the trend.

To identify seasonal patterns, a linear trend was fitted (see section 4.2.3 for more detail) for the entire period measured for each participant. This was deemed optimal when examining variability over a long period (up to 2 years) as non-linear trends such as a LOESS regression are likely to capture the variability patterns of interest (i.e. across very long periods) and therefore reduce the ability to observe seasonal fluctuations, whereas linear trends allow greater deviation from the trend. Next, the trends were subtracted from the

observed weight. Following detrending, the detrended weights were converted to relative detrended weights which reflect the relative difference in weight between a given point and the trend, as done previously (Mehrang *et al.*, 2016b). Throughout, the term "weight" is used to refer to this relative deviation from the trend.

To identify weekly patterns, the relative detrended weights were averaged for each day of the week, providing a value representing the mean relative deviation between the actual body weight and the body weight trend on each day. To identify seasonal and Christmas patterns, missing data using an exponentially weighted moving average (EWMA) from the TS Impute package (Moritz and Bartz-Beielstein, 2017) which used a moving window of 3 days each side of the central missing value (i.e. a 1-week EWMA). Imputation by EWMA was chosen based on the results of the simulation and validation analysis in chapter 5. Imputation was conducted for Christmas and seasonal analyses but not the within-week analysis because the smoothing effect of the moving average imputation reduces the differences between sequential days and therefore removes some of the variability, but this is not a concern when examining patterns over longer periods such as several months or years. Lastly, for seasonal and Christmas analyses, multiple years of data were combined on to a year-less time axis and averaged each day of the year for all participants in each analysis.

To test group differences within each analysis, individuals were grouped by gender, region, BMI and age groups to test for differences in variability patterns between baseline characteristics. All tests were conducted following data processing (e.g. detrending in addition to imputation for holiday and seasonal analyses). For the weekly analysis, differences were compared between each grouping variable for each day of the week. For the Christmas analysis, weight gain was calculated by taking the day where weight was lowest in the 1 month prior to Christmas and highest in the 1 month after Christmas and calculating the difference to define relative weight change (after detrending) in response to the holiday period. The difference in Christmas weight change by each grouping variable was then tested. For the seasonal analysis, data was grouped by season and grouping variable then the group difference in mean relative deviation was tested for each season. All group comparisons were made using a multi-factor one-way analysis of variance (ANOVA) with type III sum of squares adjusted for each grouping variable (gender, country, BMI status and age group). This method was chosen to deal with potentially unbalanced groups

and for covariance between the independent variables. Lastly, Tukey's post-hoc test was applied to significant models to investigate specific differences between groups. Full multivariate ANOVA results can be found in appendices 2-4. All analyses were conducted in R version 3.5.1 (www.r-project.org). The analysis code can be viewed on Github (Turicchi, 2020b)

6.3 Results

Participant characteristics for each analysis are given in **table 6.1** and the collection of body weight data is described in **figure 6.2**. The weekly, Christmas and seasonal analyses included 1,421, 1,062 and 1,242 participants respectively. Participants in the weekly analysis weighed themselves on average 220 times over 566 days; in the Christmas analysis on average 262 times over 603 days and in the seasonal analysis on average 243 times over 607 days.

Table 6.1. Participant characteristics

	Weekly analysis (n=1,421)	Holiday analysis (n=1,062)	Seasonal analysis (n=1,242)
Gender = women (%)	982 (69.1)	749 (70.5)	865 (69.6)
Age group (%)			
under 30 years	164 (11.5)	100 (9.4)	132 (10.6)
30 to 45 years	618 (43.5)	440 (41.4)	530 (42.7)
46 to 60 years	506 (35.6)	404 (38.0)	451 (36.3)
over 60 years	133 (9.4)	118 (11.1)	129 (10.4)
Country (%)			
Denmark	474 (33.4)	386 (36.3)	412 (33.2)
Portugal	471 (33.1)	318 (29.9)	391 (31.5)
UK	476 (33.5)	358 (33.7)	439 (35.3)
BMI status (%)			
Healthy weight	263 (18.5)	195 (18.4)	224 (18.0)
Overweight	616 (43.3)	456 (42.9)	545 (43.9)
Obese C1	335 (23.6)	259 (24.4)	303 (24.4)
Obese C2-3	207 (14.6)	152 (14.3)	170 (13.7)
Weight (kg)	84.4 (0.4)	84.2 (0.5)	84.1 (0.5)
Duration (days)	566 (4.1)	603 (3.6)	607 (2.9)
Total weight measurements	220 (4.1)	262 (4.7)	243 (4.3)

Table 6.1. *Participant characteristics in those eligible for weekly, holiday and seasonal analyses. Data provided as absolute number and relative percentage (within a given analysis) or as mean and standard deviation*

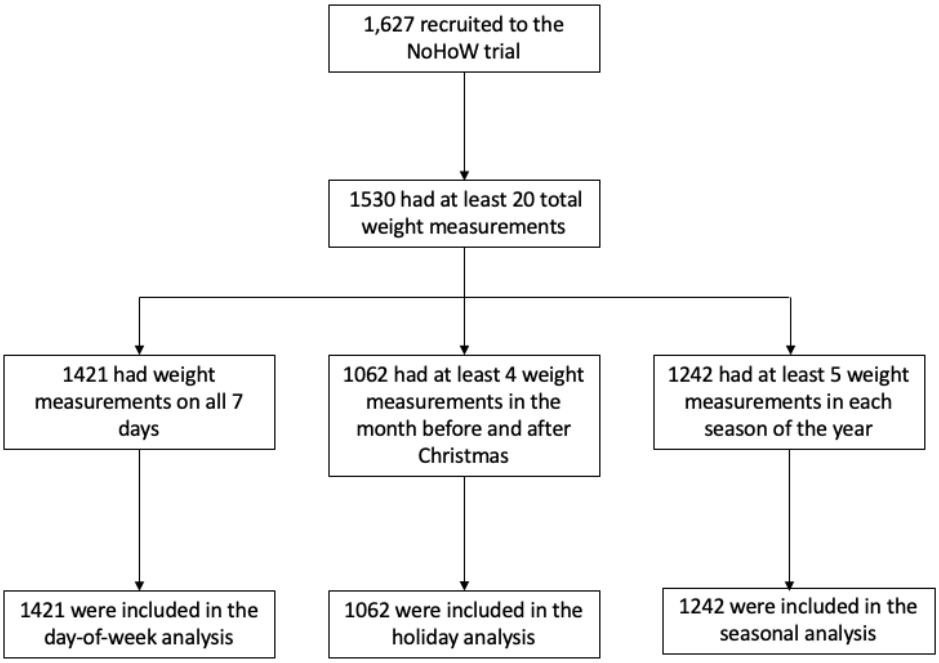


Figure 6.2. *Participant flow chart*

Distribution of weight is given by day of the week (**figure 6.3A**) and month of the year (**figure 6.3B**) relative to total possible days. The greatest proportion of data was available on Tuesday and Wednesday, with the least available on Sunday and Saturday respectively. Per month, data was most complete in January and September to November, whereas December, April and March had the greatest proportion of missing data respectively.

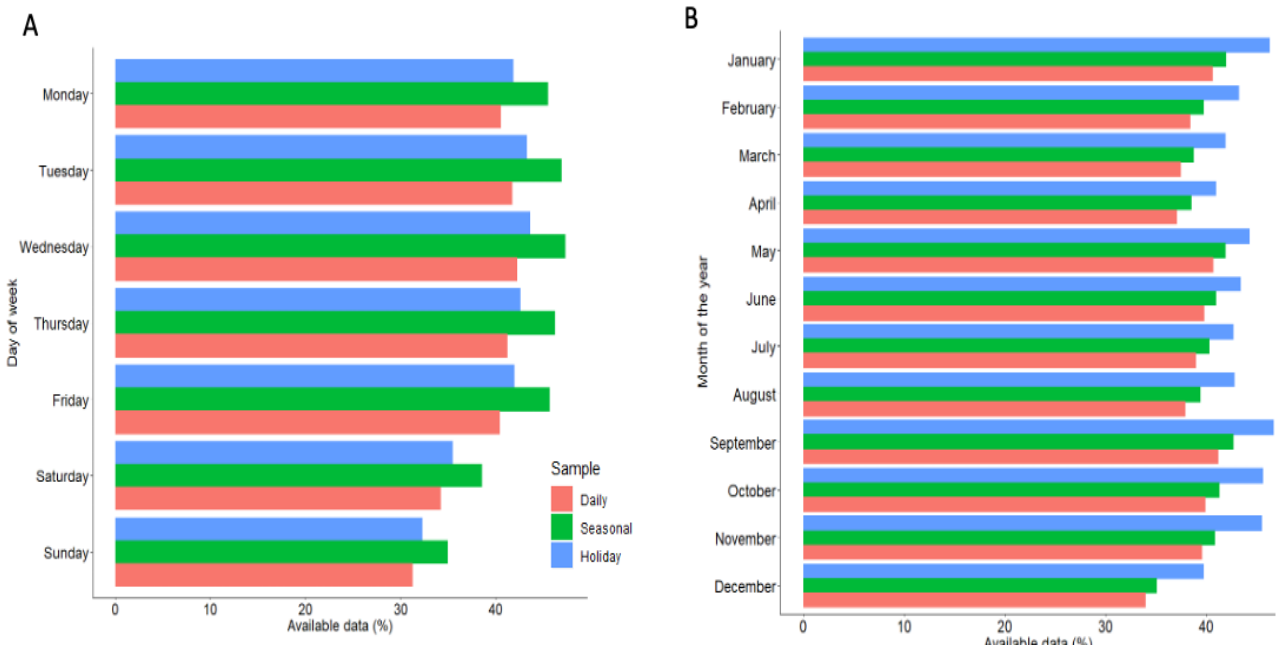


Figure 6.3. *Frequency of scale use by day of week and month of year. Frequency of weight data collected, given for each analysis (daily, seasonal and holiday). Fig (A) shows completeness of data per day of the week relative to the total amount of data possible for the given day and fig (B) shows completeness of data per month of the year relative the amount of data possible for the given year*

Self-weighing was averaged in relation to week of the trial for each participant (**figure 6.4**), showing an initial scale use of ~4 times per week which reduced to ~2.5 times per week over the course of the trial.

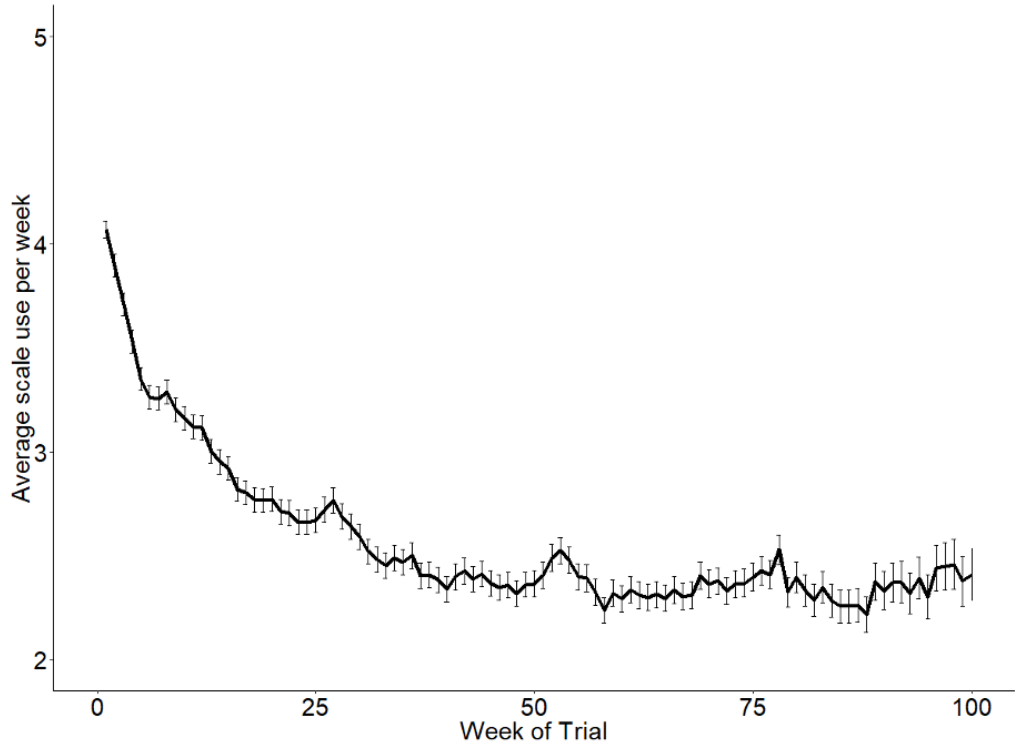


Figure 6.4. *Scale use over the duration of the trial. Mean (standard error) scale use per week over 2 years for each week in all participants from the entire sample*

6.3.1 Weekly Fluctuations in Body Weight

Within-week patterns were characterized by weekend weight gain and weekday weight reduction in all groups (**figure 6.5**). Means and standard errors are reported in **table 6.2** with between group comparisons for each day of the week. In the whole group, body weight was greatest on Monday, Sunday and Tuesday respectively, and decreased throughout the week with the lowest body weight on Friday. In the whole group, weekly body weight fluctuations of around 0.35% were observed. Both genders displayed similar

patterns, though weekly fluctuations were slightly greater in men than women (0.41% vs 0.29%) who had significantly greater weight on Monday and Sunday ($p<0.001$ for both) and lower weight on Wednesday and Thursday ($p<0.01$ for both) (**figure 6.5A**).

The weekly pattern was similar for all countries (**figure 6.5B**), though greater weekly fluctuation seemed to be present in Portugal compared to the UK and Denmark (0.41% vs 0.33% vs 0.31%, respectively). The Portugal group had a greater relative weight than both the UK and Denmark groups on Monday ($p<0.001$ for both) and lower weight than Denmark on Thursday (-0.12 (1.06) % vs -0.1 (1.0) %, $p=0.008$). Lastly, Denmark had a greater weight than UK and Portugal on Saturday ($p<0.01$ for both) and Sunday ($p<0.01$ for both).

A similar pattern was observed for BMI groups (**figure 6.5C**), though the extent of within-week fluctuation generally decreased with BMI, with the largest fluctuations observed in the healthy weight group followed by the individuals with overweight, individuals with class 1 obesity and lastly individuals with class 2-3 obesity (0.39% vs 0.38% vs 0.31% vs 0.26% respectively). Individuals with class 2-3 obesity showed significantly lower weight on Mondays compared to individuals with overweight, healthy weight ($p<0.01$ for both) and class 1 obesity ($p<0.05$). Differences were also observed on Friday where individuals with overweight had significantly lower weight than all individuals with obesity ($p<0.001$ for both) and individuals with healthy weight had a lower weight than those with class 2-3 obesity ($p<0.001$).

Differences between age groups were the most detectable (**figure 6.5D**) with the greatest fluctuations coming from 30-45 year old group, followed by under 30s, 46-60 years and lastly over 60 years (0.43% vs 0.32% vs 0.31% vs 0.24% respectively). Individuals aged 30-45 years had a higher weight than all other groups on Monday ($p<0.01$ for all). On Thursdays, weight was greater in the 46-60 years group compared to 30-45 group (-0.09 (1.06) % vs -0.13 (1.08) %, $p=0.013$) and on Fridays weight was greater in those over 46 years than in those aged 30-45 years ($p<0.05$ for all). On Sunday, greater in those aged 30 to 45 years than in those aged 46 years and above ($p<0.05$ for both).

6.3.2 Christmas Fluctuation in Body Weight

Christmas weight gain was observed in all groups (**figure 6.6**). Means and errors are reported in **table 6.3** with between group comparisons. In the whole group, increases of 1.35 (1.74)% body weight were observed, with the lowest weight in the first week of

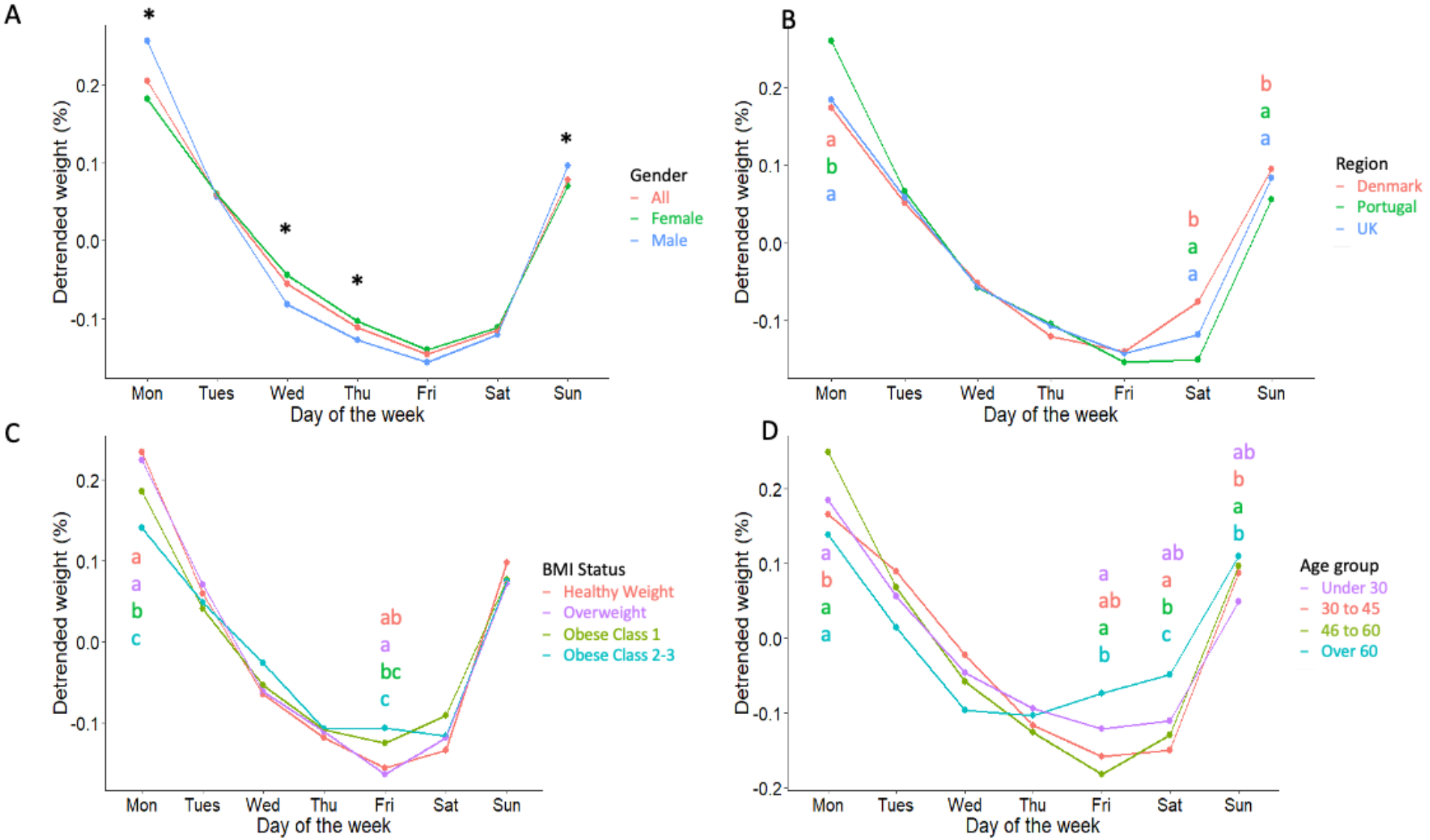

A
B
C
D
Detrended weight (%)
Day of the week
Mon
Tues
Wed
Thu
Fri
Sat
Sun
Gender
All
Female
Male
Region
Denmark
Portugal
UK
BMI Status
Healthy Weight
Overweight
Obese Class 1
Obese Class 2-3
Age group
Under 30
30 to 45
46 to 60
Over 60

Figure 6.5. *Weekly body weight fluctuations. Weekly body weight fluctuations in all individuals and by gender (A), region (B), BMI status (C) and age group (D). Body weight has been detrended and detrended weight signifies the mean relative deviation from the body weight trend on a given day of the week. Groups are presented by colour, and groups without a letter in common for each given day were significantly different (p<0.05) as tested by multi-factor ANOVA and Tukey's post hoc. Gender differences (p<0.05) are illustrated using an asterisk*

Table 6.2. Relative weight by day of the week

Group		Day of the week (relative body weight (%) (se))						
Gender		Mon	Tues	Wed	Thurs	Fri	Sat	Sun
	Men	0.256 (1.07)[a]	0.057 (1.03)	-0.081 (1.02)[a]	-0.127 (1.02)[a]	-0.156 (1.01)	-0.12 (1.07)	0.097 (1.1)[a]
	Women	0.182 (1.12)[b]	0.059 (1.09)	-0.044 (1.09)[b]	-0.104 (1.1)[b]	-0.14 (1.09)	-0.112 (1.12)	0.07 (1.14)[b]
Country	Denmark	0.173 (1.09)[a]	0.051 (1.06)	-0.052 (1.04)	-0.12 (1.06)[a]	-0.14 (1.06)	-0.076 (1.09)[a]	0.094 (1.09)[a]
	Portugal	0.259 (1.05)[b]	0.066 (0.99)	-0.057 (1)	-0.104 (1)[b]	-0.154 (1.01)	-0.15 (1.05)[b]	0.056 (1.1)[b]
	UK	0.184 (1.17)[a]	0.058 (1.16)	-0.056 (1.16)	-0.107 (1.16)[ab]	-0.142 (1.14)	-0.119 (1.17)[b]	0.083 (1.19)[b]
BMI status	Healthy weight	0.233 (1.15)[ab]	0.06 (1.12)	-0.064 (1.11)	-0.118 (1.12)	-0.156 (1.13)[ab]	-0.134 (1.16)	0.098 (1.19)
	Overweight	0.186 (1.04)[a]	0.041 (1.02)	-0.053 (1.02)	-0.108 (1.02)	-0.125 (1)[a]	-0.09 (1.04)	0.077 (1.08)
	Obese C1	0.141 (1.07)[bc]	0.049 (1.08)	-0.027 (1.07)	-0.107 (1.06)	-0.106 (1.06)[bc]	-0.116 (1.08)	0.074 (1.08)
	Obese C2-3	0.223 (1.13)[c]	0.07 (1.08)	-0.061 (1.07)	-0.11 (1.08)	-0.163 (1.08)c	-0.118 (1.12)	0.072 (1.14)
Age group	Under 30 years	0.165 (1.21)[a]	0.089 (1.14)	-0.023 (1.12)	-0.117 (1.11)[ab]	-0.159 (1.11)	-0.15 (1.19)	0.086 (1.25)
	30-45 years	0.248 (1.11)[b]	0.067 (1.08)	-0.058 (1.08)	-0.126 (1.08)[a]	-0.182 (1.09)	-0.13 (1.13)	0.095 (1.15)
	46-60 years	0.138 (1.04)[a]	0.014 (1.04)	-0.097 (1.01)	-0.104 (1.04)[b]	-0.074 (1)	-0.049 (1.03)	0.109 (1.07)
	Over 60 years	0.184 (1.09)[a]	0.056 (1.06)	-0.047 (1.06)	-0.094 (1.06)[ab]	-0.121 (1.06)	-0.111 (1.08)	0.049 (1.1)

Table 6.2. *Mean body weight relative to the non-linear trend and standard error following detrending, given for each day of the week. Letters denote results from Tukey's post-hoc tests which were adjusted for all grouping variables. Only grouping variables which were significant in a type III sum of squares multivariatle ANOVA were tested for differences between groups. Letters can be read vertically within a day and group. Groups without a letter in common were significantly different. Full multi-factor ANOVA results are provided in Appendix 6.1*

December and the greatest weight on the second day of January. Body weight decreased between January and March though remained at least 0.35% greater than the pre-Christmas weight. Christmas weight gain was similar between men and women (1.30 (1.67)% and 1.37 (1.79)%) (**figure 6.6A**). Between countries, greater body weight gain was observed in the UK compared to the Portugal (1.52 (1.70)% vs 1.13 (1.60)% respectively, p=0.011), though Denmark was similar to both groups (1.29 (1.65)%, p>0.05 for both comparisons) (**figure 6.6B**). With regards to BMI status (**figure 6.6C**) and age group (**figure 6.6D**), no significant differences in weight gain were observed (p<0.05 for all comparisons).

6.3.3 Season Fluctuations in Body Weight

Seasonal patterns in relative body weight are shown in **figure 6.7** and means and standard errors for relative weight are reported in **table 6.4** with between group comparisons. Following detrending, body weight fluctuated by around 0.8% per year in the whole group, and patterns were largely characterized by Christmas weight gain and loss during the year. Gender differences were observed (figure 6.7A); men lost weight and therefore had significantly lower weights during summer, compared to women who gained weight (0.23 (1.32) % vs 0.40 (1.19) %, p=0.034). Between countries (**figure 6.7B**), no significant differences were observed. During summer, weight was greater in both obese groups (**figure 6.7C**), in comparison to healthy weight individuals (p<0.05 for both). Between age groups, no differences were observed for all seasons (**figure 6.7D**).

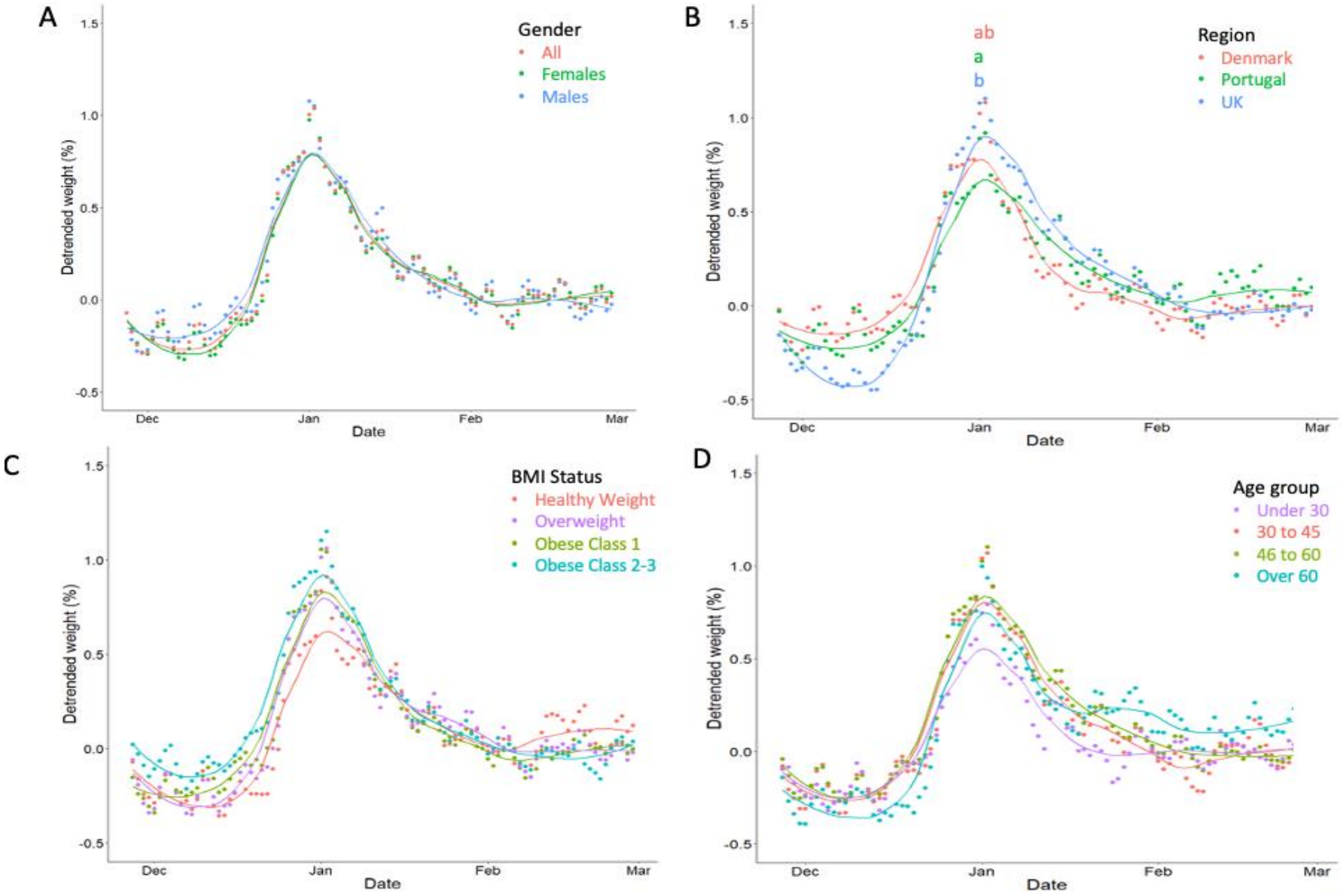

A
Gender
All
Females
Males
Detrended weight (%)
1.5
1.0
0.5
0.0
-0.5
Dec
Jan
Feb
Mar
Date
B
ab
a
b
Region
Denmark
Portugal
UK
Detrended weight (%)
Dec
Jan
Feb
Mar
Date
C
BMI Status
Healthy Weight
Overweight
Obese Class 1
Obese Class 2-3
Detrended weight (%)
Dec
Jan
Feb
Mar
Date
D
Age group
Under 30
30 to 45
46 to 60
Over 60
Detrended weight (%)
Dec
Jan
Feb
Mar
Date

Figure 6.6. *Body weight fluctuation around Christmas. Christmas body weight fluctuations in all individuals and by gender (A), region (B), BMI status (C) and age group (D). Body weight has been detrended and detrended weight signifies the mean relative deviation from the body weight trend on a given day. Groups are presented by colour, and groups without a letter in common for each given day were significantly different as tested by multi-factor ANOVA and Tukey's post hoc*

Table 6.3. Relative holiday weight change by group

Group	Christmas weight gain (%) (se)
Men	1.30 (1.67)
Women	1.37 (1.79)
Centre	
Denmark	1.29 (1.65) [ab]
Portugal	1.13 (1.60) [a]
UK	1.52 (1.70) [b]
BMI status	
Healthy weight	1.21 (1.78)
Overweight	1.32 (1.85)
Obese C1	1.40 (1.68)
Obese C2-3	1.33 (1.62)
Age group	
under 30 years	1.08 (1.62)
30 to 45 years	1.39 (1.78)
46 to 60 years	1.31 (1.58)
over 60 years	1.40 (1.85)

Table 6.3. *Mean body weight relative to the non-linear trend and standard error following detrending around the Christmas period. Letters denote results from Tukey's post-hoc tests which were adjusted for all grouping variables. Only grouping variables which were significant in a type III sum of squares multivariate ANOVA were probed for differences between groups. Letters can be read vertically within a grouping variable. Groups without a letter in common were significantly different. Full multi-factor ANOVA results are provided in appendix 6.2*

6.4 Discussion

This study aimed to identify whether body weight showed predictable responses to temporal cues (specifically the weekly, seasonal and holiday cycles) in all, and in groups of individuals varying by region, sex, age and BMI groups. In the present study weekly fluctuations in the region of 0.35% body weight were observed which were relatively consistent across groups; substantial Christmas weight gain in the region of 1.3% was shown which was not fully compensated for in following months and seasonal patterns varied between groups and were largely characterized by weight gain during the Christmas and New Year period.

6.4.1 Weekly Weight Fluctuations

Greater body weight after the weekend was observed which was greatest on Monday and decreased throughout the week reaching the lowest weight on Friday, with fluctuations being equal to around 0.35% (around 0.3kg in the present group). These observations are in line with results from previous research which has shown around 0.17kg fluctuation between Monday and Friday in 48 adults involved in a weight loss intervention in which participants were randomized into either caloric restriction or exercise arms (Racette *et al.*, 2008). Similarly, Monday and Friday were identified as the maximum and minimum weight days respectively in an analysis of 80 adults from 4 samples (Orsama *et al.*, 2014). The results of the present study support these observations using a large and diverse population using WiFi connected smart scales and show replicability in different genders, regions, ages and BMI groups.

Human behaviour is subject to both biological and environmental rhythms. The 7-day rhythm is consistent and therefore likely associated with predictable changes in behaviour which include (in some samples) weekend reductions in workplace activity and increases in dietary energy density (Czlapka-Matyasik *et al.*, 2018) characterised by increased energy, fat and alcohol intake (Jahns *et al.*, 2017) including preferences for sugar sweetened beverages, discretionary/processed foods and fast foods (An, 2016). While it might be expected that different groups have discrete behavioural responses to the weekly cycle, relatively consistent patterns of weight fluctuation were observed across all groups. Two notable exceptions from the overall pattern were evident. Firstly, those over 60 years

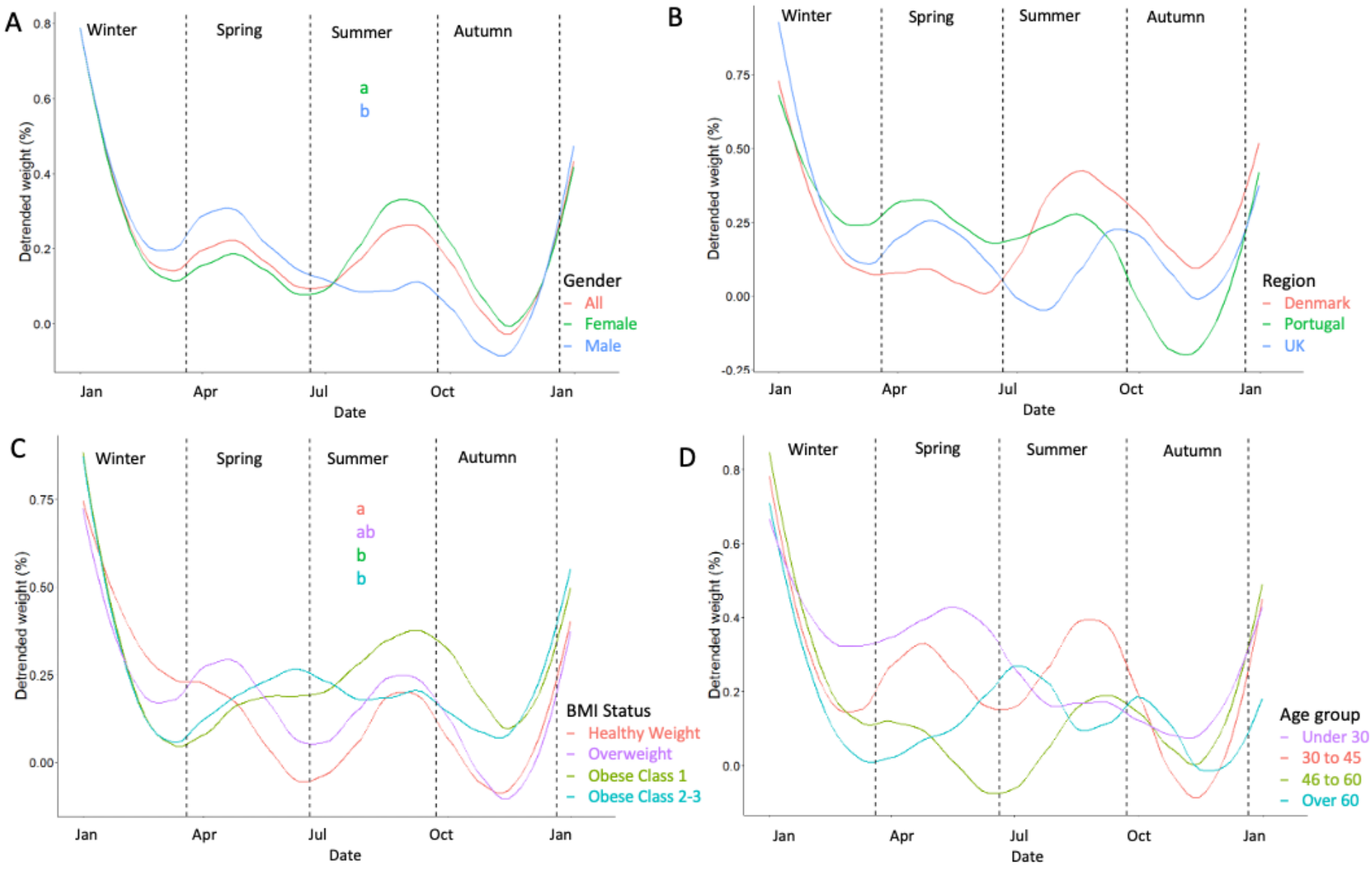

A
Winter
Spring
Summer
Autumn
a
b
Detrended weight (%)
0.8
0.6
0.4
0.2
0.0
Jan
Apr
Jul
Oct
Jan
Date
Gender
All
Female
Male
B
Winter
Spring
Summer
Autumn
Detrended weight (%)
0.75
0.50
0.25
0.00
-0.25
Jan
Apr
Jul
Oct
Jan
Date
Region
Denmark
Portugal
UK
C
Winter
Spring
Summer
Autumn
a
ab
b
b
Detrended weight (%)
0.75
0.50
0.25
0.00
Jan
Apr
Jul
Oct
Jan
Date
BMI Status
Healthy Weight
Overweight
Obese Class 1
Obese Class 2-3
D
Winter
Spring
Summer
Autumn
Detrended weight (%)
0.8
0.6
0.4
0.2
0.0
Jan
Apr
Jul
Oct
Jan
Date
Age group
Under 30
30 to 45
46 to 60
Over 60

Figure 6.7. *Seasonal body weight fluctuations in all individuals and by gender (A), region (B), BMI status (C) and age group (D). Body weight has been detrended and detrended weight signifies the mean relative deviation from the body weight trend on a given day of the year which has been given as a line for each group. Groups are presented by colour, and groups without a letter in common for each given day were significantly different as tested by multi-factor ANOVA and Tukey's post hoc*

Table 6.4. Relative seasonal weight patterns

		Spring	Summer	Autumn	Winter
Gender	Men	0.28 (1.35)	0.23 (1.32) [a]	0.02 (1.27)	0.38 (1.14)
	Women	0.21 (1.16)	0.40 (1.19) [b]	0.13 (1.03)	0.34 (0.91)
Country	Denmark	0.08 (1.42)	0.34 (1.34)	0.21 (1.25)	0.35 (1.09)
	Portugal	0.27 (1.38)	0.32 (1.39)	-0.08 (1.29)	0.32 (1.15)
	UK	0.32 (1.41)	0.39 (1.49)	0.12 (1.22)	0.39 (1.17)
BMI Status	Healthy Weight	0.18 (1.38)	0.06 (1.45) [a]	-0.02 (1.36)	0.38 (1.35)
	Overweight	0.20 (1.12)	0.31 (1.31) [ab]	0.04 (1.15)	0.32 (1.01)
	Obese C1	0.27 (1.6)	0.55 (1.70) [b]	0.24 (1.52)	0.39 (2.05)
	Obese C2-3	0.39 (1.98)	0.55 (2.17) [b]	0.14 (1.88)	0.37 (3.59)
Age group	Under 30 years	0.43 (2.15)	0.34 (1.82)	0.14 (1.91)	0.41 (1.79)
	30-45 years	0.28 (1.51)	0.46 (1.41)	0.09 (1.21)	0.34 (1.05)
	46-60 years	0.11 (1.39)	0.20 (1.39)	0.09 (1.22)	0.40 (1.01)
	Over 60 years	0.23 (2.00)	0.47 (2.11)	0.08 (1.71)	0.20 (1.78)

Table 6.4. *Mean body weight relative to the linear trend and standard error following detrending. Letters denote results from Tukey's post-hoc tests which were adjusted for all grouping variables. Only grouping variables which were significant in a type III sum of squares multivariate ANOVA were probed for differences between groups. Letters can be read vertically within a grouping variable. Groups without a letter in common were significantly different. Full multi-factor ANOVA results are provided in table appendix 6.4.*

old tended to show a less prominent weekly fluctuation. It could be postulated that many individuals over the age of 60 are in retirement and therefore may not show behavioural responses to the weekly cycle. Moreover, as appetite declines in elderly individuals, episodes of excessive intake (which are often around weekends) may become less frequent (Pilgrim *et al.*, 2015). Secondly, individuals in Portugal tended to maintain their weekday weight reduction from Friday to Saturday, whereas weight gain was observed in the UK and more so Denmark from Friday till Monday. This suggests behavioural changes occur later in the week in Portugal compared to the two other countries and may be reflective of cultural differences, such as less binge eating or drinking on Fridays.

Variability in weight has previously been associated with weight gain and obesity (Feig and Lowe, 2017; Benson *et al.*, 2020) potentially due to dysregulated (or simply inconsistency in) energy balance behaviours (Rosenbaum *et al.*, 2016) and therefore associations between BMI and weekly weight fluctuations may be expected. However, an inverse association was observed between BMI and weekly fluctuation, with healthy weight individuals displaying the greatest weekly fluctuation (0.4% vs 0.27% in individuals with class 2-3 obesity). A similar observation has been made previously by Orsama et al. (2014) and may be explained by the removal of the weight trend, meaning that greater weekly fluctuation is reflective of greater weekday compensation for weekend weight gain, whereas lack of compensation results in an upward trend (which is presently removed). This is demonstrated by the fact individuals with obesity had greater weights on Friday, but lesser reductions through the week.

6.4.2 Holiday Weight Fluctuations

Upward fluctuations in body weight were observed in the region of 1.35% in the whole group (around 1.10kg in the present group) beginning in early December and continuing until the first few days of January, independent of each individual's linear weight trend. These findings are in line with previous observations reporting around 0.2-1kg weight gain over Christmas in the general population (Díaz-Zavala *et al.*, 2017). However, less weight gain (or even weight loss) may be expected to occur in individuals engaged in a weight loss or maintenance intervention (Díaz-Zavala *et al.*, 2017; Fahey, Klesges, Kocak,

Wang, *et al.*, 2019). Therefore, in the present group comparatively large Christmas weight gains were observed. One explanation for this observation may be that individuals joining a weight loss maintenance intervention may potentially do so as they are more susceptible to weight gain (i.e. susceptibility to weight gain precedes a weight control attempt (Lowe *et al.*, 2015)), and therefore are more likely to gain weight over the Christmas period.

To quantify Christmas weight gain, previous trials have often relied on a single or a very small number of body weight measurements before and after the Christmas period (Reid and Hackett, 1999; Yanovski *et al.*, 2000; Phelan *et al.*, 2008; Wagner, Larson and Wengreen, 2012; Stevenson *et al.*, 2013). This may result in single-measurement error due to normal fluctuations related to total body water, glycogen and other factors. To overcome this, a smoothed time-series of body weight measures over the entire Christmas period and following period was generated, including a minimum of 4 weight measurements in the month before and after Christmas. Interestingly, a partial but incomplete reduction in weight following the new year until March was shown, which remained around 0.35% (or under 0.30kg) greater than weight before Christmas. This evidence supports the hypothesis that holiday weight gain may be a factor contributing to long-term weight gain (Roberts, 2009).

Holiday weight gain was greater in individuals from the UK than in those from Portugal though these differences were minor. In a previous study of holiday weight gain across countries in 2,924 adults, authors reported greater weight gain in individuals based in Germany (0.6%) compared to the United States (0.4%) and Japan (0.5%) (Helander, Wansink and Chieh, 2016) following detrending of the body weight data; and Christmas weight gain as low as 0.2% has been observed in Spain (García *et al.*, 2013). Together, these results infer that cultural differences in the behavioural response to the holiday period may be evident (though modest) and may be investigated further considering the potential role of acute holiday weight gain in longer-term weight gain.

Consistent seasonal patterns were not observed, and any pattern was largely defined by the holiday effect. No differences in seasonal patterns were observed between BMI groups. This is inconsistent with previous literature suggesting that more weight is gained by individuals with overweight and obesity in comparison to those with normal weight (Yanovski *et al.*, 2000; Díaz-Zavala *et al.*, 2017), as well as the hypothesis that holiday weight gain contributes to obesity (Roberts, 2009). However, relative rather than absolute

weights were used, and this should account for differences in initial body size and may have exaggerated weight gain in heavier individuals in previous studies (i.e. if they did not use % weight gain). Further explanation comes from the fact that the energy cost of weight gain is greater in heavier individuals, due to differences in proportions of fat and fat-free mass gained, and differences in the energy content of both tissues (Hall and Guo, 2017). Furthermore, it is likely that individuals with obesity are more likely to be gaining weight at any given period than those with normal weight and to correct for this the overall trend in body weight over a longer period was removed in order to determine the response to the Christmas period. Lastly, weight gain was similar between all individuals irrespective of age, though generally younger individuals seemed to gain less weight during the period. Interestingly, all groups remained at elevated body weights up to 2 months into the new year, suggesting that weight gained at Christmas is not fully compensated for in the subsequent period which was examined until the end of March. Together, these results can potentially inform potential targets for future weight control interventions, such as self-monitoring intervention around Christmas, was an approach taken in a recent intervention (Mason *et al.*, 2018).

6.4.3 Seasonal Weight Fluctuation

Seasonal patterns were less consistent and the most obvious pattern of weight gain in December and January is likely to be an outcome of the Christmas effect. It is worth noting that observed errors in group means were large, suggesting that these seasonal patterns are heterogenous, inconsistent and not defined by the grouping variables used presently. Previous studies have reported seasonal patterns in body weight, with one study reporting fluctuations of around 0.5kg throughout the year with a peak in winter and trough in summer in a sample of 593 American individuals (Ma *et al.*, 2006); another study reported a 1.2% increase in weight between fall and winter followed by a 0.6% decrease from winter to spring in 248 American individuals engaged in a weight loss intervention which promoted daily self-weighing (Fahey, Klesges, Kocak, Talcott, *et al.*, 2019b). Again, these studies did not adjust for overall weight trend throughout the year which may confound seasonal fluctuations (e.g. if an individual gains weight over a calendar year, winter will naturally register as a heavier season). Similar to the present results, a comprehensive analysis which used yearly detrending and aggregation of data from 10,000 randomly selected digital smart

scale users from 7 countries around the world (Mehrang *et al.*, 2016b) reported seasonal fluctuations in the region of 0.3% body weight which were inconsistent between region though every country displayed a clear holiday effect (similar to the present results).

Gender differences were observed in summer, characterized by a reduction in body weight during the season in men and an increase in women. It is possible that this is due to gender differences in physical activity, whereby men are more predisposed to partake in physical activity (Deaner *et al.*, 2012) or show physical activity increases in summer (Zhang and Yen, 2015). Together, these may influence a negative energy balance in men but not women during summer, however the large seasonal errors observed means this difference should be taken with caution. Further differences were observed between BMI groups in summer; healthy weight individuals had lower relative weight than those in obese groups. This could be explained by changes in physical activity during the summer period, as those lower in BMI generally have greater levels of physical activity (O. Lee *et al.*, 2016). No differences between countries were observed, though individuals in the UK showed a reduction in weight going from spring to summer, whereas individuals in Denmark (and less so Portugal) gained weight during this period. Further research on examining seasonal fluctuations in energy balance behaviors may help us understand some of these differences better.

6.4.4 Strengths and Limitations

The present study has several strengths. First, frequent measurements of body weight collected for up to two years allowed for the employment of time series modelling (e.g. detrending) which would be inappropriate where weight data was collected infrequently. Further, the sample sizes were large, ranging between 1,062 participants (for Christmas patterns) to 1,421 (for weekly patterns). This allowed exploration of group differences in fluctuation patterns, which have not previously been examined. Next, individuals weighed themselves on average around 2.5 times per week over 566-607 days, and restrictions were put in place to exclude participants with excessive missing data. Given that the amount of days of data being used was great (up to ~320,000 total days dependent on the analysis), more confidence can be had that the patterns observed were not random.

There were also limitations of the current analysis. Firstly, not all of the measured variability in body weight is likely to be related to energy balance behaviours. Indeed, much

of the variability may be attributable to non-energy balance components of fat-free mass (e.g. water, glycogen and gut weight; (Bhutani *et al.*, 2017a)), for a full discussion of this limitation see section 10.3. Furthermore, it was not possible to tell whether individuals adhered to the self-weighing guidance provided (i.e. first thing in the morning in light or no clothing and an empty bladder). However, it is unlikely that lack of adherence to this guidance would produce the body weight fluctuations observed. All individuals were engaged in a weight loss maintenance intervention and therefore our observations may not be representative of the general population. Adherence to self-monitoring has previously been associated with reduced weight fluctuation (Martin, Tate and Valle, 2018) and therefore patterns may be more pronounced in individuals not regularly self-weighing. Contrastingly, individuals in the present group are more likely to struggle with regulating body weight and therefore may show more pronounced patterns of fluctuation. Recruitment to the intervention was rolling, therefore initiation of self-monitoring began at different stages of the year in different individuals and this may have influenced self-weighing or energy balance behaviours. Next, individuals were grouped by baseline variables on which data is easy to collect, but it may be that these characteristics are not necessarily related to weight fluctuation and as such, further exploration determinants of fluctuations is advised. Next, although there was relatively high adherence to self-weighing, missing data was present and imputation using an EWMA was conducted (informed by a results of chapter 5) in the case of Christmas and seasonal analyses, which is second to using true (complete) data. Lastly, there was less than three years of data between 2017 and 2019 and therefore seasonal patterns had limited replicability, and therefore it was not possible to investigate year-to-year differences in seasonal patterns across many years.

6.4.5 Conclusions

Weight instability occurs at different magnitudes and across different timescales. In chapter 2, the phenomenon of intentional (and clinically significant) weight loss and weight regain was investigated. This can, under the current terminology, be termed the trend in body weight. When the trend is removed thus centering body weight around zero, the variability component remains. The variability in body weight is largely stochastic (unpredictable), to which there are many possible explanations for this including (a) the unpredictability and inconsistency of human behaviours (for an illustrated example see the

variability in measured human energy intake in **figure 6.1**); (b) unpredictable fluctuations in non-energy balance related compartments and (c) noise generated from inconsistent weighing conditions discussed above (and in full in section 4.2.1). Nonetheless, some of this variability was shown to be predictable and determined by temporal cues. These are presently referred to as fluctuations given their repetitive nature. In the present analysis, body weight fluctuations weekly and holiday fluctuations were evident, though seasonal were not. This evidence was consistent with short-term studies on weekly fluctuations in smaller groups (Racette *et al.*, 2008; Orsama *et al.*, 2014) as well as studies of holiday weight gain in which infrequent measures (i.e. pre-post Christmas) are often used, though the much greater density of body weight measurements provide a more detailed report of these patterns.

The present study highlights the influence of the temporal environment on body weight (and thus energy balance behaviors), and how these may interact with individual characteristics and cultural differences. Importantly, minor gains in body weight (such as those seen at group level within a week in the magnitude of ~0.35%) may potentially be an indicator of weight gain if not subsequently compensated for. More so, it is hypothesized that holiday weight gain may potentially contribute to weight gain at population level. These results may inform future interventions aimed at reducing periods of overconsumption and weight gain, particularly in specific groups. Future research employing smart scales should consider the impact of body weight fluctuations on weight outcomes.

Chapter 7. Associations between body weight variability, health markers and body composition

In the comprehensive literature review conducted in chapter 3, the existing evidence provided by long-term observational studies showed relatively consistent links between BWV and risk of disease (e.g. CVD or T2D) and mortality. However, this literature often fails to provide a plausible mechanism for these epidemiological associations, and other research does not consistently relate BWV or weight cycling to any changes in health markers, though there are some exceptions. Indeed, the most common pathway to disease incidence is through detrimental adaptations in traditional health markers, and body composition may form an additional component related to disease incidence. In the following chapter, associations between BWV and changes in traditional health markers and body composition were investigated.

The chapter is adapted from a publication in the International Journal of Cardiology (Jake Turicchi, Ruairi O'Driscoll, Horgan, Duarte, Inês Santos, Encantado, *et al.*, 2020). The data used was collected as part of the NoHoW trial. I was solely responsible for the conceptualisation, data analysis and primary manuscript writing of this study. All other authors were responsible for providing suggested edits.

7.1 Introduction

7.1.1 Body Weight and Cardiometabolic Health

Body weight is a primary indicator in the development of cardiometabolic disease (such as CVD and T2D) and dose-response relationships operating along exponential curves have been rigorously developed to describe the risk increase associated with moving from normal weight to obese class III (Kivimäki *et al.*, 2017). Increasing obesity prevalence worldwide has coincided with quadrupled type 2 diabetes diagnoses in the past 30 years, which is expected to rise to over 10% of the world's total population by 2045 (Forouhi and Wareham, 2019). The pathways to decreased risk are largely via lifestyle changes, surgery or pharmacological interventions, the latter two requiring involvement of healthcare services and associated costs. The most effective lifestyle changes for decreased risk of T2D (Richard F. Hamman *et al.*, 2006b) – and second most effective for addressing CVD following smoking

cessation (Keto *et al.*, 2016) – is weight loss. As little as 5% weight loss can significantly decrease the risk of obesity-related comorbidity risk through reductions in blood pressure (BP) and improved blood lipid levels and glucoregulation (Rena R Wing *et al.*, 2011a). The beneficial influence of weight loss on health has been reviewed extensively elsewhere (Ma *et al.*, 2017b).

7.1.2 Body Weight Variability and Health Outcomes

As discussed in previous chapters, body weight shows both a trend (or change) and a variability around that trend which can be measured over long (e.g. years) or short (e.g. days or weeks) periods. While lower weight (and weight loss) is consistently associated with reduced risk of obesity-related diseases, the effects of BWV are less well understood. The available evidence has been reviewed extensively in section 3.2-3.3. Some epidemiological studies have suggested large increases in the risk of a health event, such as a 53% increased risk of mortality in the highest quartile for BWV in a large and diverse population of almost 7 million Korean individuals from a national health register (Kim *et al.*, 2018). Another study showed up to double the risk of myocardial infarction or death in the most weight variable quantile of individuals with pre-existing coronary disease (Bangalore *et al.*, 2017).

Additionally, several recent meta-analyses in the past few years have concluded that BWV is associated with increased risk of T2D incidence (Kodama *et al.*, 2017), CVD (Zou *et al.*, 2019a) and mortality (Zhang *et al.*, 2019; Zou *et al.*, 2019a), though one study provided that “serious biases, such as diagnostic suspicion bias and publication bias, made it difficult to assess this association” (Kodama *et al.*, 2017). Importantly, in these analyses they there is not a selection of populations with pre-existing disease, meaning that both healthy and non-healthy study samples are included. The available epidemiological evidence (which typically spans several years or decades) is in favour of detrimental health risks owing to BWV which must be further explored.

Despite this observational evidence, no study has experimentally manipulated variability in body weight in a controlled manner and tested its more acute impact on health. Furthermore, large epidemiological studies showing increased risk tend not to attribute their results to a plausible physiological mechanism. Some evidence suggests that unstable weight may negatively impact health markers though these associations are inconsistent (see section 3.3 for a more comprehensive review). For example, in two

studies, greater retrospectively measured BWV was associated with greater blood pressure (Zeigler *et al.*, 2018) and greater prospectively measured BWV was associated with greater HbA1c (Oh *et al.*, 2019), though the change in health markers were not longitudinally measured. Cross-sectional studies reliant in weight cycling history questionnaires have shown associations between greater weight cycling and reduced HDL-C (Olson *et al.*, 2000) or decreased leptin or resting metabolic rate (Strychar *et al.*, 2009). Furthermore, a rebound in cardiometabolic health markers (meaning values increase beyond original status despite incomplete weight regain) following weight regain has been reported (Kroeger, Hoddy and Varady, 2014). Lastly, detrimental effects of weight cycling on body composition have been reported (Beavers *et al.*, 2011; Dulloo *et al.*, 2015), which may function as a pathway to metabolic disease (Dulloo and Montani, 2015).

Nevertheless, the effect of BWV on changes in health markers is inconsistent, not well studied and very often relies on self-reported weight history to define retrospectively weight instability (be that cycling or variability). Most often, studies use cross sectional designs (see **table 3.3** for summary) and rarely measure health outcomes longitudinally. Those which do measure weight prospectively, rely on infrequent measurements of body weight and do not account for the (potentially) unmeasured variability (a limitation discussed frequently throughout this thesis). Accordingly, is not clear whether BWV is independently associated with concurrent changes in health markers, in particular after adjustment for weight change. Increased frequency in the measurement of body weight can facilitate more valid estimation of BWV (as discussed in chapter 5). When aligned with repeated measured of cardiometabolic health these estimates can enable more appropriate investigation of the relationship between BWV and health. However, until recently such data has not been available in research environments.

7.1.3 Objectives

As part of a secondary investigation using data collected during the NoHoW trial (see section 4.1), the aims of the following study were to:

1. Investigate the association between 12-month BWV and concurrent changes in health markers (specifically, blood pressure, blood lipids, HbA1c and body composition), following adjustment for overall weight change

2. Investigate the association between 12-month weight change and concurrent changes in health markers, following adjustment for BWV

It was hypothesised that greater BWV would be associated with detrimental changes in health markers and body composition, and weight loss would improve markers of health and body composition.

7.2 Methods

7.2.1 Study Design

The current study used data collected as part of the NoHoW trial which is described in full in section 4.1.

7.2.2 Participants

The inclusion and exclusion criteria for recruitment to the NoHoW trial can be found in section 4.1.4.1. Additional inclusion criteria were required for inclusion in the present analysis. Participants had to have ≥20 body weight measurements over 12 months to generate estimates of weight variability, as determined as reasonable in the previous work on estimating BWV (chapter 5). Furthermore, physiological measurements (referred to below) were required to be complete at 0 and 12 months. No imputation of physiological measurements was conducted therefore participants were excluded if this criterion was not met. A sub-sample was generated who had available longitudinal dual-energy X-ray absorptiometry (DXA) measurements. This provide 955 and 439 individuals meeting sufficient data requirements for inclusion in the primary analysis and DXA sub-analysis respectively (n=439). A total of 955 individuals had available data for all outcome variables, minimum physical activity (PA) data and covariates. A participant flow diagram is shown in **figure 7.1**.

7.2.3 Physiological Measurements

Information on all measurements used is provided in full in chapter 4.1. Frequent body weight data was collected from the Fitbit Aria smart scale as described in *section 4.1.6.1*. Physiological measurements were made at 0, 6 and 12 months. Measurement of diastolic blood pressure (DBP) and systolic blood pressure (SBP), resting heart rate (RHR),

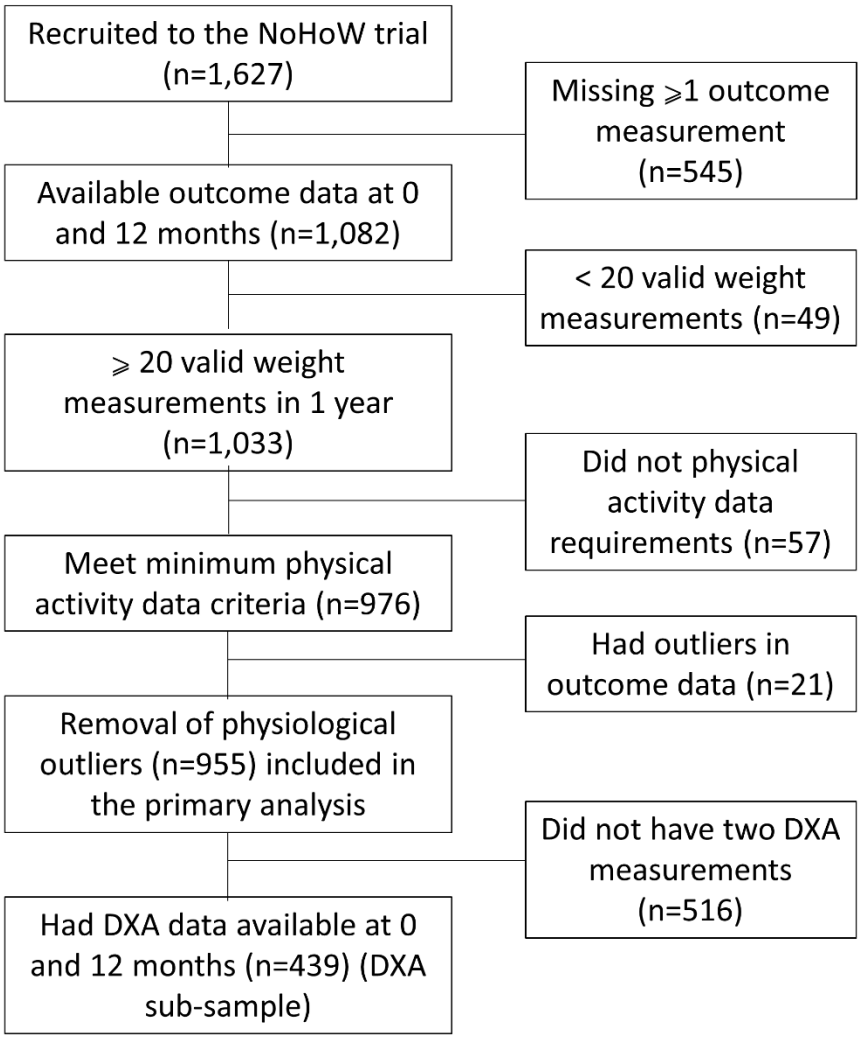


Figure 7.1. *Participant flow diagram*

blood lipids (total cholesterol, low-density lipoprotein cholesterol (LDL-C), HDL-C and triglycerides) and HbA1c are described in *section 4.1.7*.

7.2.4 Physical Activity

Data on physical activity was collected over the period of the study by the Fitbit Charge 2 device described fully in *section 4.1.6.1*. Step count was used as the primary measure of PA due to greater reliability than other measures such as energy expenditure (Feehan *et al.*, 2018; O'Driscoll *et al.*, 2018). Initial and change in physical activity were used as covariates in later statistical models. The first four weeks of physical activity data were removed as the novelty of participants receiving a new self-monitoring device (and initial problems with set up) is likely to produce sporadic increases in physical activity. Steps were aggregated to two-week daily averages. Participants were required to have valid data for at

least the first 9 months, during which at least 12 valid weeks (6 two-week blocks) were required. This was deemed enough data to estimate initial and change in PA. Initial and change in PA were estimated by generating a linear regression between time and average daily steps per 2-week block, whereby the intercept acted as initial PA, and the beta coefficient as the change in PA. An illustrated example can be seen in **figure 7.2**.

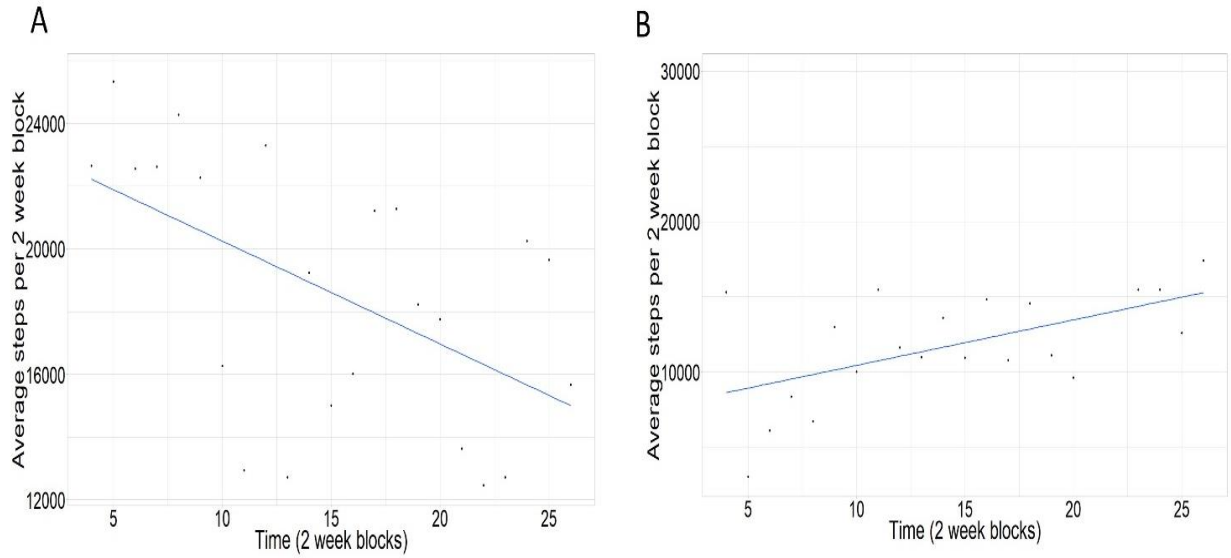


Figure 7.2. *Scatterplots from 2 example participants showing changes in physical activity (2-week average step count) over 1 year; (A) shows an initially high physical activity which reduces over time; (B) shows a moderate physical activity which increases over time*

7.2.4 Body Weight Variability

Previous studies examining associations between BWV and health have used differing calculation methods. Indeed, often multiple metrics of BWV are used, and up to 4 methods have been used in a single study recently (Nam *et al.*, 2020). This is because the relationship between BWV and health is not understood and therefore a more exploratory approach is preferable. In the current study, 4 measurements of BWV were used. Each of these have been described fully with illustrated examples in *section 4.2* but include the coefficient of variation (CV; *section 4.2.1*), the mean absolute successive variability (MASV; *section 4.2.2*), root mean square error (RMSE, *section 4.2.3*) and nonlinear mean deviation (NLMD; *section 4.2.4*). The first 3 methods have been used previously, whereas NLMD was designed as part of this and related work upon critical evaluation of available methods.

7.2.5 Statistical Analysis

Outliers were removed from body weight data collected by the Fitbit Aria scale in accordance with the physiological plausibility approach detailed in *section 4.2.1*. All key variables were assessed for normality via visual inspection of QQ plots and histograms and any variable deemed non-parametric were log transformed. Characteristics of the population at baseline were described by mean and standard deviation in the whole group and by sex due to known differences in physiological variables (particularly body composition) between sexes (**table 7.1**). Scale use was described over the course of the trial, by day of the week and by month of the year in **figure 7.3A-C** respectively. Differences between sexes were tested using student t-tests (for continuous variables) and chi-squared tests (for categorical variables). To test the main hypotheses (that greater BWV would be associated with adverse concurrent changes to health and body composition), a pre-post approach was used employing a multiple linear regression with the post-score as the outcome and pre-score as a covariate, a method which is generally preferred to regression against the change-score (Vickers and Altman, 2001). All continuous variables were standardised by taking the mean and standard deviation of all variables, subtracting the mean and dividing by the standard deviation. Weight change (%) was calculated as the difference between weight at baseline and 12-months.

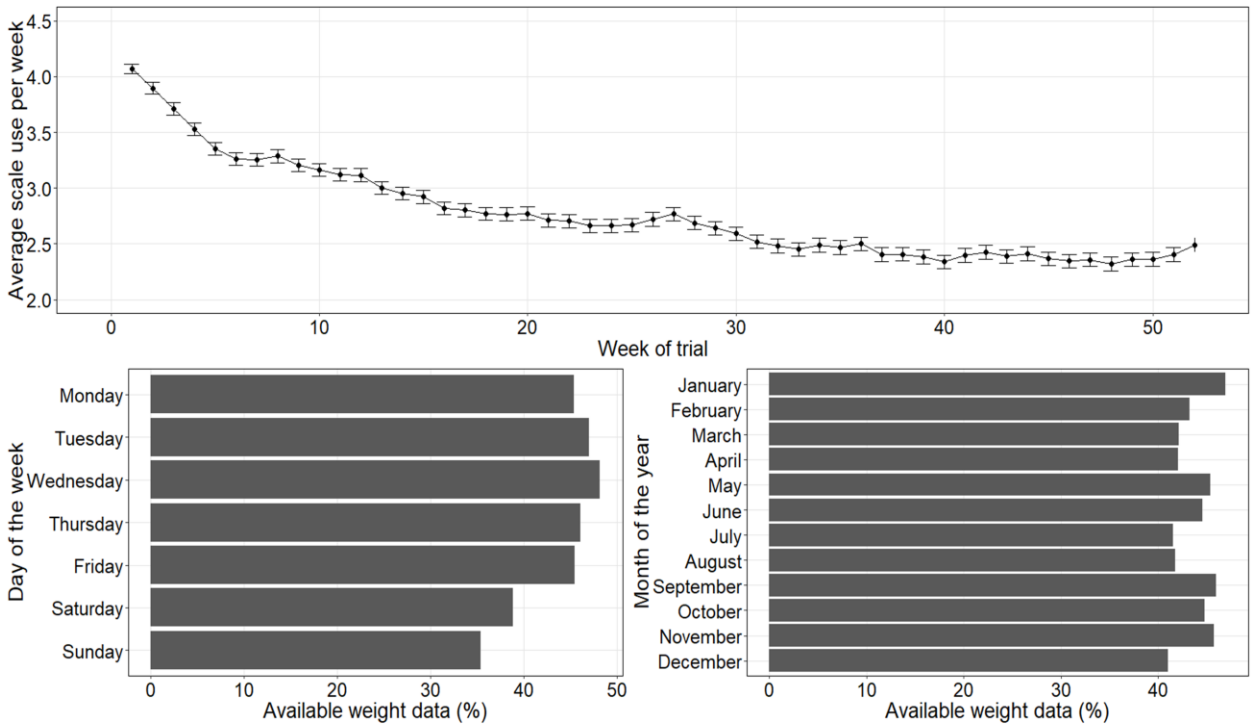


Figure 7.3. (A) *Scale use over the duration of the trial. Mean (standard error) scale use per week over the course of the trial for each week in all participants from the entire sample; (B) Frequency of scale use by day of week and (C) month of year. Frequency of weight data collected, given for each analysis (daily, seasonal and holiday). Fig (B) shows completeness of data per day of the week relative to the total amount of data possible for the given day and fig (C) shows completeness of data per month of the year relative the amount of data possible for the given year*

Three regression models were generated to test the primary hypotheses. Firstly, model 1 which included only the baseline outcome (i.e. health marker) value, weight change (%) and BWV. Secondly, model 2 included the same variables as model 1 and with additional adjustment for basic characteristics: age, sex and BMI. Lastly model 3 included the same variables as model 2 plus adjustment for initial and change in PA (steps). This was done due to the known confounding effect of PA on the relationship between weight, health and body composition. Each model was run for each health outcome and for all four methods of estimating BWV. The models were run in a separate sub-sample for those with data available for body composition measured by DXA (n=439). Full details of the DXA sub analysis are provided in **appendix 7.1.** Interactions between weight change and BWV estimates were examined but found no significant associations therefore left these out of all models. All p-values within models were adjusted for multiple comparisons using the Bonferroni-Holt method. Model results are given in **tables 7.2-7.3** which summarise the associations of weight change and BWV on outcome variables using standardized β-coefficients, standard errors and p-values. In order to compare the effect size of BWV estimates and weight change on outcomes, the change in the adjusted R^2 value of the model when the variable of interest (BWV estimate or weight change) was added to the model (which was complete except this variable) was used. As a sensitivity analysis, the data was separated into a 6-month BWV period and a follow-up period (where change in cardiometabolic markers was measured) - full details can be viewed in **appendix 7.2.** Associations were deemed significant at $p<0.05$. All analyses were conducted in R (version 3.5.1).

7.3 Results

7.3.1 Primary Analysis

Baseline characteristics are presented in **table 7.1.** A total of 955 (653 women) met the criteria for inclusion. The group had a mean weight loss of 11.8 (±5.1) % in the 12-months prior to recruitment. On average, participants were aged 45.3 (±11.5) years, overweight (BMI=29.4 (±5.0) kg/m^2) and achieved above number of recommended steps per day (Tudor-Locke *et al.*, 2011) (mean steps = 10,833 (±3,469)) around baseline. Average values for all health measures were within normal range (i.e. not hypertensive, hyperglycaemic or hyperlipidaemic (Houston *et al.*, 2005)). Over 12 months, weight change was on average +0.56 (6.6) % (ranging from -30.8 % to +36.3 %); SBP and DBP decreased by 1.7 (10.6) and 0.3 (6.8) mmHg respectively and RHR increased by 1.3 (8.5) bpm. Total cholesterol increased by 0.19 (0.66) mmol/L; LDL-C decreased by a 0.05 (0.66) mmol/L; HDL-C increased by 0.15 (0.30) mmol/L; triglycerides increased by 0.21 (0.81) mmol/L and HbA1c increased by 0.09 (0.20) %. Body fat measured by BIA decreased by 0.50 (5.0) %. Waist and hip circumferences were 93.9 (13.7) and 109.1 (10.8) cm respectively, resulting in an average WHR of 0.86 (0.09). Over 12 months, participants weighed themselves on average 159 (89) times, the frequency of which decreased over the 12-month period (see **figure 7.3A** for change in self-weighing over the trial).

Tables 7.2- 7.3 provide summary results (for BWV and weight change) from a total of 144 linear models (12 health outcomes, 4 methods of estimating BWV and 3 levels of model adjustment). Associations between BWV and health markers varied by the outcome variable and method used but were generally non-significant and inconsistent. No significant associations were observed between any measure of BWV and DBP, RHR, HDL-C or percent body fat. A significant inverse association was seen between NLMD and SBP for model 1 (β = -3.4 (1.5), p=0.026) but for no other methods or model adjustments. Significant, direct associations were observed for LDL-C between some methods of BWV and in some models, though results were generally inconsistent. Similarly, some models showed direct significant associations for triglycerides and HbA1c, though results varied between methods

Table 7.1. Participant Characteristics

Variable	All (n=955)	Male (n=302)	Female (n=653)	P-value
Centre (%)				<0.001
Denmark	354 (37.1)	63 (20.9)	291 (44.6)	
Portugal	310 (32.5)	175 (57.9)	135 (20.7)	
UK	291 (30.5)	64 (21.2)	227 (34.8)	
Age (years)	45.29 (11.5)	43.54 (10.81)	46.10 (11.81)	0.001
BMI (kg/m^2)	29.43 (5.08)	29.10 (4.44)	29.57 (5.35)	0.184
Previous weight loss (%)	11.8 (5.5)	11.2 (5.1)	12.1 (5.6)	<0.001
Weight (kg)	84.2 (16.5)	91.27 (15.7)	80.88 (15.8)	<0.001
Initial steps	10816 (3493.7)	11584 (3842.0)	10461 (3262.8)	<0.001
Number of body weight measurements	158 (89)	160 (90)	157 (89)	<0.001
SBP (mmHg)	122.17 (14.76)	127.39 (13.64)	119.75 (14.64)	<0.001
DBP (mmHg)	76.54 (8.86)	80.08 (8.61)	74.91 (8.50)	<0.001
HR (bpm)	65.43 (10.30)	62.28 (10.20)	66.88 (10.03)	<0.001
Cholesterol (mmol/L)	4.90 (1.01)	4.78 (0.91)	4.96 (1.06)	0.01
LDL-C (mmol/L)	2.77 (0.85)	2.80 (0.75)	2.75 (0.90)	0.416
HDL-C (mmol/L)	1.58 (0.41)	1.42 (0.33)	1.65 (0.41)	<0.001
Triglycerides (mmol/L)	1.21 (0.68)	1.22 (0.71)	1.21 (0.67)	0.806
HbA1c (%)	5.17 (0.34)	5.20 (0.31)	5.15 (0.35)	0.039
Fat free mass (kg)	51.8 (9.6)	61.83 (7.80)	47.11 (6.22)	<0.001
Fat mass (kg)	51.77 (9.62)	29.44 (10.94)	33.76 (12.04)	<0.001
Body fat (%)	37.79 (8.62)	31.45 (7.28)	40.73 (7.55)	<0.001
Hip (cm)	109.13 (10.76)	106.09 (8.21)	110.53 (11.49)	<0.001
Waist (cm)	93.91 (13.71)	99.22 (13.07)	91.45 (13.30)	<0.001
WHR	0.86 (0.09)	0.93 (0.08)	0.83 (0.07)	<0.001

Table 7.1. *Baseline characteristics reported as mean and standard deviation unless stated otherwise. P-values denote results of student t-tests for continuous variables and chi-squared tests for categorical variables between sexes. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.*

and adjustments and in direction and magnitude. A significant association was observed between BWV (by NLMD) and WHR, though this association was not present for any other methods of BWV. The greatest variance was explained in the direct significant relationship between RMSE and change in LDL-C (1%), with all other relationships explaining <0.9% of the variance in outcomes and most explaining 0% of the change.

With regards to weight change, in all models and after adjustment for BWV by all methods, 12-month percent weight change was consistently associated with changes indicative of improved health, with direct associations observed between weight change and changes in SBP ($p<0.001$ for all), DBP ($p<0.001$ for all), RHR ($p<0.001$ for all), total cholesterol ($p<0.05$ for all); LDL-C ($p<0.001$ for all); triglycerides ($p<0.001$ for all), HbA1c ($p<0.001$ for all) and an inverse association with changes in HDL-C ($p<0.05$ for all). Weight loss was also associated with reduced percent body fat by BIA ($p<0.001$ for all) and reduced WHR ($p<0.001$ for all). The variance explained (R^2 change) by addition of weight change to multivariate models was greatest for changes in percent body fat (10.4-11.1%) followed by changes in DBP (4.2-4.7%), SBP (3-4%), RHR (2-2.4%), triglycerides (1.8-2.4%), HbA1c (1.4-1.6%), WHR (1.6-1.9%), HDL-C (0.3-0.4%), total cholesterol (0.2-0.3%), and lastly LDL-C (0.1-0.2%).

7.3.2 DXA sub-analysis

Baseline characteristics of the DXA sub-sample and associated model results are provided in **appendix 7.1**. A summary of the results can be viewed in **table 7.3**. The 439 individuals in this sub sample gained on average 0.9 (6.2) % body weight, accompanied by a 0.06 (4.7) % increase in body fat. Weight change was directly associated with change in body fat ($p<0.001$ for all analyses) which explained between 9-11% of the variance. Significant, inverse associations between BWV (by CV and RMSE) and body fat (by DXA) were observed in all models ($p<0.05$ for all), though these explained <0.5% of the change in body fat. No associations were observed for other measures of BWV.

7.4 Discussion

This was the first study to examine associations of high-precision BWV estimates (i.e. using frequently tracked body weights) and weight change with concurrent changes in

Table 7.2. Association between weight variability measures, weight change and changes in cardiometabolic health

		Outcomes															
		SBP		DBP		Heart rate		Cholesterol		LDL-C		HDL-C		Triglycerides		HbA1c	
Model	Predictor	β (SE)	P	β (SE)	P	β (SE)	P	β (SE)	P	β (SE)	P	β (SE)	P	β (SE)	P	β (SE)	P
1	NLMD	-3.14 (1.44)	0.04	-1.96 (0.95)	0.051	0.83 (1.19)	0.484	0 (0.11)	0.999	0.08 (0.04)	0.067	-0.02 (0.1)	0.827	-0.22 (0.11)	0.042	0.02 (0.03)	0.541
	Weight change	0.37 (0.05)	<0.001	0.28 (0.03)	<0.001	0.24 (0.04)	<0.001	0.01 (0)	0.065	-0.01 (0)	<0.001	0.01 (0)	0.022	0.02 (0)	<0.001	0.01 (0)	<0.001
	CV	0.13 (0.24)	0.603	0.13 (0.16)	0.423	0.16 (0.2)	0.409	0.02 (0.02)	0.22	0.02 (0.01)	0.017	0.01 (0.02)	0.553	-0.02 (0.02)	0.384	0.01 (0.01)	0.014
	Weight change	0.38 (0.05)	<0.001	0.29 (0.03)	<0.001	0.25 (0.04)	<0.001	0.01 (0)	0.027	-0.01 (0)	<0.001	0.01 (0)	0.019	0.01 (0)	<0.001	0.01 (0)	<0.001
	RMSE	-0.35 (0.47)	0.616	0 (0.31)	0.997	-0.14 (0.39)	0.735	0.07 (0.04)	0.062	0.07 (0.01)	<0.001	0.02 (0.03)	0.432	-0.07 (0.04)	0.063	0.01 (0.01)	0.154
	Weight change	0.36 (0.05)	<0.001	0.28 (0.03)	<0.001	0.24 (0.04)	<0.001	0.01 (0)	0.022	-0.01 (0)	<0.001	0.01 (0)	0.017	0.01 (0)	<0.001	0.01 (0)	<0.001
	MASWV	-1.7 (0.98)	0.109	-1.24 (0.64)	0.071	0.44 (0.81)	0.589	-0.04 (0.07)	0.553	-0.03 (0.03)	0.252	0.05 (0.07)	0.42	-0.17 (0.07)	0.016	0.02 (0.02)	0.335
	Weight change	0.37 (0.05)	<0.001	0.28 (0.03)	<0.001	0.24 (0.04)	<0.001	0.01 (0)	0.045	-0.01 (0)	<0.001	0.01 (0)	0.025	0.02 (0)	<0.001	0.01 (0)	<0.001
2	NLMD	-1.02 (1.41)	0.547	-1.01 (0.95)	0.334	1.17 (1.2)	0.334	0.06 (0.11)	0.661	0.04 (0.04)	0.404	0.06 (0.1)	0.556	-0.13 (0.11)	0.253	0.02 (0.03)	0.51
	Weight change	0.42 (0.04)	<0.001	0.31 (0.03)	<0.001	0.25 (0.04)	<0.001	0.01 (0)	0.02	-0.01 (0)	<0.001	0.01 (0)	0.006	0.02 (0)	<0.001	0.01 (0)	<0.001
	CV	-0.03 (0.24)	0.901	0.04 (0.16)	0.82	0.01 (0.2)	0.971	0.03 (0.02)	0.166	0.02 (0.01)	0.015	0.02 (0.02)	0.307	-0.03 (0.02)	0.171	0.01 (0.01)	0.026
	Weight change	0.42 (0.05)	<0.001	0.31 (0.03)	<0.001	0.25 (0.04)	<0.001	0.01 (0)	0.006	-0.01 (0)	<0.001	0.01 (0)	0.002	0.02 (0)	<0.001	0.01 (0)	<0.001
	RMSE	-0.12 (0.46)	0.789	0.07 (0.31)	0.809	-0.26 (0.39)	0.597	0.09 (0.04)	0.017	0.06 (0.01)	<0.001	0.05 (0.03)	0.146	-0.06 (0.03)	0.117	0.01 (0.01)	0.259
	Weight change	0.42 (0.05)	<0.001	0.31 (0.03)	<0.001	0.25 (0.04)	<0.001	0.01 (0)	0.004	-0.01 (0)	<0.001	0.01 (0)	0.002	0.02 (0)	<0.001	0.01 (0)	<0.001
	MASWV	-0.77 (0.95)	0.491	-0.84 (0.64)	0.216	0.82 (0.81)	0.314	-0.02 (0.07)	0.865	-0.04 (0.03)	0.155	0.06 (0.07)	0.327	-0.11 (0.07)	0.132	0.02 (0.02)	0.431
	Weight change	0.43 (0.04)	<0.001	0.31 (0.03)	<0.001	0.25 (0.04)	<0.001	0.01 (0)	0.014	-0.01 (0)	<0.001	0.01 (0)	0.006	0.02 (0)	<0.001	0.01 (0)	<0.001
3	NLMD	-1.17 (1.41)	0.46	-1.04 (0.95)	0.412	1.29 (1.2)	0.282	0.07 (0.11)	0.588	0.03 (0.04)	0.499	0.07 (0.1)	0.549	-0.14 (0.11)	0.316	0.02 (0.03)	0.646
	Weight change	0.44 (0.04)	<0.001	0.31 (0.03)	<0.001	0.23 (0.04)	<0.001	0.01 (0)	0.057	-0.01 (0)	<0.001	0.01 (0)	0.026	0.02 (0)	<0.001	0.01 (0)	<0.001
	CV	-0.04 (0.24)	0.867	0.03 (0.16)	0.905	0.02 (0.2)	0.926	0.03 (0.02)	0.14	0.02 (0.01)	0.021	0.02 (0.02)	0.277	-0.03 (0.02)	0.214	0.01 (0.01)	0.025
	Weight change	0.44 (0.05)	<0.001	0.31 (0.03)	<0.001	0.23 (0.04)	<0.001	0.01 (0)	0.021	-0.01 (0)	<0.001	0.01 (0)	0.011	0.02 (0)	<0.001	0.01 (0)	<0.001

RMSE	-0.16 (0.46)	0.732	0.06 (0.31)	0.907	-0.24 (0.39)	0.61	0.09 (0.04)	0.019	0.06 (0.01)	<0.001	0.05 (0.03)	0.115	-0.06 (0.04)	0.127	0.01 (0.01)	0.223
Weight change	0.44 (0.05)	<0.001	0.31 (0.03)	<0.001	0.23 (0.04)	<0.001	0.01 (0)	0.016	-0.01 (0)	<0.001	0.01 (0)	0.009	0.02 (0)	<0.001	0.01 (0)	<0.001
MASWV	-0.81 (0.95)	0.442	-0.85 (0.64)	0.274	0.85 (0.81)	0.292	-0.02 (0.07)	0.771	-0.04 (0.03)	0.195	0.07 (0.07)	0.342	-0.11 (0.07)	0.17	0.02 (0.02)	0.441
Weight change	0.44 (0.04)	<0.001	0.31 (0.03)	<0.001	0.23 (0.04)	<0.001	0.01 (0)	0.043	-0.01 (0)	<0.001	0.01 (0)	0.026	0.02 (0)	<0.001	0.01 (0)	<0.001

Table 7.2. *Summary results from 3 multiple linear regression models predicting changes in health outcomes. Results are given as standardised β values and associated standard errors and significance values for the two predictors of interest. Model 1 was adjusted for baseline values of the outcome, weight change and weight variability (separate models for each method of estimating weight variability). Model 2 was adjusted for model one plus baseline BMI, age and sex. Model 3 was adjusted for model 2 plus initial and change in physical activity estimated from Fitbit devices. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; NLMD, non-linear mean deviation; CV, co-efficient of variation; RMSE, root-mean square-error; MASWV, mean average successive weight variability.*

Table 7.3. Association between weight variability measures, weight change and changes in body composition

		Outcome									
			Fat mass (kg)	Fat-free mass (kg)		Body fat (%)		Waist-hip ratio		Body fat (DXA) (n=439)	
Model	Predictor	β (SE)	P	β (SE)	P	β (SE)	P	β (SE)	P	β (SE)	P
1	NLMD	-0.77 (0.54)	0.206	-0.62 (0.5)	0.283	-0.18 (0.61)	0.773	-0.014 (0.006)	0.024	-1.53 (0.78)	0.066
	Weight change	0.73 (0.02)	<0.001	0.13 (0.02)	<0.001	0.45 (0.02)	<0.001	0.002 (0)	<0.001	0.47 (0.03)	<0.001
	CV	-0.1 (0.09)	0.266	-0.04 (0.08)	0.655	-0.05 (0.1)	0.624	-0.002 (0.001)	0.08	-0.48 (0.14)	0.001
	Weight change	0.73 (0.02)	<0.001	0.13 (0.02)	<0.001	0.45 (0.02)	<0.001	0.002 (0)	<0.001	0.46 (0.03)	<0.001
	RMSE	0.25 (0.18)	0.156	-0.36 (0.16)	0.036	0.28 (0.2)	0.16	-0.003 (0.002)	0.135	-0.73 (0.27)	0.011
	Weight change	0.74 (0.02)	<0.001	0.13 (0.02)	<0.001	0.45 (0.02)	<0.001	0.002 (0)	<0.001	0.46 (0.03)	<0.001
	MASWV	-0.54 (0.37)	0.195	0.08 (0.34)	0.824	-0.72 (0.42)	0.112	-0.005 (0.004)	0.199	-0.51 (0.69)	0.614
	Weight change	0.73 (0.02)	<0.001	0.13 (0.02)	<0.001	0.45 (0.02)	<0.001	0.002 (0)	<0.001	0.48 (0.03)	<0.001
2	NLMD	-0.73 (0.53)	0.202	-0.41 (0.49)	0.468	-0.17 (0.59)	0.78	-0.009 (0.006)	0.12	-1.54 (0.81)	0.136
	Weight change	0.74 (0.02)	<0.001	0.15 (0.02)	<0.001	0.45 (0.02)	<0.001	0.002 (0)	<0.001	0.48 (0.03)	<0.001
	CV	-0.14 (0.09)	0.125	-0.03 (0.08)	0.754	-0.13 (0.1)	0.184	-0.001 (0.001)	0.288	-0.46 (0.14)	0.003
	Weight change	0.73 (0.02)	<0.001	0.15 (0.02)	<0.001	0.44 (0.02)	<0.001	0.002 (0)	<0.001	0.46 (0.03)	<0.001
	RMSE	0.25 (0.17)	0.152	-0.33 (0.16)	0.045	0.25 (0.19)	0.201	-0.001 (0.002)	0.478	-0.71 (0.28)	0.027

	Weight change	0.74 (0.02)	<0.001	0.14 (0.02)	<0.001	0.46 (0.02)	<0.001	0.002 (0)	<0.001	0.46 (0.03)	<0.001
	MASWV	-0.62 (0.36)	0.097	-0.11 (0.33)	0.853	-0.61 (0.4)	0.149	-0.005 (0.004)	0.182	-0.54 (0.69)	0.536
	Weight change	0.74 (0.02)	<0.001	0.15 (0.02)	<0.001	0.45 (0.02)	<0.001	0.002 (0)	<0.001	0.48 (0.03)	<0.001
3	NLMD	-0.7 (0.53)	0.24	-0.41 (0.49)	0.511	-0.13 (0.59)	0.822	-0.01 (0.006)	0.142	-1.53 (0.81)	0.135
	Weight change	0.73 (0.02)	<0.001	0.15 (0.02)	<0.001	0.44 (0.02)	<0.001	0.002 (0)	<0.001	0.47 (0.03)	<0.001
	CV	-0.13 (0.09)	0.145	-0.02 (0.08)	0.854	-0.13 (0.1)	0.196	-0.001 (0.001)	0.361	-0.44 (0.14)	0.005
	Weight change	0.72 (0.02)	<0.001	0.15 (0.02)	<0.001	0.44 (0.02)	<0.001	0.002 (0)	<0.001	0.46 (0.03)	<0.001
	RMSE	0.25 (0.17)	0.173	-0.32 (0.16)	0.061	0.25 (0.19)	0.196	-0.001 (0.002)	0.508	-0.7 (0.28)	0.037
	Weight change	0.74 (0.02)	<0.001	0.15 (0.02)	<0.001	0.45 (0.02)	<0.001	0.002 (0)	<0.001	0.45 (0.03)	<0.001
	MASWV	-0.61 (0.36)	0.112	-0.12 (0.33)	0.919	-0.6 (0.4)	0.173	-0.005 (0.004)	0.227	-0.57 (0.69)	0.619
	Weight change	0.73 (0.02)	<0.001	0.15 (0.02)	<0.001	0.44 (0.02)	<0.001	0.002 (0)	<0.001	0.47 (0.03)	<0.001

Table 7.3. *Summary results from 3 multiple linear regression models predicting changes in body composition. Results are given as standardised β values and associated standard errors and significance values for the two predictors of interest. Model 1 was adjusted for baseline values of the outcome, weight change and weight variability (separate models for each method of estimating weight variability). Model 2 was adjusted for model one plus baseline BMI, age and sex. Model 3 was adjusted for model 2 plus initial and change in physical activity estimated from Fitbit devices. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; NLMD, non-linear mean deviation; CV, co-efficient of variation; RMSE, root-mean square-error; MASWV, mean average successive weight variability.*

markers of cardiometabolic disease and body composition. It was found that weight loss across 12 months was consistently associated with improvements in all indices of health and reduced percent body fat (as measured by both BIA and DXA). Associations between 12-month BWV and changes in cardiometabolic health markers were weak and inconsistent between models. Direct associations between BWV (by RMSE and CV) and change in percent body fat (by DXA) were observed which were significant in all models but explained no more than 0.5% of the observed effect. In the sensitivity analysis (see **appendix 7.2**) which employed a longitudinal structure by temporal separation of exposure and outcome, the results of the primary analysis were supported such that there was no consistent effect of BWV.

7.4.1 Associations Between BWV and Change in Health Markers and Body Composition

The associations between BWV and health outcomes were inconsistent between models and generally explained around 0% of the variance in health marker responses. This is inconsistent with some previous evidence (largely in relation to weight cycling rather than BWV, as research on BWV and health markers is sparse) - for example, a previous study showed significant associations between greater self-reported history of weight cycling history and lower HDL-C in 485 women, however observed no associations on blood pressure, glucose and other blood lipids (Olson *et al.*, 2000). In a similar study, self-reported weight cycling history in 121 women was associated with increased waist circumference, resting metabolic rate (per kg) and adiponectin, however no impact on the metabolic risk factors measured in the present study (Strychar *et al.*, 2009). In another study, self-reported weight cycling increased the risk of hypertension after 2 years (Schulz *et al.*, 2005), with similar results reported by a recent study which suggested this effect was mediated by increased visceral adipose tissue (Zeigler *et al.*, 2018). No associations between any measure of BWV and body composition or WHR were found, as hypothesised previously (Rodin *et al.*, 1994; Montani, Schutz and Dulloo, 2015a). Results from an analysis of 3,632 Framingham health study participants showed an increased risk of becoming metabolically unhealthy (67%); getting type 2 diabetes (58%) and getting hypertension (74%) in those defined as having high BWV compared to stable body weight (Sponholtz *et al.*, 2019). However,

individuals with high BWV were also 163% more likely to have obesity. Conversely, some studies have shown no associations between measures of weight instability (be that weight cycling or BWV) and health markers (see **table 3.3** for a detailed review).

Further physiological evidence in favour of a detrimental effect comes from a string of recent animal studies exposing mice to weight cycling (see section 3.4.2 for a full review) which have shown detrimental effects on glucose (Schofield *et al.*, 2017) and insulin (Simonds, Pryor and Cowley, 2018b) levels, inflammatory markers (Li *et al.*, 2018) and hepatic steatosis (Barbosa-da-Silva *et al.*, 2012), though again some studies show no effect (see **table 3.4** for a synthesis of available evidence). Notably, these animal model studies have the advantage of being able to accurately manipulate body weight, though physiological effects cannot necessarily be extrapolated to humans. However, the relative magnitude of weight manipulation in animal models is often of considerably greater magnitude than measured here.

Some evidence has suggested that weight instability (specifically in this instance, weight cycling) has detrimental effects of body composition due to the repartitioning of weight from FFM to FM. This is suggested to occur because the fraction of FFM lost during weight loss is greater than that regained upon weight recovery (Dulloo, Miles-Chan and Schutz, 2018), though is hypothesised to operate specifically in lean individuals (Dulloo *et al.*, 2015) primarily because individuals with overweight and obesity have greater FM stores to protect against greater amounts of FFM loss during weight loss (Forbes, 1987; Hall, 2007). In the present study, no consistent associations between BWV and body composition changes by bioelectrical impedance were observed. However, in the subsample of individuals with available DXA measurements, greater BWV (as calculated by RMSE and CV) was consistently (in all model adjustments) associated with decreased body fatness (after adjustment for overall weight change), though these explained no more than 0.5% of the variance in body fat change. This could be considered inconsistent with the above hypothesis, however three important caveats to this result are notable: (a) these effects are miniscule and probably of no substantial value when considering body composition changes over 12-months; (b) the present sample had overweight or obesity, and the effect was hypothesised by Dulloo et al. to operate in originally lean individuals and (c) the magnitude of measured weight variability is not analogous to large weight cycles of >20% body weight from which the original hypothesis was generated. Further research examining the

associations of weight instability and changes in body composition are required over longer periods using multi-compartment models of body composition to account for changes in the composition of FFM, which are more likely related to water fluctuations (Bhutani *et al.*, 2017b).

7.4.2 Associations Between Weight Change and Change in Health Markers

As expected, the associations between weight loss and improvements in health markers are well-supported by results from observational studies (Lorna S Aucott *et al.*, 2016; Sabaka *et al.*, 2017), clinical trials (Richard F Hamman *et al.*, 2006; Rena R Wing *et al.*, 2011a) and meta-analyses (Ma *et al.*, 2017b). By standardising regression coefficients, direct comparisons between the magnitude of each relationship could be made (in addition to variance explained or R^2). Following adjustment, the strongest associations with 12-month weight change were seen for changes in SBP and percent body fat, followed by DBP and heart rate. Associations with changes in blood lipids and HbA1c were minor, consistent with previous research showing that body weight is more closely related to blood pressure than lipids (Wadden, Anderson and Foster, 1999; Rena R Wing *et al.*, 2011a), potentially because blood lipids are more strongly influenced by diet or exercise (Clifton, 2019). To adjust for the potentially confounding effect of PA, initial and change in steps recorded from the Fitbit Charge 2 was added to model 3, though this did not significantly affect models.

7.4.3 Strength and Limitations

This study has several strengths. BWV was estimated using frequent measures of body weight (~3 times per week) over 12 months which attenuates the potential error associated with infrequent measurements used to estimate BWV in previous studies. Multiple methods of calculating BWV were employed due to heterogeneity in the statistical approaches used in previous studies. A new method of calculating BWV was applied based on critical evaluation of present methods (see *section 3.1*), termed NLMD, which aimed to overcome the assumption of linearity associated with previous methods. Weight data was collected using Wi-Fi-connected smart scales, overcoming the biases associated with self-reported data.

There are also limitations to consider. First, the composition of weight changes which contribute to the BWV estimates is unknown and could be related to fluctuations in

total body water (see section 10.3 for a detailed discussion of this limitation). The sample were recent weight losers (mean of 11.8% weight loss in the past 12-months) and had therefore experienced recent health improvements which may limit subsequent responses. This is supported by the observation that the sample were, on average, obese at baseline (BMI=29.4 kg/m^2) yet all mean baseline health measures were within healthy range. It has been hypothesised that BWV is a risk factor for disease in populations with pre-existing disease (Zoppini *et al.*, 2008; Lorna S Aucott *et al.*, 2016; Bangalore *et al.*, 2017) and therefore effects may be limited in this (on average) metabolically healthy sample. The BWV observed in the current sample who were aiming to maintain recent weight loss may not be representative of the general population as discussed previously (*section 6.4.4*). Next, the sample was comprised mostly of individuals with overweight and obesity, though it is hypothesised that BWV has greater effect on health and body composition in lean individuals (Montani, Schutz and Dulloo, 2015a). The exposure (to BWV) and outcomes (changes in health markers) were measured concurrently over the same time period and therefore causality cannot be inferred. To address this, a sensitivity analysis was conducted with a longitudinal structure (investigating the effect of 0-6-month BWV and weight change on subsequent changes in outcome variables), though results did not differ (see appendix 7.2 for full details). Lastly, cardiometabolic measurements were only made over 12 months, though many longitudinal studies showing detrimental effects of BWV occur over several years or decades.

7.5 Conclusions

In chapter 3, the impact of retrospective and prospectively measured BWV on cardiometabolic health was comprehensively reviewed and it was concluded that over the long-term there is reasonable evidence to believe that BWV is potentially a risk factor for disease and mortality, but also concluded that there is no clear physiological mechanism identified in the aetiology of this association. The most likely pathway for this association (via detrimental effects to traditional risk factors) was considered by examining associations between BWV and changes in the primary risk factors for cardiometabolic disease. This was done for a limited period of 12-months. There was little evidence to support the hypothesis that BWV has any substantial association with changes in risk factors for cardiometabolic

disease or body composition over a 12-month measurement period in a sample who had recently lost ~11% body weight, though weight loss was consistently associated with health benefits as expected.

7.6 Future Study of Body Weight Variability and Health

This leaves the question of why might BWV act as a risk factor for disease? In a series of medical literature, the concept visit-to-visit (V2V) variability (i.e. variability in a given health marker, independent of the mean value) has been proposed to be a pathway to disease incidence and mortality. A recent meta-analysis concluded that V2V blood pressure was an independent risk factor for both CVD and mortality (Diaz *et al.*, 2014), with similar reports provided by studies on V2V cholesterol concentrations (Lee *et al.*, 2018; Gu *et al.*, 2019) and V2V HbA1c (Li *et al.*, 2020). Given the knowledge that each of these health markers generally track changes in body weight (e.g. a reduction in weight causes a reduction in blood pressure, as shown above), it could be plausible that the variability in body weight is a cause of V2V variability. In this regard, BWV would not need to affect the mean value, but instead the variability. Further research should aim to investigate the associations between BWV and V2V health marker variability in the aetiology of disease incidence using longitudinally collected markers of health.

Another possibility is that physiological variability is a proxy for underlying disease, or disease status/progression (such as in samples where disease incidence is an eligibility criterion). This disease status (diagnosed or undiagnosed) may disturb physiological homeostasis in a manner which exaggerates weight and/or health variability. At follow-up, such individuals are then more likely to have encountered a health event or death. Indeed, studies aiming to examine BWV in healthy population do generally screen for health conditions, however, these may be undiagnosed or in the early stages, and may function to confound results made based on several years (or decades) of follow-up.

Nonetheless, in order to progress the study of the relationship between BWV and health, appropriately designed study which collect frequent measurements of body weight tracked longitudinally over several years, coinciding with both longitudinal measurement of health markers and ideally follow-up periods in which hard outcomes can be quantified are required.

Chapter 8. Associations Between Short-Term Body Weight Variability and Longer-Term Weight Outcomes

The NoHoW trial was designed to tackle the problem of weight regain following weight loss. Weight regain is a complex phenomenon which has been reviewed extensively from physiological, biopsychological and behavioural perspectives, as discussed in section 1.3. Identifying key predictors of weight regain is an important task, and more so, being able to identify these early on in an intervention would be highly useful. One novel risk factor which has recently been identified for weight gain or less successful weight loss maintenance is BWV. In the following section, a comprehensive analysis is conducted which investigates the associations of initial body weight variability and later weight outcomes in the NoHoW trial.

The chapter is adapted from a publication in the International Journal of Obesity (J. Turicchi *et al.*, 2020). The data used was collected as part of the NoHoW trial. I was solely responsible for the conceptualisation, data analysis and primary manuscript writing of this study. All other authors were responsible for providing suggested edits.

8.1 Introduction

8.1.1 Identification of Weight Outcome Predictors

In various weight loss and maintenance interventions, individual success is difficult to predict and considerable interindividual variability is often observed in body weight responses to a given intervention (Williamson, Atkinson and Batterham, 2018). In predictive (baseline) models, predictors often explain up to 20-30% of the variance in weight loss maintenance (or weight regain) and in many models these predictors are the sum of other predictors (i.e. show multicollinearity between predictors), with constituent predictors accounting for much smaller sums of the variance (Stubbs *et al.*, 2011). In some cases, including the large European DiOGenes trial (McConnon *et al.*, 2012) and the NoHoW trial (personal communication, RJ Stubbs and G Horgan), most of the variance in weight outcomes remains unexplained after modelling characteristic, physiological and self-reported psychological and behavioural factors together. For example, in a re-analysis of the DiOGenes data, a statistical model for the theory of planned behaviour using a substantial

amount of relevant variables explained a maximum of 11% of the variance in weight regain (McConnon *et al.*, 2012).

Evidence from meta-analyses and systematic reviews has identified some consistent predictive factors from medium to longer-term weight loss and maintenance studies. These include self-regulatory factors (Teixeira *et al.*, 2015a; Varkevisser *et al.*, 2019), particularly self-weighing (Madigan *et al.*, 2015b; Zheng *et al.*, 2015b); motivation and self-determination (Pedro J Teixeira *et al.*, 2012) and behavioural factors such as greater physical activity (Hall and Kahan, 2018) and consistent eating patterns (Wing and Phelan, 2005). In addition, participant adherence as well as greater and more prolonged trial engagement (Gill *et al.*, 2012) have been associated with success, while attrition is generally believed to be an indicator of weight relapse. Some evidence suggests weight history variables, including previous dieting prevalence (Lowe *et al.*, 2006), weight cycling (Hart and Warriner, 2005) and weight suppression (Stice *et al.*, 2011) may predict increased future weight, though whether these factors are a proxy or a cause of increased weight is unclear (Lowe, 2015). Nonetheless, each of these factors are likely to explain only minor fractions of the variance in weight changes, as with most pre-treatment predictors. Indeed, standardization of predictive constructs using established frameworks and objectively tracked data may improve the resolution by which weight outcomes can be predicted. Recently, the use of Wi-Fi connected physical activity and body weight tracking devices has allowed for real-time collection of data which can be assessed in real time and may potentially be used for prediction.

8.1.2 Early Predictors of Weight Outcomes

Identifying early predictors of weight loss or maintenance success improves the ability to personalise intervention features and identify those individuals who require further intervention. Furthermore, evidence suggests that collecting data on early predictors (e.g. within the first 4 weeks of a trial) may provide substantially greater predictive value than baseline predictors (Handjieva-Darlenska *et al.*, 2010b). The most common early predictor of weight loss success is initial weight loss (Elfhag and Rossner, 2005; Nackers, Ross and Perri, 2010; Casazza *et al.*, 2015; Miller, Nagaraja and Weinhold, 2015). Other early-treatment predictors shown to be associated with longer-term outcomes include first-month increases in dietary restraint and healthy lifestyle ratings, shown in 186 women with

overweight and obesity undergoing a 12-month weight loss intervention (James *et al.*, 2018) as well as initial adherence and engagement (Jiandani *et al.*, 2016).

In the DiOGenes trial, which used a low-calorie diet (~800kcal) to reduce body weight by >= 8% over 8 weeks, initial weight loss at 1 and 3 weeks were strongly associated with weight loss at week 8, together explaining 68% of the variance in weight change. Authors showed that a 1-week weight loss of >= 2.6kg could predict a weight loss of >= 10kg at 8 weeks with around 70% sensitivity and specificity (Handjieva-Darlenska *et al.*, 2010b). Weight change in the initial 1 and 2 months of a lifestyle intervention was shown to predict weight change as far as 8-years in the future in 2,290 participants of the LOOK AHEAD trial, with substantial effect sizes reported (Unick *et al.*, 2015). Indeed, initial weight loss is likely to be indicative of engagement with behaviour change and actual changes in energy balance, and therefore is an objective measure. Collecting objective data during interventions may have considerable predictive value, however only a few early predictors have been identified. Body weight variability is another objective marker which may potentially be used to predict intervention success.

8.1.3 Short-term Body Weight Variability

As discussed previously, as a time series variable, body weight has both a trend (e.g. loss or gain) and an associated variability around that trend, which is termed BWV. While the associations between short and longer-term weight change seem well established, whether short-term BWV influences longer-term weight changes is unclear and only a handful of studies have prospectively examined this relationship. In two earlier studies, Lowe and colleagues found direct associations between BWV measured at the start of a weight loss intervention (i.e. over 6 or 12 weeks (Feig and Lowe, 2017)) or, in the initial 26 weeks of an observational study (Lowe *et al.*, 2015), and longer-term weight outcomes at 12-24 months. In one study, only 3 body weights were used to estimate BWV over 26 weeks (Lowe *et al.*, 2015) which limits the resolution of BWV estimates. The second study used weekly lab-based body weights (Feig and Lowe, 2017), however, reliance on weekly lab-based measurements increases both participant and research burden substantially and thus reduces the scalability of such investigations.

One solution to this problem is to collect body weight data using Wi-Fi connected smart scales which can be used in large groups at home with little burden. In a recent study,

which was a retrospective analysis of data collected from 24,009 smart scale users who declared that they were engaged in a weight loss attempt, positive associations between initial 12-week BWV and weight changes at 48, 72 and 96 weeks were observed. However, these models were not sufficiently adjusted for confounding factors and effects were statistically attenuated following adjustment for age. Furthermore, the influence of (a) the method of BWV and (b) the measurement duration of BWV on the observed effects was not investigated. Lastly, none of the aforementioned studies were conducted in individuals engaged in a weight loss maintenance intervention.

8.1.4 Objectives

As part of a secondary investigation using data collected during the NoHoW trial (see section 4.1), the aim of the following study was to:

1. Investigate the associations of short-term (6, 9 and 12 week) BWV and longer term (6, 12 and 18 month) weight change in subjects who recently achieved ≥5% weight loss
2. Investigate the influence of measurement duration and follow-up duration on the observed associations

It was hypothesised that greater BWV in the short-term would be associated with increased weight in the longer term; and that both longer BWV measurement durations and follow-up durations would show increased effect sizes.

8.2 Methods

8.2.1 Study Design

The present study was an ad hoc analysis of data collected as part of the NoHoW trial which is detailed extensively in section 4.1.

8.2.2 Participants

Full eligibility criteria for the NoHoW trial is provided in section 4.1.4.1. A participant flow diagram is provided in **figure 8.1**. For inclusion in the present analysis, the following criteria must have been met: (1) ≥10 weight measurements over the first ≥5 weeks (n=1,335); (2) ≥15 weight measurements over the first ≥8 weeks (n=1,224) and (3) ≥20

weight measurements over the first ≥10 weeks (n=1,223) – a total of 1,056 participants met these requirements. This allowed short-term BWV to be calculated over three durations (6, 9 and 12 weeks). Also, body weights at outcome periods of 6 months (n=1369), 12 months (n=1256) and 18 months (n=1072) were all required, defined as the closest weight to 182, 365 and 547 days, within a 2-week window either side of this day. A total of 980 participants met these criteria. A 1-month range around the specified time point was allowed to increase the inclusion of more participants who fell within this time window without limiting the temporal separation between outcome periods (if a larger time range was used). This duration was later used as a numeric covariate to account for individual differences in the duration of the follow-up period. If a weight was not available within 2 weeks either side, the participant was excluded from the analysis. This left a final sample size of n=715.

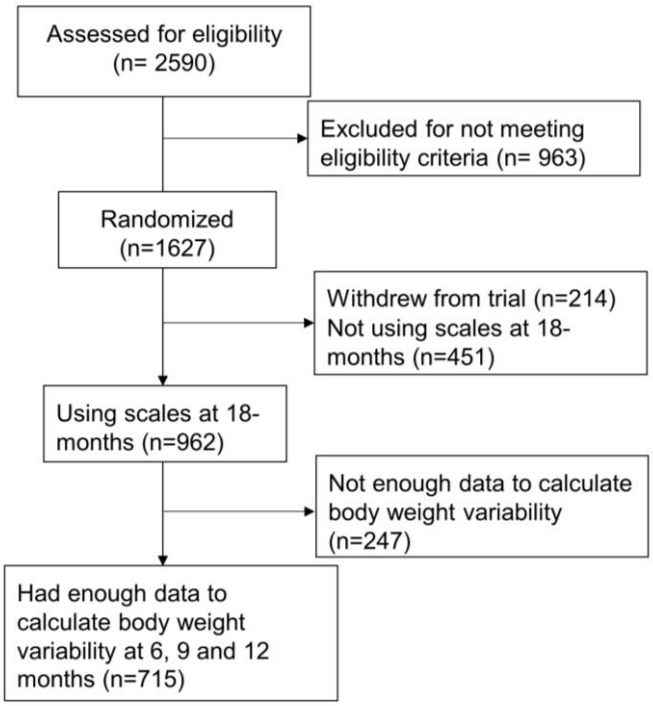


Figure 8.1 *Participant flow diagram*

8.2.3 Prior Weight Loss

Participants were asked to provide verified evidence (by a health professional, weight loss counsellor/friend, weight loss programme record booklet, diary or smartphone app or before/after photographs) of their highest weight and lowest body weights in the 12 months prior to recruitment. Twelve-month weight loss was calculated as the difference

between the highest and lowest weight, and converted to relative (%) weight loss, which was used as a covariate in model 2.

8.2.4 Body Weight

Body weight data was collected via the Fitbit Aria scale, the measurement tool is described in detail in section 4.1.6.1. Scale use was described as average use per week over the 18-month period, and percentage use per day and month respectively (**figure 8.2**). Body weight data was not imputed, as informed by previous simulation-validation research by this group which showed that imputation serves to bias (underestimate) variability, which is largely a stochastic process (Jake Turicchi, O'Driscoll, Finlayson, Duarte, Antonio L Palmeira, *et al.*, 2020).

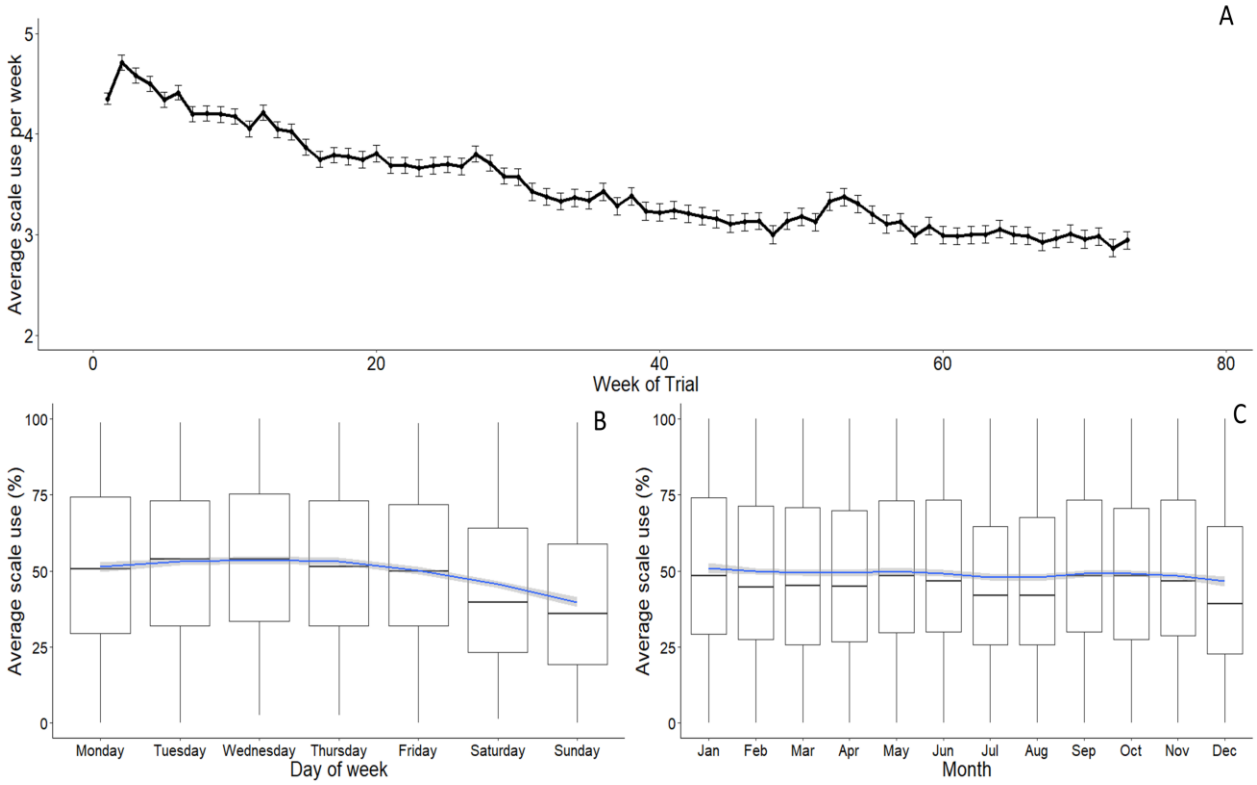


Figure 8.2. *Description of the frequency of participant smart scale use throughout the trial in eligible participants (n=715). (A) Mean scale use and error per week over 18-months of the trial; (B) scale use on each day of the week as a percentage of total available days for that day; (C) scale use on each month of the year as a percentage of total available days for that month*

8.2.5 Body Weight Variability

Body weight variability was calculated by linear (root mean square error; RMSE) and non-linear (nonlinear mean deviation; NLMD) methods. These methods are described in section 4.2.2. All BWV values outside of 4 standard deviations from the mean were removed to filter outliers, as done previously (Benson *et al.*, 2020). Each of these metrics were calculated for the first 6, 9 and 12 weeks of the trial, in participants with sufficient data. The correlations (Pearson) between standardized estimates of BWV and weight change during the initial 6, 9 and 12-week BWV periods were calculated (**Appendix 8.1**) These durations were chosen after consulting previous research (Feig and Lowe, 2017; Benson *et al.*, 2020).

8.2.6 Statistical Analysis

The current analysis was not originally powered to test the primary hypothesis of this study and therefore should be considered exploratory. Body weight data from scales was screened for outliers based on limits of physiological plausibility of weight change (see section 4.2.1 for information on data cleaning). All key variables were assessed for normality via visual inspection of QQ plots and histograms. Characteristics of the analysed sample at baseline were described by mean and standard deviation or percentage for categorical variables in **table 8.1** and compared to the entire NoHoW sample at baseline. To describe weight changes over the trial, mean weight change over 18-months was plotted (**figure 8.3A**), as was the association between baseline and change in weight (**figure 8.3B**). To test our primary hypotheses, the difference between the final weight in the BWV period (e.g. at 6, 9 or 12 weeks), and the follow-up weight (e.g. at 6, 12 and 18 months) was calculated, and this change-score was converted to relative (%) change by dividing by the final weight in the BWV period (and multiplied by 100). These values were treated as the outcomes, generating 9 exposure-outcome combinations. Scatterplots with linear trendlines were generated for each combination (**figure 8.4**). BWV metrics were standardised to z-scores before visualisation and analysis to improve comparability.

Next, 2 multivariate linear regression model designs were produced. Models were generated for (a) each exposure-outcome combination and (b) each method of calculating BWV, creating a total of 18 combinations for each model design (36 total models). First, crude models were generated including the weight change-score as the outcome, and BWV as the predictor (adjusted for weight at the end of the BWV period and duration of the

follow-up period). Second, model 2 was additionally adjusted for number of weight measurements used to calculate BWV, age, sex, previous weight loss and trial arm. Sex*BWV interactions were examined but found no significant effects so did not include these in models. Results are summarised in **table 8.2**. Additionally, an illustrated summary of the primary results is shown in **figures 8.5-8.6**. Note that delta adjusted R^2 refers to the change in R^2 upon addition of the BWV variable to the model. Full model results for all covariates can be found in appendix 8.2. As an ad-hoc test, the difference between percentage weight change at +/- 1 SD of BWV was examined in our strongest model to explore the clinical value of the regression results. This was done by subtracting (low BWV) and adding (high BWV) one SD from the mean of the BWV measure and then taking the mean of the weight change in each group. All analyses were done in R statistics version 3.4. The statistical code can be found in R and Python on GitHub (Turicchi, 2020b). In all statistical tests, a p-value <0.05 was accepted as a marker of statistical significance allowing hypothesis testing to be conducted in an exploratory manner. The alpha level was not adjusted due to the exploratory nature of the analysis (Althouse, 2016; Rubin, 2017).

8.3 Results

Baseline characteristics and number of weight measurements used to calculate BWV are presented in **table 8.1** and compared to the complete sample at baseline. Both the eligible and total sample were similar at baseline but over time, the eligible sample regained less weight than the total sample at 18-months (0.9% vs 1.9%, p<0.01). Scale use over the 18-month period is presented (**figure 8.2A**), alongside scale use per day of the week (**figure 8.2B**) and month of the year (**figure 8.2C**). Mean scale use was initially ~4.5 times per week in weeks 1-4 and reduced to ~3 times per week by 18 months. Change in body weight (**figure 8.3A**) was around -1.1% at 6months, +0.2% at 12 months and +1.2% at 18-months, however there was considerable variability around these means (see **figure 8.3B**). Baseline body weight was weakly inversely associated with weight change at 18-months (**figure 8.3B**; r= -0.1, p=0.016).

Table 8.1. Participant characteristics

Variable		Baseline Characteristics: Eligible (n=715)	Full sample (n=1,627)
Centre n (%)	Denmark	259 (36.2)	536 (32.9)
	Portugal	237 (33.1)	536 (32.9)
	UK	219 (30.6)	555 (34.1)
Sex n (%)	Men	233 (32.6)	510 (31.3)
	Women	482 (67.4)	1117 (68.7)
Study arm (%)	1	172 (24.1)	400 (24.6)
	2	183 (25.6)	403 (24.8)
	3	177 (24.8)	416 (25.6)
	4	183 (25.6)	408 (25.1)
BMI (kg/m^2)		29.2 (5.0)	29.6 (5.4)
Age (years)		45.8 (11.5)	44.1 (11.9)
Baseline weight (kg)		84.3 (16.5)	84.8 (17.3)
Previous 12-month weight loss (kg)		11.4 (6.3)	11.7 (6.5)
(%)		11.9 (5.4)	12.1 (5.6)

	Longitudinal Data				
Weight change during the trial	Kg	%	Kg	%	n
6 months	-1.2 (5.0)	-1.4 (5.6)	-0.3 (4.7)	-0.2 (5.2)	1379
12 months	-0.3 (6.3)	-0.2 (7.0)	0.4 (6.1)	0.7 (6.9)	1263
18 months	0.6 (7.0)	0.9 (7.9)	1.5 (6.8)	1.9 (7.7)	1180

Number of weight measurements available (n)	
6 weeks	28 (9)
9 weeks	41 (13)
12 weeks	53 (18)

Weight change during variability period		
	kg	%
6 weeks	-1.1 (2.5)	-1.3 (3.0)
9 weeks	-1.2 (2.9)	-1.4 (3.5)
12 weeks	-1.3 (3.2)	-1.5 (3.9)

Table 8.1. *Participant characteristics of the eligible sample reported as mean (SD) or percentage where denoted*

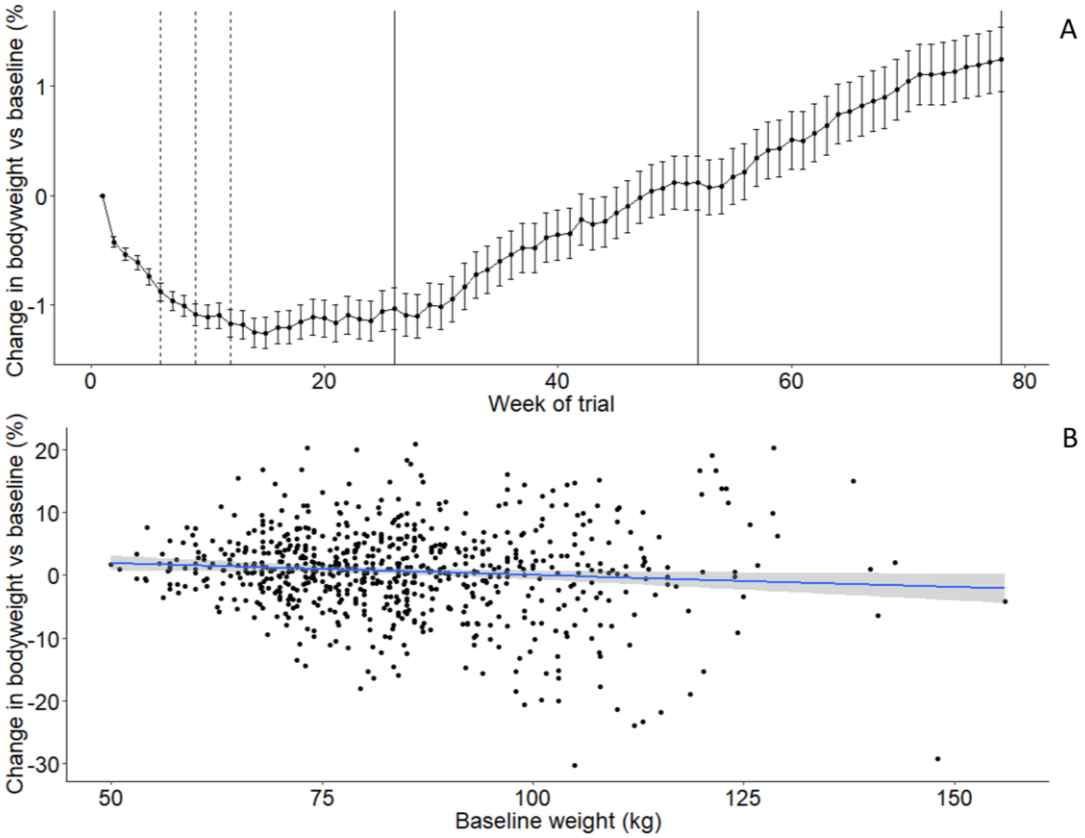


Figure 8.3. *Changes in body weight over the trial in in eligible participants (n=715). (A) Mean percentage change in body weight and error each week from baseline over 18-months; (B) scatterplot with linear trendline showing association between baseline body weight and change in body weight at the end of the trail (18-months)*

Associations for each exposure-outcome combination are illustrated in figure 8.4. The strength of these associations generally increased with both increasing BWV measurement duration and follow-up duration.

Results from multivariate linear regressions are summarised in **table 8.2**. In crude models, greater 6-week BWV by NLMD predicted greater weight change at 6, 12 and 18 months ($p<0.009$ for all), and greater 6-week RMSE predicted greater 18-month weight change ($p=0.019$). Greater 9-week NLMD predicted higher weight at all timepoints ($p<0.003$ for all), and greater RMSE predicted increased weight at 12 ($p=0.009$) and 18 months ($p<0.001$). Lastly, greater 12-week NLMD predicted greater weight at each time point ($p<0.004$ for all), and 12-week RMSE also predicted increased weight at each timepoint ($p<0.049$ for all). The greatest effect size was observed for 12-week RMSE (adjR^2=4.7%) and

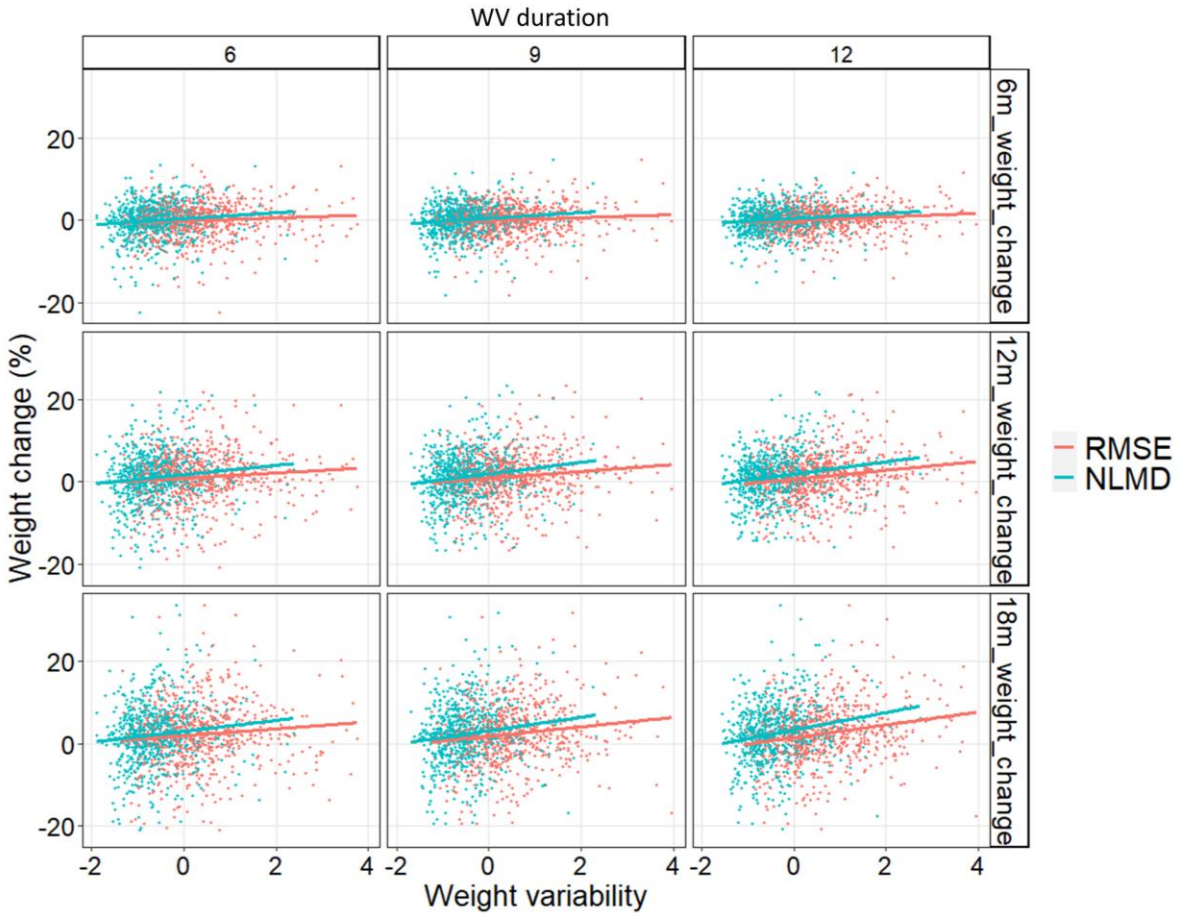


Figure 8.4. *Association matrix between short-term body weight variability (BWV) and longer-term weight change shown using scatterplot with linear trendlines. Combinations of three BWV durations (6, 9 and 12 weeks, horizontal) and three weight change periods (6, 12 and 18 months, vertical) are illustrated. BWV estimates have been generated using two methods: root mean square error (red, RMSE) and non-linear mean deviation (blue, NLMD)*

NLMD (adjR^2=3.4%) predicting 18-month weight change. The mean weight change at 18-months for low (-1 SD from mean) 12-week RMSE was -0.4 (SD 7.2) % and for high (+1 SD from mean) 12-week RMSE was +4.6 (SD 7.3) %, resulting in ~5% difference in body weight change at 18-months between high and low 12-week RMSE groups.

Following adjustment in model 2, 6-week BWV by all methods was no longer a predictor of weight change at any period. Greater 9-week NLMD predicted increased weight at 12 and 18 months ($p<0.015$ for both) but not at 6 months ($p=0.05$). Greater 9-week RMSE predicted increased weight at 18-months ($p=0.018$). Greater 12-week NLMD predicted greater weight at 12 and 18 months ($p<0.007$ for both) but not at 6-months ($p=0.082$); and greater 12-week RMSE predicted increased weight at 12 and 18 months ($p<0.002$ for all).

Table 8.2. Associations between short term weight variability and longer-term weight changes

			Model 1 (crude)			Model 2 (adjusted)		
Weight Variability measure	Weight change period (months)	WV duration (weeks)	β (SE)	P-value	$AdjR^2$	β (SE)	P-value	$\Delta AdjR^2$
NLMD	6	6	0.745 (0.258)	0.008	0.012	0.569 (0.263)	0.138	0.006
RMSE	6	6	0.175 (0.153)	0.253	0.003	0.13 (0.155)	0.605	0.001
NLMD	6	9	0.744 (0.229)	0.002	0.014	0.594 (0.233)	0.05	0.009
RMSE	6	9	0.193 (0.137)	0.159	0.003	0.148 (0.139)	0.642	0.002
NLMD	6	12	0.631 (0.199)	0.003	0.016	0.482 (0.204)	0.082	0.007
RMSE	6	12	0.267 (0.118)	0.049	0.009	0.256 (0.119)	0.096	0.006
NLMD	12	6	1.156 (0.374)	0.004	0.011	0.857 (0.384)	0.092	0.007
RMSE	12	6	0.446 (0.221)	0.088	0.003	0.278 (0.227)	0.501	0.002
NLMD	12	9	1.439 (0.358)	<0.001	0.02	1.101 (0.371)	0.014	0.012
RMSE	12	9	0.611 (0.214)	0.009	0.009	0.432 (0.22)	0.151	0.005
NLMD	12	12	1.501 (0.334)	<0.001	0.026	1.116 (0.348)	0.006	0.014
RMSE	12	12	0.938 (0.198)	<0.001	0.029	0.803 (0.203)	0.001	0.021
NLMD	18	6	1.344 (0.453)	0.006	0.009	1.081 (0.466)	0.093	0.007
RMSE	18	6	0.694 (0.267)	0.019	0.007	0.494 (0.276)	0.331	0.004
NLMD	18	9	1.773 (0.44)	<0.001	0.02	1.429 (0.456)	0.008	0.013
RMSE	18	9	0.988 (0.261)	<0.001	0.017	0.779 (0.27)	0.018	0.011
NLMD	18	12	2.151 (0.414)	<0.001	0.034	1.739 (0.433)	0.001	0.022
RMSE	18	12	1.487 (0.243)	<0.001	0.047	1.306 (0.251)	<0.001	0.036

Table 8.2. *Linear regression results showing associations between short term body weight variability measured by two methods (root mean square error; RMSE and non-linear mean deviation (NLMD) over 6, 9 and 12 weeks and longer-term weight outcomes over 6, 12 and 18 months in 715 individuals engaged in a weight loss maintenance intervention. Model 1 is a crude model. Model 2 is adjusted for the difference between the exact date (e.g. 12-months = 365 days) and the actual day of the final body weight in that period (e.g. 370 days = +5, 360 days = -5), body weight at the end of the BWV period, gender, age, number of body weights collected during variability period, study arm, change in weight during the variability period, weight loss in 12-months prior to recruitment. In model 2, ΔR2 refers to the change in Adjusted R2. All raw multivariate regression results for all covariates in the models can be viewed in Appendix 8.2*

The greatest effect sizes were observed for 12-week RMSE ($\Delta AdjR^2$=3.6%) and NLMD ($\Delta AdjR^2$=2.2%) predicting 18-month weight change.

8.4 Discussion

8.4.1 Associations between Body Weight Variability and Longer-Term Weight Outcomes

This study examined the association between short-term body weight variability and subsequent longer-term weight outcomes in a large group of European individuals engaged in a weight loss maintenance intervention. Greater BWV as assessed by NLMD consistently predicted greater weight change across almost all models, and RMSE predicted greater weight change across most models, even following adjustment for several covariates. However, effect sizes were modest (R^2 = <5%) though in a similar direction and magnitude to previous similar investigations (Lowe *et al.*, 2015; Feig and Lowe, 2017; Benson *et al.*, 2020). Despite modest effect sizes, the high 12-week RMSE group (i.e.+1 SD) showed a mean of 5% greater weight change at 18-months than the low 12-week RMSE group (i.e. -1 SD), suggesting that measured BWV may potentially have clinical significance in weight management settings. Nevertheless, it is important to view the observed effect sizes in relation to those associated with short term weight change (rather than variability) which have explained up to 68% of the variance in later weight changes (Handjieva-Darlenska *et al.*, 2010b) in the DiOGenes trial. Indeed, from these results it is possible that adding initial

BWV to early weight change may provide further predictive capacity for longer-term weight outcomes.

As the effect of BWV on weight management is a not well studied, a comprehensive exploratory approach was taken by examining effects across 3 exposure and follow-up periods, using 2 estimates of BWV and using both crude and adjusted linear models. Three exposure periods allowed examination of the effect of BWV measurement duration on the predictive value of BWV on longer-term weight change. Measured over 6 weeks, BWV explained little variation in longer-term weight outcomes (up to $AdjR^2$ = 1.2%), though this increased at 9-weeks (up to $AdjR^2$ = 2%) and again at 12-weeks (up to $AdjR^2$ = 4.7%) in univariate models. This is consistent with previous reports; one study showed that BWV over 12-weeks had greater predictive value than at 6-weeks in predicting longer-term weight (Feig and Lowe, 2017). This is likely because the data collected during the BWV period consists of both signal (e.g. real fluctuation related to energy balance behaviours) and noise (e.g. inconsistent scale use - such as fed vs unfed, clothed vs unclothed - and changes in water and gut storage volumes), and the longer measurement period results in an improved ability to detect the signal. Based on these results, measurement periods of BWV over 12-weeks are recommended for potential value in partially predicting successful weight loss maintenance. Indeed, it is important to keep the measurement period as short as possible given that the aim is to assess early predictors, therefore using upwards of 12-weeks may defeat this purpose.

Greater effect sizes were observed as the follow-up duration increased, consistent with previous reports (Feig and Lowe, 2017; Benson *et al.*, 2020). This may be since the duration between the end of the BWV period and the end of weight change period is limited (i.e. in the case of 6 months) meaning there is less variance in weight change occurring over this period to predict (see **figure 8.4** for an illustration). It could also be that the dysregulation in energy balance inferred from BWV takes a longer time to translate into weight gain. Benson et al. reported that the positive association between 12-week BWV and weight change increased in effect size with longer follow-up durations, however at 72 and 96 weeks associations were attenuated following adjustment for age (Benson *et al.*, 2020). In the present study, the associations observed remained significant after adjustment for age, sex, prior weight loss and number of scale measurements, with some reductions in the observed effect sizes. Sex and BMI interactions with BWV were investigated informed by

previous reports by Feig (Feig and Lowe, 2017) and Benson (Benson *et al.*, 2020) but no significant effects were found.

Multiple methods of calculating BWV were included as done previously in the study of disease risk (Kim *et al.*, 2018). This was done because (a) the mechanism linking BWV to longer-term weight outcomes is unclear and (b) the relationships observed may be a confounded by the method of estimating BWV. Similar results were observed between both methods, which are two similar statistical approaches but involve linear (RMSE) and non-linear (NLMD) trendlines being fitted to the body weight data over time. The implication of the polynomial function applied in NLMD means that it is more sensitive to smaller day-to-day fluctuations, but less sensitive to larger fluctuations over longer periods, often referred to as weight cycling. In some cases, including the strongest associations, the regression coefficients were greater by NLMD, but the variance explained (R^2) was greater by RMSE. The former is likely caused by the lower range of units for NLMD compared to RMSE (since non-linear regression naturally fits closer to the data, the residuals are smaller, therefore summary NLMD values are smaller). The energy balance-related mechanisms linked BWV and weight increases are not clear and require further investigation. It was possibile that BWV estimates may be correlated with the number of available weights and, since self-weighing is a consistent predictor of weight management success (Zheng *et al.*, 2015a; Shieh *et al.*, 2016), may confound the observed results. However, BWV were only very weakly ($r<0.1$) correlated with the number of weight measurements, and the models were adjusted to rule out any confounding effect.

8.4.2 Potential Causes of Body Weight Variability

Two questions pertaining to the observed results remain unclear: (a) what are the causes of BWV? (b) why is greater BWV linked to longer-term increases in weight? Firstly, BWV may reflect intentional and/or unintentional fluctuation in energy balance behaviours, in addition to fluctuations in water and food storage unrelated to energy balance behaviours (Bhutani *et al.*, 2017b), and these causes may differ across time within an individual, as well as between individuals. Bhutani et al., 2017 showed that when measuring free-living fluctuations in body composition, around 84% of the weight changes were attributable to fluctuations in FFM (with substantial changes in total body water accounting for most of this), and thus most of the BWV measured presently is probably not related to

changes in energy balance behaviours. This is consistent with complementary work by Heymsfield et al conducted using data from the CALERIE trial who showed that the early stages of weight change are composed largely of FFM, and this is mostly water (Heymsfield *et al.*, 2011). Frequent measurements of body composition using multicompartment models may improve our understanding of BWV.

Intentional and non-intentional BWV may have discrete mechanisms relating to weight management. For instance, intentional weight loss is often followed by weight regain, together termed weight cycling which is often positively associated with future weight gain (Kroke *et al.*, 2002; A. E. Field *et al.*, 2004), as is self-reported dieting (Pietiläinen *et al.*, 2012). It is suggested that high dietary restraint associated with dieting clusters with high disinhibition (in some individuals) (Westenhoefer, 1991; Johnson, Pratt and Wardle, 2012) and that these eating behaviour traits in combination are associated with uncontrolled eating (Bryant *et al.*, 2010), and weight gain in the longer term. Greater BWV has been associated with increased neural food reward responses (Winter *et al.*, 2017), again suggesting it may be related to binge eating or hedonic hunger.

Unintentional weight fluctuation may also occur, perhaps as a function of binge-restriction cycles, which have been shown to occur on weekends vs weekdays (Orsama *et al.*, 2014; Jake Turicchi, Ruairi O'Driscoll, Horgan, Duarte, Antonio L. Palmeira, Larsen, *et al.*, 2020) or in response to environmental cues such as the Christmas period. This may be due to variance in energy intake which has been associated with (a) greater absolute energy intake and (b) poorer weight outcomes in a behavioural weight loss trial (Rosenbaum *et al.*, 2016), though it may simply be a proxy marker of poor self-regulation of energy balance behaviours. Energy balance and behavioural mathematical models have shown associations between intermittent compliance with a prescribed energy intake and body weight loss plateau (Thomas *et al.*, 2014), again supporting our observations. It is also possible that genetic factors predisposing susceptibility to weight gain are expressed as BWV in the short term. Interventions aiming to promote dietary adherence and consistency in eating behaviour may function to partially reduce BWV and that this may have downstream effects on longer-term weight management, although based on the findings of this study these effects would be mild. Whether BWV is a cause or proxy (i.e. just a marker of inconsistent energy balance behaviours which are the actual cause) of modest weight gain effects is

unclear and further research is required to examine interactions between acute energy balance variability, BWV and longer-term weight outcomes.

8.4.3 Strengths and Limitations

Our study has several strengths. This was the first study to examine the effect of BWV on longer-term weight outcomes in a large group of individuals actively engaged in a weight loss maintenance intervention and found results consistent with previous studies in other groups, though observed effect sizes were minor. A combination of different exposure and follow-up durations, BWV calculation methods and statistical adjustments were used, resulting in 36 total models. Data was collected using Wi-Fi-connected smart scales, and this may help overcome the participant/researcher burden of site visits and the biases of self-report. Furthermore, it means that these investigations can be made remotely in large populations. However, the device is not a research-grade tool and may have error associated with it, and consistency in weighing conditions cannot be ensured. Twelve weeks of BWV measurement was found to be optimal for effect size, and longer follow-up durations for weight changes (e.g. at 12-18 months) showed greater effect sizes than shorter ones (e.g. 6-months). Frequent body weight data was collected, averaging around 4 weights per week during the BWV period. This allowed our estimates of BWV to measure within-week variability, whereas previous studies have measured between-week variability (Feig and Lowe, 2017; Benson *et al.*, 2020). In chapter 6, clear within-week body weight fluctuations were shown (characterised by weekend weight gain and weekday weight loss), and thus our measures of BWV will have included these smaller fluctuations, which may be important for weight management.

There are also some limitations. The variability measured included noise from uncalibrated scales and inconsistent weighing conditions (clothed vs unclothed, night vs day, hydrated vs dehydrated), and it was not possible to differentiate these factors from true weight change (see section 10.3 for a full discussion of this limitation). The present results are specific to individuals with previous weight loss (~11-12%) who had overweight or obesity and were engaged in a weight loss maintenance intervention. However, similar associations were found in ~24,000 individuals who had, on average, normal weight and were not taking part in an intervention (Benson *et al.*, 2020).

8.5 Conclusions

In conclusion, greater early BWV was associated with poorer subsequent weight management in the longer term in a large group of European individuals engaged in an evidence-based weight loss maintenance intervention, but effect sizes were minor and explained no greater than 5% of weight outcomes. Though research examining these associations is limited to only a few studies, our observations were similar in direction and magnitude, and persisted across different models and adjustments, in favour of a robust though modest effect which requires further investigation. Future studies should consider the causes of BWV and the psychological and behavioural mechanisms linking BWV to increased body weight. Furthermore, weight management interventions may potentially aim to minimize BWV by promoting consistency in energy balance behaviours (such as daily adherence to diet) and may incorporate smart scales in research and clinical environments to assess risk of poor weight management.

Chapter 9. An Exploratory Investigation of the Relationships Between Psychology, Behaviour and Body Weight Variability

In the previous chapter, the finding that prior body weight variability (BWV) has a modest impact on subsequent longer-term weight regulation raises several questions surrounding the aetiology of BWV and the mechanisms by which it relates to weight regulation. Furthermore, evidence from chapter 3 provided reasonable grounds to suggest that BWV is potentially a risk factor for disease and mortality, and as such, its causes are of clinical interest. Yet, little is understood about the aetiology of BWV and much of the evidence comes from earlier weight cycling studies which, as discussed, are limited in their comparability to the objective measurement of BWV. The NoHoW study provided an opportunity to conduct a comprehensive, exploratory analysis designed to examine both baseline predictors of BWV and bi-directionality in these relationships using the data made available by the original design of the trial.

The following study is currently under review at Digital Health (SAGE), the following title and author list pertain to the submitted draft: “An exploratory data-mining analysis of the psychological and behavioural predictors of body weight variability in individuals engaged in a weight loss maintenance trial” by J Turicchi, R O’Driscoll, MR Lowe, C Duarte, GS Finlayson, AL Palmeira, J Encantado, I Santos, SC Larsen, BL Heitmann, RJ Stubbs

9.1 Introduction

Body weight change occurs as a function of both prolonged energy balance and non-energy balance related fluctuations (e.g. changes in total body water). Measured BWV therefore is a combination of both, and the contribution of either cannot be discerned without regular multicompartment models of body composition (see section 10.2 for a full discussion). Assuming then, that BWV is partly related to acute fluctuations and longer-term changes in energy balance behaviours (e.g. energy intake [EI] and physical activity [PA]), it is possible to investigate associations between BWV and psychometric tools which attempt to measure these energy balance behaviours (i.e. self-reported questionnaires). Furthermore, behaviours can typically be related to psychological factors. For example, weight shame and body image concerns (which are psychological constructs but not behavioural measures by

definition) have been shown to be associated with increased binge eating severity (Duarte, Pinto-Gouveia and Ferreira, 2017). Similarly, low motivational factors have been related to reduced amounts of PA conducted (Pedro J. Teixeira, Carraça, *et al.*, 2012). Thus, measuring both self-reported behaviours in addition to psychological factors may contribute to a better mechanistic understanding of the aetiology of BWV (or, at least, the energy balance related component of BWV).

Few studies have related objectively measured BWV to psychological and behavioural factors. However, many more studies have drawn cross-sectional comparisons between self-reported historical weight cycling and psychological and behavioural factors (see section 9.1.1 below). While self-reported weight cycling is discrete from BWV, the literature can be used to provide a wider background for the present analysis.

9.1.1 Associations Between and Psychological and Behavioural Factors and Self-Reported Weight Cycling

A relatively broad spectrum of psychological and behavioural factors have been related to weight cycling history. Most commonly, measures of uncontrolled eating have been a focus and this is likely related to the idea that relapses in the reduction of EI required to achieve weight loss is a primary cause of weight regain (Hall and Kahan, 2018). Binge eating, which refers to a loss of control overeating resulting in episodes of excess energy consumption (i.e. binges) has been positively associated with weight cycling history in a range of studies (de Zwaan *et al.*, 1994; Bartlett, Wadden and Vogt, 1996; Venditti *et al.*, 1996; Womble *et al.*, 2001; Borges *et al.*, 2002a; Marchesini *et al.*, 2004; Petroni, Villanova, Avagnina, Fusco, Fatati, Compare and Marchesini, 2007; Roehrig *et al.*, 2009; de Zwaan, Engeli and Müller, 2015a). These include associations in large samples such as in 1889 Italian individuals with obesity or a clinical sample of 217 Brazilian women with pre-existing eating disorder diagnoses (Borges *et al.*, 2002a). Dietary disinhibition, as typically measured by the Three Factor Eating Questionnaire (Stunkard and Messick, 1985) has also been commonly associated with a history of weight cycling (Carmody, Brunner and St Jeor, 1995; Bartlett, Wadden and Vogt, 1996; Grave *et al.*, 1996; Marchesini *et al.*, 2004; Strychar *et al.*, 2009). Other factors such as emotional eating (Keller and Siegrist, 2015) and food reward sensitivity (de Zwaan, Engeli and Müller, 2015a) have been cross-sectionally related to weight cycling history. There is therefore evidence that a spectrum of uncontrolled eating

(described previously by Vainik et al may be related to BWV (Vainik *et al.*, 2015)). Importantly, often in these studies (e.g. (Bartlett, Wadden and Vogt, 1996) titled "The Consequences of Weight Cycling") it is argued that, given weight cycling is measured retrospectively and thus precedes the eating behaviour measurement in the present, that observed associations are a consequence of weight cycling (e.g. that weight cycling increases binge eating). However, these associations are not evidence of a negative effect of weight cycling on psychological or behavioural factors given their cross-sectional nature. Indeed, BMI and weight cycling are often positively related (Borges *et al.*, 2002a; Marchesini *et al.*, 2004), as are BMI and uncontrolled eating factors such as binge eating (de Zwaan, 2001), and therefore the association between uncontrolled eating and weight cycling may simply be due to the fact that weight cyclers are commonly heavier.

Adverse psychological factors including depression (Hasler *et al.*, 2005; Petroni, Villanova, Avagnina, Fusco, Fatati, Compare and Marchesini, 2007; de Zwaan, Engeli and Müller, 2015a), stress (Barnes and Tantleff-Dunn, 2010) and helplessness (Carmody, Brunner and St Jeor, 1995; Foreyt *et al.*, 1995) have been related to weight cycling, again with authors at times stipulating that these are effects of weight cycling rather than associations. Depression is thought to have bidirectional relationships with overeating/undereating and obesity (Luppino *et al.*, 2010; Pan *et al.*, 2012) and therefore may be indicative of individuals who fluctuate in EI over short or long periods and this may contribution towards associations with weight cycling. Furthermore, stress has been related to uncontrolled eating (i.e. "stress eating") (Yau and Potenza, 2013) which partially explain the association with weight cycling from a behavioural perspective. Additionally, two related constructs which have been associated with weight cycling in the literature are poor body image perception (Grave *et al.*, 1996; Casebeer, 1997; Toray and Cooley, 1997; Friedman, Schwartz and Brownell, 1998; Osborn *et al.*, 2011; Fazzino *et al.*, 2017) and weight dissatisfaction (Toray and Cooley, 1997). Body image and weight concerns often coincide with binge eating issues (Duarte, Pinto-Gouveia and Ferreira, 2014) and again this may provide a behavioural pathway through which these psychological factors may influence body weight.

9.1.2 Associations Between Psychological and Behavioural Factors and Body Weight Variability

Only a few studies have examined the associations between prospectively measured BWV, energy balance-related behaviours and associated psychological constructs. Feig and Lowe (2017) reported inverse associations between self-reported emotional eating and power of food ("hedonic hunger") scales and short-term (6 and 12-week) BWV, as well as positive associations with adverse psychological factors such as perceived societal pressure (Feig and Lowe, 2017). Similarly, results from 4,774 participants in the LOOK AHEAD study which estimated BWV over 8 years using yearly weight measurements reported that greater baseline binge eating and depression, and lower mental health ratings were associated with greater subsequent 8-year BWV (Pacanowski *et al.*, 2018). Elevated activation of brain regions associated with reward and emotion-regulation (medial prefrontal cortex, cingulate cortex, and insula) and lower activation in self-referential processing regions (praecuneus) in response to palatable food presentation (but not cues) was related to subsequent 3-year BWV (Winter *et al.*, 2017). The reliance on yearly body weights in the latter two studies limit the resolution with which BWV can be estimated, though recent technological advances have allowed for regular tracking of body weight using Wi-Fi connected smart scales, allowing more high-fidelity measures of BWV. The question of whether BWV is associated with or partially accounts for changes in psychological and behavioural factors remains unclear. Indeed, no previous study has used a prospective design to test the temporal precedence of potentially causal factors of BWV by examining associations between BWV and change in psychological dispositions.

No study has examined the associations between weight history and prospectively measured BWV. Weight history variables, such as dieting, weight cycling and weight suppression (WS) may be indicative of short or longer-term tendencies to fluctuate in body weight, or gain body weight (Lowe *et al.*, 2019), and this could potentially be related to eating disorders since WS was recently shown to be a risk factor for multiple eating disorders (Stice *et al.*, 2020). However, the associations between baseline weight history and prospectively measured BWV has not yet been examined.

9.1.3 Exploratory Research Approaches

In the NoHoW study which forms the context for the subsequent analysis, the number of self-reported psychological and behavioural variables was great (92 variables from 27 scales were collected). These variables relate to a range of overarching theories and themes within the dual-process theory of reflective and reactive processes (Dassen *et al.*, 2018), including self-regulation, emotion regulation, affectivity, wellbeing and their potential impact on energy balance behaviours (see section 4.1.8 for further detail). Importantly, the associations between the vast majority of these variables and BWV has never been investigated and their role in the aetiology of the phenomenon is unclear. Traditional research methods using hypothesis testing are well-established if the set of independent variables to consider is fixed and small and a priori hypotheses are known (Heinze, Wallisch and Dunkler, 2018). However, in instances where potentially predictive variables are numerous and the analysis is exploratory, more unstructured and unsupervised analyses may be preferable (Islam *et al.*, 2018; Alashwal *et al.*, 2019). These approaches allow numerous variable relationships to be examined without testing a pre-specified hypothesis. For example, in a backwards stepwise regression, a large number of predictive variables can be entered into a regression model and the final model returns a small number of variables which explain the greatest variance in the outcome variable. Such an approach, under the current circumstances, was deemed optimal to allow investigation of new variables relating to BWV and build a model which best explains BWV outside of the restrictions of traditional hypothesis-testing designs.

9.1.4 Objectives

Using the data collected during the NoHoW trial, the aims of the current exploratory analysis were threefold:

1. To develop a data-driven baseline model of prospectively measured BWV;
2. To use unsupervised clustering methods to examine how clusters of baseline variables psychological, behavioural and weight history variables relate to BWV
3. To examine bi-directionality in these relationships over time.

9.2 Methods

9.2.1 Study Design

The present study was an ad hoc analysis of data collected as part of the NoHoW trial which is detailed in section 4.1.

9.2.2 Participants

Full eligibility criteria for the NoHoW trial is provided in section 4.1.4.1. A participant flow diagram is provided in **figure 9.1**. The present analysis used both a baseline sample and longitudinal sample based on availability of data. Individuals in the baseline sample (n=1049) were required to have no missing self-report data at baseline and sufficient body weight data to calculate BWV (detailed below); and in the longitudinal sample (n= 822) participants were required to have no missing self-report data at baseline, 6 and 12-months in addition to sufficient body weight data to estimate BWV over 12-months (see criteria below for detail).

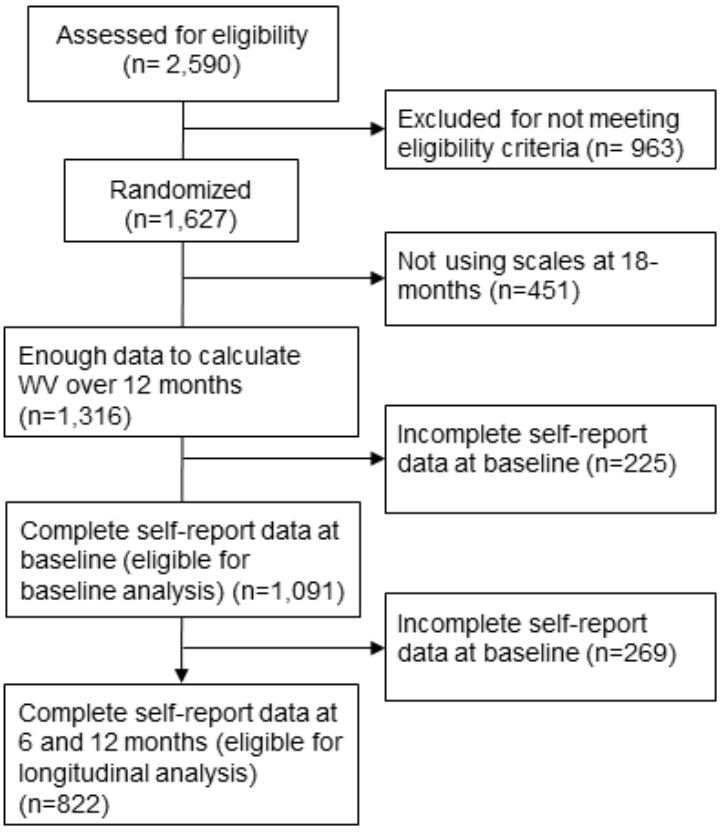


Figure 9.1. *Participant flow diagram*

9.2.3 Body Weight Variability

For inclusion, participants were required to have ≥30 body weights over ≥9 months to obtain an appropriate estimate of 12-month BWV (Jake Turicchi, O'Driscoll, Finlayson, Duarte, A L Palmeira, *et al.*, 2020). Weight variability was calculated using the root mean square error (RMSE) method as used previously as described in section 4.2.3. Only one measurement of BWV was used in this analysis due to the fact there are a substantial number of explanatory variables thus using multiple measures of BWV would result in an exponential number of models being generated. RMSE was chosen as it is more sensitive to larger fluctuations in body weight, which are more likely to be related to energy balance behaviours rather than fluctuations in the composition of FFM which may occur between days.

9.2.3 Psychological and behavioural measurements

Selection of variables

The scales included were based on the original design of the NoHoW trial which aimed to test a self-regulation and emotion regulation intervention. Given that there were 27 scales providing data on 92 factors (see section 4.1.8 for information on all scales), a selection of variables most statistically relevant to the outcome variable (BWV) was conducted. For inclusion in further models, a bivariate Pearson correlation of $r<-0.1$ or $r>0.1$ with BWV was arbitrarily selected as a cut-off (all correlations are available in appendix 9.1). If a factor in a scale was related to BWV, the whole scale was included. The variables listed below therefore reflect those which met the criteria for inclusion in the later stages of the data driven analyses. These data were collected at 0, 6 and 12 months.

Eating behaviour

Eating behaviour was assessed using the 51 item Three Factor Eating Inventory (TFEQ) (Stunkard and Messick, 1985) which assessed dietary disinhibition, restraint and hunger. The scale is commonly used to assess dietary behaviour and has been shown to have acceptable reliability and validity in both overweight and obese samples (Bohrer, Forbush and Hunt, 2015). Binge eating was assessed using the Binge Eating Scale (BES) (Gormally *et al.*, 1982) which is shown to have very good reliability and validity (Duarte, Pinto-Gouveia and Ferreira, 2015) in women.

Body image and weight satisfaction

Body image was assessed using the Body Image Acceptance And Action Questionnaire (BIAAQ) (Sandoz *et al.*, 2013) which is a 12-item self-report scale designed to measure body image-related psychological flexibility, namely the extent to which an individual openly and fully accepts the ongoing perceptions, thoughts, beliefs, and feelings about his or her body. It is shown to have high consistency, reliability and validity (Ferreira, Pinto-Gouveia and Duarte, 2011). Next, the Weight Focused Self-Criticism/Self-Reassuring Scale (WFSCRS) (Duarte *et al.*, 2019), a 22-item scale was used which assesses participant's thoughts and feelings about themselves related to weight, body shape and eating. Two subscales (based on their factor loading onto one larger factor) were collapsed: the hated and the inadequate self, providing an overall score for weight-focused self-criticism (WFSC). The scale has been reported to have high internal reliability, construct, and discriminant validity (Duarte *et al.*, 2019).

Depression and mental wellbeing

Mental wellbeing was assessed using the Warwick And Edinburgh Well Being Scale (WEWBS) (Tennant *et al.*, 2007), a 14-item, positively worded scale assessing one factor which has been shown to have very high reliability and validity (Tennant *et al.*, 2007; Stewart-Brown *et al.*, 2009). The 21-item Depression, Anxiety and Stress Scale (DASS) (Lovibond and Lovibond, 1995) was used, which is commonly employed to assess mental health and shows excellent psychometric properties (Antony *et al.*, 1998).

Emotion regulation

The Engaged Living Scale (ELS) (Trompetter *et al.*, 2013) was used which is a 16-item scale with 2 subscales, valued living and life fulfilment and 1 general underlying factor. The overall score was used in the present analysis. The scale is a process-specific measure to assess an engaged response style as conceptualized in acceptance and commitment therapy and relates well to psychological well-being, anxiety/depression, acceptance, mindfulness, and pain interference in daily life (Trompetter *et al.*, 2013). Self-compassion was assessed using The Compassion Attributes And Actions Scales (CAAS) (Gilbert *et al.*, 2017) which assesses sensitivity to suffering, sympathy, non-judgemental, empathy, distress tolerance and care for wellbeing. Lastly, the Difficulties in Emotion Regulation Scale (DERS) (Gratz and Roemer, 2004) was employed, a widely used scale which shows high consistency and validity (Hallion *et al.*, 2018) which assesses non-acceptance of emotional responses,

difficulties engaging in goal- directed behaviour, impulse control difficulties, limited access to emotion regulation strategies and lack of emotional clarity.

9.2.4 Weight History Measurements

The following data relating to weight history was collected: (1) previous dieting attempts: 'how many times have you attempts to lose weight?'; (2) previous weight losses: 'how many times have you lost 5kg?'; (3) highest weight in last 12-months (used to calculate 12 month WS by subtracting baseline weight) and (4) highest weight in lifetime (used to calculate lifetime WS by subtracting baseline weight). Where weight history data was incomplete (in < 5% of the sample), mean or mode imputation was used.

9.2.5 Statistical analysis

Data and Sample Description

Baseline characteristics are provided in **table 9.1** for both study samples. QQ-plots and histograms were generated to test key (non-ordinal) variables for normality. Measures of RMSE violated the assumptions of normality and therefore log transformation was performed. All analyses were conducted in R version 3.7 and all analysis code can be found at on Github (Turicchi, 2020b). In all statistical tests, a p-value <0.05 was accepted as a marker of statistical significance. Where multiple testing is conducted, the alpha level was not adjusted due to the exploratory nature of the analysis (Althouse, 2016; Rubin, 2017).

General Linear Regression

In our baseline analysis, the association between baseline psychometric score and 12-month BWV was tested in univariate (model 1) and adjusted (model 2) models which are reported in **table 9.2**. Model 2 was adjusted for baseline sex, age, BMI, trial centre and trial arm. In a recent study, BWV was shown to be moderated partly by age, gender, BMI and region (Jake Turicchi, Ruairi O'Driscoll, Horgan, Duarte, Antonio L. Palmeira, Larsen, *et al.*, 2020). In model 2, additional testing for gender and BMI (BMI was categorised into <25, 25-30, 30-35 and >35 kg/m^2) interactions were conducted with each psychometric variable, based on the evidence that BWV may interact with gender or BMI (Benson *et al.*, 2020).

Stepwise Regression

Next, backwards stepwise regressions (**table 3**) were conducted on baseline psychological variables (model 1) and psychological plus weight history variables (model 2), with 12-month BWV as the outcome. A backward stepwise regression starts with all possible

explanatory variables and then discards the least statistically significant variables. The discarding stops when each variable remaining is considered the best subset of variables in maximising the model effect (R^2). Stepwise regressions were conducted using the StepAIC function from the MASS package in R (Ripley, 2020) the use of which in stepwise regression was reviewed recently (Zhang, 2016). Statistically, this means that the noise generated by non-significant predictors is reduced and a parsimonious model is created (Goodenough, Hart and Stafford, 2012) which was in line with our aim to produce the best baseline model for prediction of BWV. Stepwise regression has been shown to perform similarly at selecting true predictors compared to other appropriate methods in the study of variable selection (Genell *et al.*, 2010).

Unsupervised Clustering

A limitation of stepwise regression is that it attempts to optimize a model to explain the greatest variance in the outcome (i.e. BWV), and in doing so, removes all other variables which do not fit the final model. Given that it was already identified that each variable remaining is (to some extent) related to BWV, this approach was chosen to extend this analysis by using an unsupervised clustering approach, based on the knowledge that human psychological processes and behaviours often tend to cluster (Conry *et al.*, 2011; Nudelman and Shiloh, 2016). The two most common clustering techniques are hierarchical clustering and partitioning relocation methods (e.g. K-means). Both methods are based on minimizing the distance (in this and most cases, the Euclidean distance (Lele and Richtsmeier, 1991) is used) between data points (participants) within a cluster and maximising the distance between different clusters. To avoid reliance on a single clustering method, two methods of clustering participants at baseline were conducted and later compared. Scaling was conducted before clustering to generate Z-scores for each included baseline psychometric variable.

To generate the K-means clusters, the ‘kmeans’ function was used from the ‘stats’ package in R. The K-means is an iterative process built on an expectation-maximization algorithm (Jung, Kang and Heo, 2014) which aims to group similar data points (participants) together and discover underlying patterns. An optimal number of clusters was determined from a majority vote of 24 different methods (using the ‘NbClust’ package (Charrad *et al.*, 2014)).

Next, an agglomerative clustering approach was used which works in a bottom-up manner, initially considering each participant as a single element (leaf). At each step of the algorithm, the two clusters that are the most similar are combined into a new bigger cluster (nodes). This procedure is iterated until all points are members of just one single big cluster (root). Specifically, Ward's method of hierarchical clustering was used using the 'hclust' function of the 'stats' package in base R (R Core Team, 2019), which is suggested for exploratory data analysis as it minimizes the within-cluster variance compared to other hierarchical methods (Konopka *et al.*, 2018). The result is a tree which can be plotted as a dendrogram. Based on the height of the roots, there was deemed to be 4 discernible clusters by hierarchical method.

Differences between these baseline clusters were tested for each psychometric variable as well as 12-month BWV using a type 3 sum of squares ANOVA and significant models were tested using Tukey's post-hoc test (**table 8.4**). This was done for both clustering methods. Additionally, 12-month weight changes were compared across each cluster to investigate if these clusters relate to longer-term weight outcomes.

Bi-directional relationship testing

Lastly, an investigation of whether (a) initial (6 month) BWV predicted subsequent change in psychometric variables (i.e. change between 6 and 12 months) and (b) initial change in psychometric variables predicted subsequent BWV was conducted. For (a) BWV was calculated over the first 6 months and used in a general linear model to predict subsequent change in each variable, adjusting for the variable value at 6 months (e.g. the pre-change score). For (b) change in psychometric variables were calculated between baseline and 6months and used to predict BWV calculated between 6 and 12 months, adjusted for initial (6-month) BWV and baseline psychometric score. The results can be viewed in **table 9.5**.

9.3 Results

Of the 1627 participants recruited, 1091 and 822 individuals had sufficient data for inclusion in the baseline and longitudinal analyses respectively of which ~70% were female with a mean age of 45.3 years and mean BMI of 29.5 kg/m^2. Age, gender (%) and BMI did

not differ between included and excluded participants. Sample characteristics are provided in **table 9.1** and baseline psychometric scores are listed in **appendix 2**.

9.3.1 Baseline Regressions

Univariate regression results (**table 9.2**) showed significant baseline associations between all variables (apart from TFEQ hunger) and 12-month BWV, with effect sizes for psychometric and weight history variables reaching 4.5% (binge eating) and 5.5% (lifetime WS) respectively, reducing to 2.4% and 5% following adjustment. Adjustment in general linear model 2 (for sex, age, BMI, trial centre and trial arm) reduced all effect sizes but did

Table 9.1. Sample characteristics in baseline and 12-month samples

Characteristic		Baseline (n=1091)	Longitudinal (n=822)
Gender n (%)	Male	331 (30.3)	248 (30.2)
	Female	760 (69.7)	574 (69.8)
Study arm n (%)	1	274 (25.1)	209 (25.4)
	2	276 (25.3)	210 (25.5)
	3	267 (24.5)	199 (24.2)
	4	274 (25.1)	204 (24.8)
Centre n (%)	Denmark	356 (32.6)	254 (30.9)
	Portugal	342 (31.3)	254 (30.9)
	UK	393 (36.0)	314 (38.2)
Age (years)		44.8 (11.7)	45.7 (11.6)
BMI (kg/m^2)		29.6 (5.3)	29.4 (5.05)
Weight loss attempts n (%)	1-2 times	190 (17.4)	143 (17.4)
	3-5 times	358 (32.8)	268 (32.6)
	6-10 times	220 (20.2)	172 (20.9)
	more than 10 times	323 (29.6)	239 (29.1)
Times lost ≥ 5kg (n)		2.7 (1.0)	2.7 (1.0)
12-month weight suppression (%)		10.4 (6.2)	10.50 (6.5)
Lifetime weight suppression (%)		11.1 (5.6)	11.29 (5.7)

Table 9.1. *Sample characteristics for baseline and 12-month longitudinal samples. Values are provided as mean (standard deviation) for continuous and n (%) for categorical variables*

not attenuate any significant effects. When testing for gender interactions in general linear model 2, an interaction with stress (p=0.023) was observed, such that stress had a greater positive association with BWV in females. No other gender interactions were found. Only

BMI interactions with WS (lifetime and 12-month) were observed, such that prior WS was more strongly associated with subsequent BWV in all groups above normal weight (<25 km/m^2) (p<0.038 for all groups).

9.3.2 Stepwise Regressions

Backwards stepwise regression results are shown in **table 9.3**. In model one (only psychometric variables), the final model (R^2=6.3%, p<0.001) consisted of five variables and greater 12-month BWV was associated with greater binge eating (β(SE)=0.011(0.002), p<0.001), lower hunger (β(SE)=0.013(0.004), (p<0.002) and lower self-compassion (β(SE)= -0.002(0.001), p=0.042) at baseline. Non-significant results were observed for weight-

Table 9.2. Associations between baseline psychometric and weight history variables and subsequent 12-month weight variability

	Univariate			Adjusted*		
Psychometric variables	β (SE)	$AdjR^2$	p-value	β (SE)	$\Delta AdjR^2$	p-value
Anxiety	0.016 (0.005)	1.1%	<0.001	0.012 (0.005)	0.5%	0.011
Binge Eating	0.011 (0.002)	4.5%	<0.001	0.009 (0.002)	2.4%	<0.001
BIAAQ	-0.004 (0.001)	3.3%	<0.001	-0.004 (0.001)	1.7%	<0.001
Depression	0.015 (0.003)	2.0%	<0.001	0.011 (0.003)	1.1%	<0.001
DERS	0.004 (0.001)	1.8%	<0.001	0.003 (0.001)	0.8%	0.001
Enriched Living	-0.006 (0.001)	2.0%	<0.001	-0.005 (0.001)	1.4%	<0.001
Self-Compassion	-0.005 (0.001)	1.8%	<0.001	-0.004 (0.001)	0.9%	0.001
Stress	0.009 (0.003)	1.1%	0.001	0.006 (0.003)	0.3%	0.024
Disinhibition	0.016 (0.003)	2.1%	<0.001	0.011 (0.004)	0.7%	0.002
Hunger	0.006 (0.003)	0.3%	0.087	0.002 (0.003)	0.0%	0.615
Restraint	0.008 (0.003)	0.5%	0.016	0.008 (0.003)	0.4%	0.014
Mental wellbeing	-0.006 (0.001)	1.9%	<0.001	-0.005 (0.001)	0.8%	0.001
WFSC	0.006 (0.001)	3.2%	<0.001	0.005 (0.001)	1.8%	<0.001
Weight history variables						
12m weight suppression	0.013 (0.002)	4.3%	<0.001	0.012 (0.002)	3.9%	<0.001
Lifetime weight suppression	0.014 (0.002)	5.5%	<0.001	0.013 (0.002)	5.0%	<0.001
Weight loss attempts	0.035 (0.011)	1.0%	0.001	0.041 (0.012)	1.0%	<0.001
Times lost 5kg	0.057 (0.012)	2.2%	<0.001	0.074 (0.012)	3.0%	<0.001

Table 9.2. *Associations between baseline psychometric and weight history variables and objectively measured 12-month BWV in 1091 participants of the NoHoW trial. Results are provided as*

standardized regression coefficients and associated standard errors, and adjusted R2 values, or, in model 2, the change in adjusted R^2 upon addition of the variable to the model. Abbreviations: BIAAQ (Body Image Acceptance and Action Questionnaire), DERS (Difficulties Regulating Emotions Scale), WFSC (Weight Focused Self Criticism)

focused self-criticism (-0.002 (0.001), p=0.09) and restraint (0.005 (0.003), p=0.1). In model two (R^2=11.1%, p<0.001), five variables were significantly associated with greater 12-month BWV: greater binge eating (β(SE)=0.01(0.002), p<0.001); greater depression (β(SE)=0.007(0.003), p=0.03); lower hunger (β(SE)= -0.009(0), p=0.018); greater times lost 5kg (β(SE)=0.028(0.012), p=0.016) and greater lifetime WS (β(SE)=0.013(0.002), p<0.001).

Table 9.3. Stepwise regression results

	SW Model 1 (AdjR^2=6.3%)				SW Model 2 (AdjR^2=11.1%)		
Variable	β (SE)	t-value	p-value	Variable	β (SE)	t-value	p-value
Binge eating	0.011 (0.002)	4.86	<0.001	Binge eating	0.01 (0.002)	5.00	<0.001
WFSC	-0.002 (0.001)	-1.69	0.092	Depression	0.007 (0.003)	2.17	0.03
Hunger	-0.013 (0.004)	-3.17	0.002	Hunger	-0.009 (0)	-2.37	0.018
Restraint	0.005 (0.003)	1.58	0.114	Time lost 5kg	0.028 (0.012)	2.42	0.016
Self-Compassion	-0.002 (0.001)	-2.03	0.042	All time WS	0.013 (0.002)	7.68	<0.001

Table 9.3. *Results from two baseline stepwise regression analyses predicting 12-month body weight variability. Stepwise Model 1 includes baseline psychological variables only; SW Model 2 includes both baseline psychological and additionally weight history variables. Results are provided as standardized regression coefficients and associated standard errors and adjusted R2 values. Abbreviations: SW (stepwise), WFSC (Weight Focused Self Criticism), WS (weight suppression)*

9.3.3 Clustering Analyses

Unsupervised cluster analyses revealed an optimal cluster number of 3 and 4 for k-means and hierarchical clustering, respectively. Differences between each variable are provided in **table 9.4**. For the K-means analysis, cluster 3 showed significantly greater BWV than cluster 1 (41% greater) and cluster 2 (30% greater). All groups were significantly different for all comparisons except for restraint in which cluster 2 and 3 were similar.

Notably, cluster 3 was defined by significantly greater uncontrolled eating (greater binge eating, disinhibition, hunger); greater negative affect (lower mental wellbeing, body image flexibility; greater depression, stress, anxiety, weight-focused self-criticism) and lower emotional control (greater difficulties regulating emotions, lower self-compassion and enriched living) than both other clusters. Body weight change at 12-months was modestly but significantly higher in cluster 3 (+0.38%) vs cluster 1 (+0.1%) and 2 (+0.31%) respectively. In the hierarchical clustering, 4 discernible clusters emerged. Cluster 4 showed 36-44% greater BWV than all three other clusters. Similar to the K-means cluster analysis, group 4 showed significantly greater scores on binge eating, negative affectivity (depression, anxiety, stress, weight-focused shame) and emotional control, lower mental wellbeing, enriched living, body image flexibility and self-compassion. Cluster 4 also showed significantly greater 12-month weight change (+1.1%) than clusters 1 (+0.14%), 2 (-0.08%) and 3 (+0.57%).

Table 9.4. Differences between baseline clusters

	K-means clusters			Hierarchical clusters			
Factor*	Cluster1 (n=461)	Cluster2 (n=481)	Cluster3 (n=149)	Cluster1 (n=432)	Cluster2 (n=370)	Cluster3 (n=174)	Cluster4 (n=115)
Weight variability (RMSE)	0.32	0.38	0.54	0.37	0.32	0.36	0.57
Wellbeing	56.7	50.27	40.49	48.95	56.60a	55.57a	39.89
Binge eating	6.61	14.30	21.07	14.81	6.01	11.84	20.78
Stress	9.61	12.42	18.07	12.93	9.29	10.93	18.90
Depression	8.02	9.69	16.75	10.28	7.95a	8.41a	17.45
Anxiety	7.93	8.85	12.24	9.00	7.83	8.40	12.99
WFSC	10.06	20.91	33.84	22.27	9.54	14.57	35.21
Enriched Living	64.41	56.03	49.31	54.39	64.09a	63.30a	50.16
Hunger	3.91	6.76	8.54	6.71a	3.22	7.22a	8.53
Restraint	10.66	11.49a	11.48a	10.96a	10.69a	11.95b	12.02b
Disinhibition	6.49	10.17	11.72	10.25	6.04	9.37	11.67
BIAAQ	68.57	51.04	38.82	49.84	69.68	59.46	37.33
Self-compassion	64.06	55.45	48.58	53.89	62.53	65.04	49.64
DERS	23.65	33.79	52.77	35.18	23.41	27.78	55.01
12m weight change (%)	0.10	0.31	0.38	0.14	-0.08	0.57	1.12

Table 9.4. *Differences in psychological variables between clusters. Results are provided for two clustering analyses (K-means and Hierarchical clustering).*Where differences were not significant ($p<0.05$), non-significant differences were between groups denoted by similar letters determined by type III sum of squares ANOVA with Tukey post-hoc. All other group comparisons were significantly*

different. Comparisons were made within clustering methods (i.e. not compared between k-means and hierarchical clusters. Abbreviations: RMSE (Root Mean Square Error), WFSC (Weight Focused Self Criticism), BIAAQ (Body Image Acceptance and Action Questionnaire), DERS (Difficulties Regulating Emotions Scale)

9.3.4 Bi-directional Relationships

Table 9.5 reports the effect of 6-month BWV on subsequent 6-month change in psychometric variables. Greater initial BWV resulted in significant increases in binge eating (2.193(0.494), p<0.001) and disinhibition (0.57(0.219), p=0.009) were observed in addition to decreases in body image flexibility (-2.835(1.002), p=0.005) and mental wellbeing (-1.642(0.707), p=0.02). In the other direction (initial 6-month change in psychometric variables predicting BWV from 6-12 months), there were no significant associations between change in any psychological variable and BWV (after adjustment for initial BWV and baseline psychological variable value).

Table 9.5. Reciprocal relationship testing between body weight variability and change in psychological variables

	Associations of initial BWV on subsequent change in psychological variables			Associations of initial change in psychological variables on subsequent BWV		
Psychometric Variable	β (SE)	ΔAdjR^2	p-value	β (SE)	ΔAdjR^2	p-value
Anxiety	0.112 (0.27)	0.0%	0.679	-0.008 (0.005)	0.3%	0.099
Binge eating	2.193 (0.494)	2.2%	<0.001	0.002 (0.002)	0%	0.484
BIAAQ	-2.835 (1.002)	0.9%	0.005	-0.001 (0.001)	0.1%	0.257
Depression	0.292 (0.335)	0.1%	0.383	-0.003 (0.004)	0.1%	0.33
DERS	1.667 (0.868)	0.4%	0.055	0 (0.001)	0%	0.734
Disinhibition	0.57 (0.219)	0.8%	0.009	0.003 (0.005)	0%	0.485
Enriched Living	-1.084 (0.721)	0.2%	0.133	0.001 (0.001)	0.1%	0.404
Hunger	0.281 (0.238)	0.2%	0.238	0.006 (0.004)	0.2%	0.196
Restraint	0.036 (0.263)	0.0%	0.891	-0.003 (0.004)	0.1%	0.431
Self-Compassion	-1.848 (0.999)	0.3%	0.065	0 (0.001)	0%	0.95
Stress	0.342 (0.364)	0.1%	0.348	0 (0.003)	0%	0.951
Wellbeing	-1.642 (0.707)	0.6%	0.02	0 (0.002)	0%	0.808
WFSC	0.731 (0.699)	0.1%	0.296	-0.001 (0.002)	0%	0.511

Table 9.5. *On the left shows longitudinal associations between initial (6-month) body weight variability and subsequent change in psychological and behavioural variables from 6 to 12 months.*

On the right shows longitudinal associations between initial (6-month) change in psychological variables and subsequent body weight variability from 6 to 12 months. Models are adjusted for baseline psychological value and results are provided as standardized regression coefficients and associated standard errors and change adjusted R2 values. Abbreviations: BIAAQ (Body Image Acceptance and Action Questionnaire), DERS (Difficulties Regulating Emotions Scale), WFSC (Weight Focused Self Criticism)

9.4 Discussion

This exploratory analysis examined psychological and behavioural predictors of 12-month BWV over 1 year in a large group of individuals engaged in the NoHoW weight loss maintenance intervention (Scott *et al.*, 2019). Direct associations between baseline uncontrolled eating factors (binging, disinhibition) were found and coincided with greater restrained eating. Further, greater weight-focused self-criticism and lower body image flexibility were associated with 12-month BWV, as was lower mental health and greater depression, stress, anxiety, emotional regulation and self-compassion. The regression results were supported by both our k-means and hierarchical clustering analyses which showed that each of these variables were associated with greater BWV generally clustered together in a smaller group of individuals who showed significantly greater BWV (up to 45% higher BWV in the most variable clusters). Further, those in the 'high-BWV' clusters also showed significantly greater body weight change over 12-months than those in other clusters, consistent with the results of chapter 8 which showed that greater short-term BWV predicted increased body weight at 12-18 months. Weight history variables, particularly WS but also weight loss attempts and successful weight losses, were directly associated with 12-month BWV. Lastly, our analysis of change scores in psychometric variables provided novel evidence of reciprocal relationships among the variables studied, with low 6-month BWV being associated with higher scores of self-reported binge eating and disinhibition, as well as lower scores of body image flexibility and mental wellbeing.

Our results are consistent with previous objective and self-reported studies into the determinants of weight cycling. Indeed, a common finding of studies relying on self-reported measures of weight cycling history is an association with binge eating. These studies often focus on clinical disordered eating samples (de Zwaan *et al.*, 1994; Roehrig *et al.*, 2009) though similar trends have been found in commercial weight loss programs

(Borges *et al.*, 2002a; Petroni, Villanova, Avagnina, Fusco, Fatati, Compare, Marchesini, *et al.*, 2007) and non-clinical samples (Venditti *et al.*, 1996; de Zwaan, Engeli and Müller, 2015a). Similarly, loss of control (Elder *et al.*, 2008) and disinhibited eating (Strychar *et al.*, 2009) have been implicated in body weight cycling. Two other factors; (a) low weight/body image satisfaction (Casebeer, 1997; Osborn *et al.*, 2011) and (b) negative affect (de Zwaan, Engeli and Müller, 2015a) are often associated with self-reported weight cycling. Interestingly, the association of BWV with stress was marginally more prominent in women than men, perhaps explained by evidence suggesting that women are more susceptible to emotional/stress eating than men (Beydoun, 2014). Importantly, the effect sizes observed were minor (in the region of 1-4% for psychometric variables and up to 5.5% for WS) and were reduced (but not statistically attenuated) by adjustments for key characteristics.

9.4.1 Stepwise Regressions

Next, in stepwise regression model 1 (psychometric variables only), there was a coinciding stepwise inclusion of higher binge eating, hunger, weight-related shame and lower self-compassion. The coinciding associations of both elevated uncontrolled (binge) and controlled (restrained) eating with BWV is logical given that most energy balance-related weight change occurs as a function of energy intake (Hall *et al.*, 2012) and temporal variability in eating behaviour may therefore present as variability in body weight. The inclusion of (lower) self-compassion and (higher) weight-focused shame indicates the role of negative affectivity in this tension between cognitive control and loss of control of eating behaviour. In model 2, the introduction of weight history variables resulted in stepwise inclusion of lifetime WS and previous successful weight losses (≥5kg) in the final model, in addition to depression, explaining >11% of the variance in BWV. This is the first time that the relationship between BWV and weight loss history has been examined. Interestingly, WS was more strongly associated with BWV in individuals with overweight and obesity than those with normal weight. Given that WS was calculated as percent weight change, this effect cannot be related to absolute body size. This association may be explained by evidence suggesting that WS has been shown to be associated with disordered and binge eating (Lowe *et al.*, 2007; Javaras *et al.*, 2008; Stice *et al.*, 2020). It is likely that successful weight losses (>5kg) are a proxy measure for historical weight cycling and as such simply

reflect a continuation of prior behaviours but do indicate that assessing weight history can be useful in predicting likelihood of subsequent BWV.

9.4.2 Clustering Analyses

Motivated by the knowledge that psychological processes and associated behaviours cluster (Conry *et al.*, 2011; Nudelman and Shiloh, 2016), and that single-factor relationships alone are unrepresentative, multiple unsupervised clustering algorithms were applied to psychometric variables at baseline in order to examine how identified phenotypes (i.e. clusters) of individuals relate to subsequent BWV. Despite differences in the optimal cluster number (n=3 for K-means and n=4 for hierarchical clustering), both approaches produced one cluster which showed ~30-45% higher BWV than the other clusters, and this cluster showed greater average scores in uncontrolled eating, negative affectivity, body and weight concerns and difficulties regulating emotions (consistent with the regression results). Importantly, a comparison of overall 12-month weight change between these clusters revealed that the cluster which demonstrated high BWV also had significantly increased weight compared to the other clusters, though these differences were modest (ranging from +0.1 to +1.1%). This is consistent with evidence that BWV is weakly related to weight gain or less weight loss (Feig and Lowe, 2017; Benson *et al.*, 2020) also shown in chapter 8, and thus strategies may be implemented to address this.

9.4.3 Longitudinal Analysis

To our knowledge, no previous study has examined relationships relating psychological and behavioural factors to BWV. Therefore, it has not been clear whether psychological processes are simply associated with prospectively measured BWV, or whether BWV influences these processes. Greater initial (6-month) BWV predicted slight increases in binge eating and disinhibition scores; and significant decreases in body image flexibility and mental wellbeing scores. This is in part consistent with an early review concluding that weight cycling may have some detrimental psychological effects relating to eating behaviour and negative affectivity (Foster, 1997), though this was extended to include several unexplored psychological and behavioural factors. Similar to baseline prediction, the observed effect sizes relating to the variance in change explain were small (up to 2.2%). Nevertheless, the implication is that variability in body weight may potentially

be related to both eating control and negative affectivity which requires further investigation, ideally over longer durations than 12-months.

9.4.4 Strengths and Limitations

This study has several strengths. First, frequent (~3x per week) measures of body weight were used to estimate BWV over a period of 1 year. Similar analyses have used yearly body weights [15], a small amount (3) of body weights [22] or collected data for only 12-weeks (Feig and Lowe, 2017). Data on 92 psychometric variables from 27 scales was collected and used an exploratory and data-driven approach to identify a model best explaining BWV, initially by removing unrelated variables and then using unsupervised techniques. A data-driven approach was preferred as (a) very little prior evidence exists on which to generate a-priori hypotheses and (b) due to the original structure of the trial there was a substantial number of potentially predictive variables. BWV was measured objectively and longitudinally and BWV and change in psychometric variables were separated in time in order to implicate novel causative associations using a change score analysis. Associations between weight history and BWV were revealed, providing further novel evidence implicating the role of WS in the aetiology of WV.

There are also limitations to consider. The modest effect sizes highlight multiple key points of interpretation. First, BWV is not only related to energy behaviours but also to fluctuations in FFM compartments (e.g. water, glycogen and gut contents) which are not strongly related to behaviour and thus cannot relate to psychometric scales. In a recent study measuring the composition and energy density of 2-week weight fluctuations using regular DXA measurements, it was found that 84% of short-term weight fluctuations were due to changes in FFM (with highly significant changes in total body water), and the energy content of the observed weight fluctuations was modest. Not only this, but issues associated with self-weighing at home including inconsistent weighing conditions (time of day, gut fullness and variance in clothing clothing) or decalibration of smart scales may add additional noise to the measurement of BWV. Indeed, in a recent review on BWV (Lowe, Benson and Singh, 2020), there is a discussion of the ‘signal in the noise’, whereby the signal signifies energy balance components of measured BWV (i.e. fluctuation of weight which has an attributable energy component), and the noise represents everything else. This is one important caveat to consider in the interpretation of these modest results, specifically that

significant effects are present but small and any potential phenomenon under scrutiny may be affected by (a) measurement error in the estimate of BWV and (b) the ability of psychometric scales to validly and reliability reflect true human energy balance behaviours consistently, both between and within individuals.

Next, all psychometric and weight history variables are self-report and therefore subject to certain biases (Rosenman, Tennekoon and Hill, 2011). The extent to which questionnaires measure actual psychological processes and behaviours is unclear, as highlighted recently in relation to self-report measures of dietary intake (Dhurandhar *et al.*, 2015). However, while there is error associated with most of these measurements, significant effects were still observed consistent with previous literature. Next, the sample was engaged in a weight loss maintenance intervention and therefore generalizability of results to other samples may be limited, though further research is required to confirm this. This may be particularly relevant when considering the role of WS, which is the most prominent finding in this sample. Further, only examined 6 and 12-month associations were examined, though these relationships may operate over longer periods.

9.5 Conclusions

To conclude, a data-driven exploratory analysis of BWV was conducted which showed that objectively measured BWV in a weight loss maintenance environment is modestly related to uncontrolled eating factors and negative affective factors (specifically to low body image acceptance, and to feelings of depression and low mental wellbeing). Higher restrained eating coincided with higher uncontrolled eating, implicating the potential role of inconsistency of eating behaviour in BWV aetiology though associations were modest. Further, WS and lifetime weight losses were both directly associated with BWV and may indicate a predictive factor in development of the psychological risk for BWV. Each baseline factor associated with BWV was observed to cluster in a “low eating control/high negative affect” cluster in two discrete clustering analyses, providing suggestion for a psychological phenotype prone to increased BWV. These high-BWV clusters were shown to have modestly increased weight at 12-months compared to other clusters, providing some mechanistic evidence of the associations observed in chapter 8. Additionally, it was shown that initial 6-month BWV was associated with higher uncontrolled eating and negative

affective factors, though again effect sizes were minor under the current conditions. Given the cyclical nature of BWV, identification of such causative relationships may potentially provide novel insights into the relationships between prospectively measured BWV and psychological health, though the present analysis was exploratory, and confirmation is required. Future studies of BWV aligned with accurate measurement of body composition and objectively tracked energy balanced behaviours may help isolate energy-related fluctuations which are of greater scientific relevance to psychological and behaviour factors studied.

Chapter 10. Final Discussion

This PhD aimed to apply novel methods and unique data to advance the scientific understanding of body weight variability (BWV). The specific aims were to (a) consider factors associated with weight loss which affect weight regain (i.e. looking specifically at a single cycle); (b) improve and understand the errors associated with calculations of BWV; (c) study whether BWV has predictable temporal patterns; (d) investigate whether BWV over 12-18 months impacts traditional markers of health and body composition; (e) examine whether short-term BWV measured over 6-12 weeks influences longer-term weight management and lastly (f) explore the psychological and behavioural causes and consequences of BWV.

Indeed, most energy balance research deals with the impact of weight loss and gain over prolonged periods on outcomes of interest (i.e. physiological, psychological or behavioural factors). However, as with most time series data (i.e. any data which can be plotted as a function of time), there is an associated variability component coinciding with the trend (change) in weight. Previous literature has either (a) ignored this variability component or (b) dealt inappropriately with it through poor definition and measurement. Ignoring the variability component would be to say that (for example) a given amount of weight loss affects health similarly regardless of the path taken to get there (i.e. whether there was a linear or cyclical weight pattern). This is typical of studies investigating associations between weight loss and health. Studies which do examine the influence of BWV on health most often measure body weight infrequently (every 6-24 months) and the limitations of this approach have been discussed extensively throughout the thesis (e.g. see section 3.1).

Nonetheless, results from the epidemiological literature have generally suggested that body weight variability (BWV) is a risk factor for all-cause mortality, type 2 diabetes (T2D) and cardiovascular disease (CVD), as evidenced by the literature review conducted in chapter 3 in addition to numerous recent meta-analyses relating greater BWV to risk of mortality (Zhang *et al.*, 2019), CVD (Zou *et al.*, 2019b) and T2D incidence (Kodama *et al.*, 2017). The increased risk reported by some studies was not minor. For example, in 29,316 Scottish men and women with diabetes, a 149% increase in the risk of all-cause mortality was reported in those in the highest quartile of BWV defined by the coefficient of variation

and measured over 2 years (Aucott et al. 2016). Another study, published recently in the New England Journal of Medicine, showed a 136% increase in the risk of stroke for those in the highest quintile of BWV, in 9509 patients with coronary artery disease (Bangalore *et al.*, 2017). Many studies also reported significant effects in the absence of pre-existing disease criteria, suggesting it is not an effect specific to unhealthy individuals. For example, in the two largest studies to date which used data from national health registries, the risk of T2D incidence was shown to increase by 10% in around 4 million Japanese adults in the highest BWV group (Park *et al.*, 2019) and the risk of all-cause mortality and myocardial infarction increased by 53% and 14% respectively in the highest quantile in a sample of almost 7 million Korean adults (Kim *et al.*, 2018).

Accordingly, this intriguing set of results from recent literature set the context for an investigation of BWV as the primary research issue of this PhD based on (a) a significant literature suggesting its role in deterioration of health combined with (b) it's current measurement limitations; (c) a lack of physiological understanding of its effects and (d) little understanding of its psychological and behavioural correlates. The NoHoW trial weight loss maintenance trial provided a unique opportunity to advance the understanding of BWV as frequent measurement (~2-3 time per week) of body weight using WiFi connected smart scales was conducted in up to 1,627 individuals for 18-months. However, this type of data does not lend itself easily to simple BWV calculations, and there is potential for differences in data availability or erroneous data to substantially bias BWV estimates thus analyses. Indeed, it was a crucial first step to have confidence in BWV estimates for use in later studies.

10.1 Summary of PhD Findings

The initial segment of the PhD (chapter 2) aimed to take a wider look at factors affecting weight cycling by using a single cycle of loss and regain as a model for longer-term weight cycling (given the absence of long-term objective weight cycling data). In two complementary studies, one of which a systematic review and meta-regression of 52 groups experiencing weight loss and weight regain (Turicchi *et al.*, 2019) and the second, a re-analysis of the Diet, Obesity and Genes (DiOGenes) trial (Jake Turicchi, O'Driscoll, Finlayson, Duarte, Hopkins, *et al.*, 2020). These studies looked at 3 factors of weight loss: the amount,

rate and composition of weight loss, and how these affected subsequent weight outcomes following weight loss. The impact of the composition of weight loss on appetitive factors was also assessed as a potential pathway linking functional changes in body composition and psychology.

Both studies showed that greater amounts of weight loss predicted greater magnitudes of regain. Indeed, this favours the concept of a physiological adaptation to weight loss which increases with weight loss, and is inconsistent with the hypothesis that greater weight loss may lead to better weight outcomes due to adoption and honing of skills and behaviours associated with better weight management (Elfhag and Rossner, 2005). It was also found that greater rates of weight loss were associated with greater subsequent weight regain, and this effect was largely driven by greater weight regain following rapid weight loss by very-low calorie diet. Greater rates were not, however, found to be associated with larger reductions in fat free mass (FFM), as found by others (Chaston, Dixon and O'Brien, 2007). Using individual-level data, it was shown that greater fractions of FFM loss during weight loss predicted greater weight regain in men (but not women), in addition to being associated with an increased appetite (again, in men but not women).

In chapter 3, a literature review which examined the evidence relating instability in body weight (be that weight cycling of BWV) to health and weight outcomes was conducted. Firstly, the measurement of weight cycling and BWV were examined, concluding that (a) the definitions of weight cycling are extremely heterogenous and little consensus exists on the operationalisation of the term and (b) the calculation of BWV is limited by infrequent body weight measurements and assumptions of linearity in long-term weight change. Second, the majority of results from long-term epidemiological studies were in favour of a detrimental effect of BWV on risk of all-cause mortality, cardiovascular disease (death or incidence) and type 2 diabetes incidence, though the methods used, and data collected varied significantly between studies. Next, it was shown that in studies examining the influence of BWV or weight cycling on traditional metabolic risk factors for disease, there was no consistent evidence relating instability in body weight to the worsening of metabolic effects. However, in a separate literature concerned with weight cycling in animal studies, some evidence did suggest weight cycling may lead to deterioration in control of glucose/insulin metabolism as well as reduced immune system function and increased inflammation, effects which have not been sufficiently studied in humans. Lastly, evidence from a small select sample of

available studies suggested that greater BWV measured over the short-term (i.e. 6-26 weeks) predicted increased weight (or less weight loss) in the longer-term (i.e. 1-3 years).

In chapter 5, a simulation and validation study (Jake Turicchi, O'Driscoll, Finlayson, Duarte, A L Palmeira, *et al.*, 2020) was conducted which aimed to (a) develop a conservative data cleaning method; (b) test how well body weight data can be imputed and (c) test whether data should be imputed or left as missing in order to most accurately calculate BWV. Data cleaning is important in the calculation of BWV because outliers and erroneous data are registered as a substantial variation from the mean, functioning to inflate BWV estimates. Nevertheless, the removal of true data should always be avoided where possible. As such, a conservative approach was taken informed by literature on extreme weight losses and gains under conditions of starvation and massive overfeeding, and weights were removed where the rate of change was deemed physiologically implausible.

Imputation was tested by taking participants with (near) complete data, and randomly or non-randomly removing increments of data at rates of 20% ranging from 20% to 80%. Imputation of body weight was difficult and imputation strategies typically either (a) reverted towards a moving average (smoothed) body weight or (b) attempted to impute daily variability in body weight, but not accurately when compared to the observed variability. Notably, time series data are often defined by their stochastic or deterministic properties. A completely stochastic time series is one which is entirely unpredictable based on previous observations, whereas a deterministic time series is partially or entirely predictable. It appears that the variability component of body weight is highly stochastic which is why, even when using 10 different imputation strategies including multivariate machine learning approaches, the variability was not well imputed. This is likely due to (a) the complexity of free-living human behaviour and (b) the unpredictability of fluctuating compartments of FFM, namely water, glycogen and gut weight, together with the uncertainties associated with participants self-weighing at home (e.g. variability in clothing worn, bladder empty or not). Importantly, this imputation performance testing does not necessarily need to apply to the study of BWV, but instead can inform future studies using frequently collected body weight data. Indeed, in the past, several studies have examined how to minimize bias in data collected by activity trackers (Catellier *et al.*, 2005; Borghese *et al.*, 2019; R. O'Driscoll *et al.*, 2020) and this study provided the first similar information in relation to body weight tracking.

Lastly, it was shown that leaving data as missing did not substantially bias BWV estimates (with underestimations of only 8% being associated with ~80% missing data), whereas BWV calculation following imputation generally resulted in substantial underestimation of values. This is in contrast to physical activity or accelerometery data, where ignoring missing data functions to bias activity estimates (R. O'Driscoll *et al.*, 2020). However, the difference is that in relation to BWV it is the variability that is of interest, and in activity it is the sum, and imputation of approximate mean data is much simpler than imputing variability, particularly when the data is highly stochastic. Indeed, imputation has previously been performed when estimating BWV (Benson *et al.*, 2020), and this study provides a validated recommendation against such approaches.

Next, the question of whether BWV could be defined by predictable temporal patterns was investigated, and this study formed the first ever descriptive account of body weight fluctuations across weeks, seasons and the holiday period in groups varying in age, BMI, geographical region and gender (Jake Turicchi, Ruairi O'Driscoll, Horgan, Duarte, Antonio L. Palmeira, Larsen, *et al.*, 2020). It was shown that body weight fluctuated within a week, characterised by weekend weight gain and weight loss during the week, with fluctuations averaging ~0.35% per week at group level though errors were substantial suggesting significant individual variability. This effect was shown even following detrending (removal of the overall trend in body weight). The trend in body weight may function to confound fluctuation analysis if not appropriately dealt with – for example in an individual gaining on average 1kg per month, weight would always be ~0.25kg greater at the end of the week. Detrending centres the body weight around 0 allowing fluctuations to be independently investigated. The weekday result is consistent with epidemiological evidence surrounding eating behaviours on weekends, which generally show an increased intake of fatty foods and alcohol on weekends (An, 2016; Jahns *et al.*, 2017). Small group differences relating to gender, region, age and BMI were observed but these were very modest overall and generally all groups followed a similar pattern.

Over Christmas, upward fluctuations in the region of 1.4% body weight at group level were observed after adjustment for linear weight change over the wider period, which reduced following Christmas but was not completely compensated for by March. This lack of compensation for acute weight gain over Christmas is supportive of the hypothesis that weight gain at population level may be partially attributable to holiday weight gains which

are never lost (Roberts, 2009). Consistent fluctuation patterns across the seasons of the year were not observed, inconsistent with previous evidence which has shown increased body weight during winter and decreases in summer (Mehrang *et al.*, 2016a). However, this observation may largely relate to the Christmas effect.

Overall, this study suggested that some degree of the BWV measured is not completely stochastic but does have some predictable properties in response to temporal variables (e.g. day of the week). Nonetheless, when day of the week was used as an additional predictive variable in multivariate imputation methods (in chapter 5), it did not improve imputation performance.

Following validation of the methods of estimating BWV and description of temporal body weight patterns, an examination into the associations between BWV and health, weight and psychological outcomes were conducted in chapters 7, 8 and 9 respectively. These investigations were conceptualised in response to existing literature on BWV and weight cycling which suggested that BWV is (a) a health risk; (b) a risk for future weight gain and (c) detrimental to psychological health.

In chapter 7, a comprehensive analysis of the associations between concurrent 12-month BWV and changes in cardiometabolic health markers and body composition was conducted (Jake Turicchi, Ruairi O'Driscoll, Horgan, Duarte, Inês Santos, Encantado, *et al.*, 2020). The design of the study was conceptualised to test the hypothesis that BWV increases risk of CVD, T2D and all-cause mortality through detrimental changes to traditional risk factors. Given that lipids and blood pressure are strongly associated with risk of CVD, and HbA1c for T2D, it is plausible that BWV negatively impacts these markers of health and thus risk of disease. Furthermore, some evidence has suggested that instability in body weight (specifically weight cycling) can negatively impact body composition by causing repartitioning of mass from FFM to FM due to differences in the rate of protein turnover during weight gain and loss (Dulloo *et al.*, 2015) though this effect is hypothesised to be specific to lean individuals. Furthermore, there is evidence provided by animal model studies that experimentally weight cycled mice showed dysregulated metabolism (see section 3.4.2 for a full review of the animal literature).

Four methods of calculating BWV were used, which was an approach taken recently by another study examining the influence of BWV on health (Kim *et al.*, 2018) in order to conduct a robust analysis which was not confounded by the method of BWV calculation. All

analyses were adjusted for weight change (and objectively measured physical activity) given the known associations between weight loss and health. Altogether 144 models examining BWV-health associations were generated, however, no consistent associations between BWV and changes in health markers were observed, whereas weight loss consistently improved all markers of health. An entire sensitivity analysis was conducted (appendix 7.2) in which initial 6-month BWV was used to predict change in health markers the 6- to 12-month period, however, these results confirmed the original null association.

Several reasons for this null effect are possible. Firstly, the duration of the study was limited to 12-months however many of the studies examining associations between BWV and risk of disease measure BWV for several years and often decades, with similar follow-up durations. Indeed, it may be that (a) BWV must be measured for longer durations or (b) a delayed effect requires a follow-up period to be registered. Next, it has been hypothesised that instability in body weight (specifically weight cycling) is a pathway to metabolic disease in lean individuals (Dulloo and Montani, 2015; Montani, Schutz and Dulloo, 2015a) though the present sample examined had overweight and obesity. Dulloo and Montani also use examples of substantial weight cycles (e.g. losses and regains of >20% body weight in the Minessota Starvation Study (Keys *et al.*, 1950)) when hypothesising about the detrimental effects of weight cycling. However, it is likely that the BWV measured presently is not as extreme as in the Minnesota Study. Furthermore, it is not possible to be certain what the measured BWV represents as both fluctuations in fat mass and fat free mass compartments (specifically, gut weight, glycogen and associated water) as well as measurement error are all likely to contribute to the measured BWV (this is discussed in greater detail in the limitations section below).

This study failed to elucidate a potential mechanism linking BWV to risk of disease. Indeed, it could be that BWV is in fact not a risk factor and the reported associations are confounded by the presence of underlying disease and unintentional weight loss which may go unreported (see chapter 3 for a full discussion of the limitations of this epidemiological literature). Another possibility relates to literature which suggests that variability in health markers (for example blood pressure variability) is a risk factor for disease independent of the absolute blood pressure value as shown in a recent meta-analysis (Stevens *et al.*, 2016). Similar results have been shown for variability in other cardiometabolic health markers including glucose and cholesterol (Kim *et al.*, 2018). As such, it could be that BWV functions

to increase health marker variability without directly influencing the mean value and this potential mechanism requires further study.

In chapter 8, the potential role of using short-term BWV as an indicator of longer-term weight loss maintenance was examined (J. Turicchi *et al.*, 2020). Recent research in the past five years from Lowe and colleagues (Lowe *et al.*, 2015; Feig and Lowe, 2017; Benson *et al.*, 2020) has purported that greater BWV measured over 6-26 weeks may predict weight gains at 1-3 years. This evidence comes from a select few studies from a single research group and further investigation and replication was required. Furthermore, methodological limitations of these studies (discussed fully in section 3.5) may potentially detract from the conclusions reached. Also, this result was yet to be replicated in a large group of individuals who recently lost weight and engaged in a weight loss maintenance intervention.

The results supported the previous works of Lowe and colleagues both in direction and magnitude, suggesting that greater BWV measured over 9 and 12 weeks predicted increased weight at 12 and 18 months. Shorter exposure (to BWV) durations (6-weeks) and follow-up durations (6-months) were associated with reduced effect sizes, reaching statistical significance in some but not all models. The effect sizes reached were modest and did not explain >5% of weight outcomes over the period. This was not surprising given that early or baseline prediction of weight loss and maintenance outcomes in interventions typically results in small proportions of the variance explained (Stubbs *et al.*, 2011). This is likely owing to 2 main reasons: (1) weight loss and/or maintenance is a highly complex and multifactorial process and therefore single or even groups of predictors are unlikely to explain much variance and (2) the predictors used are often self-reported traits and states (e.g. eating behaviours, negative affect, personality, self-regulatory factors etc) and the extent to which these relate consistently to actual human behaviour is unclear. The present study overcomes limitation (2) by using an objective measurement of physiology and therefore does not succumb to limitations of self-report.

Despite modest effect sizes, an additional analysis was conducted in order to attribute an interpretable value to the reported model effect sizes. In the strongest model (the model in which 12-week RMSE was used to predict weight outcomes at 18-months) 1 standard deviation was added and subtracted from the mean RMSE value, and the difference in the mean weight change of the groups at both extremes was calculated. A 5% difference in weight changes between groups at 18-months was shown, which is a clinically

significant effect. Notably, it is possible that the modest effect sizes of the regression models are partially attributable to the fact that mean weight change in the NoHoW trial was around half a kilogram over 18-months yet ranged from -30% to +35%. This might explain why a relatively small effect size (R^2=5%) relates to a big difference in weight change at 18-months.

It was hypothesised by Lowe et al that BWV predicts weight gain as BWV is a reflection of unstructured or disordered eating behaviours and that it is these behaviours that, over time, translate to weight gain. In one study, it was shown that short term BWV was weakly correlated ($r<0.2$, $p<0.05$) with eating behaviour variables such as preoccupation with food and power of food scales (Feig and Lowe, 2017). Nonetheless, the extent to which BWV is a measurement of actual fluctuations in energy balance is debatable (see limitations below for full discussion). Instead, it is likely that there is a minor 'energy balance signal' in a much greater amount of noise, an idea presented in a recent narrative review (Lowe, Benson and Singh, 2020) and this fact limits the ability to discover strong associations between BWV and weight outcomes. Further study of BWV alongside (a) frequent measurements of multi-compartment models of body composition and (b) objective tracking of energy balance components (EE and EI) will facilitate a much greater ability to study associations between BWV and weight management (see recommendations for future study below).

In relation to above, the causes of BWV are unclear due to (1) a historically poor ability to measure instability in body weight (be that via retrospective questionnaires or prospective infrequent weight measurements) and (2) a lack of potentially explanatory variables aligned with BWV. The NoHoW study presented a unique opportunity to address this gap in the evidence. The original design of the study facilitated the inclusion of a substantial number of self-reported psychological, behavioural and weight history variables from both established and novel scales and data was collected longitudinally allowing change scores to be generated. This presented an opportunity to explore the causes and consequences of BWV but coincided with a problem in that there were too many predictive variables for traditional hypothesis testing, and also a lack of previous literature or theory upon which to generate a priori hypotheses. Accordingly, an exploratory approach was taken aiming to best understand (a) baseline prediction of BWV and (b) the longitudinal consequences of BWV on self-reported psychological and behavioural factors. Indeed,

undefined and unsupervised statistical approaches are often preferred in these circumstances (Islam *et al.*, 2018; Alashwal *et al.*, 2019), though rarely applied in obesity research. This was done using numerous statistical approaches, including unsupervised approaches such as stepwise regression and multiple clustering techniques (hierarchical clustering and K-means clustering) to take baseline variable associations with 12-month BWV. Bi-directional relationship testing was also conducted to examine whether initial BWV impacts subsequent change in psychological or behavioural factors, and whether initial change in psychological or behavioural factors impacts subsequent BWV.

Some common themes emerged from the analyses conducted. Generally, baseline binge eating (and, less so, disinhibition) was greater in those with greater 12-month BWV, and this coincided with greater restrained eating (stepwise model 1). This is supportive of the model suggested by Lowe and colleagues that variability in eating behaviours (i.e. individuals switching from restrained eating to disinhibited eating) partially contributes to BWV. It also agrees with the earlier result than body weight is gained during weekends (and over the holiday period) and is then lost during the week – a cyclical pattern which is likely owed to fluctuations in eating behaviour. This pattern of overindulgence and restriction is likely to only explain very modest amounts of the variance in BWV, with no eating behaviour variable surpassing R^2=4.5%. The result is also consistent with earlier weight cycling research showing cross-sectional associations between self-reported weight cycling and binge eating (Venditti *et al.*, 1996; Borges *et al.*, 2002b; Petroni, Villanova, Avagnina, Fusco, Fatati, Compare and Marchesini, 2007; de Zwaan, Engeli and Müller, 2015b). Other commonly associated variables included low body image acceptance and high weight shame. Indeed, it has been shown that binge eating often coincides with low perceived body image and greater weight shame (Duarte, Pinto-Gouveia and Ferreira, 2017) and these may impact the aetiology of BWV in some individuals.

Weight suppression and previous weight losses were two of the strongest predictors of 12-month BWV (though effect sizes were still modest at R^2 <6%). The association of previous weight losses and subsequent BWV suggests a continuation of prior behaviours, in that those who historically diet repetitively and regain weight continue to do so in the trial. Weight suppression has often been associated with binge eating in both clinical eating disorder samples and non-clinical groups (Lowe *et al.*, 2007, 2020; Stice *et al.*, 2020). Furthermore, those with greater weight suppression have been reported to experience

greater body image concerns in a non-clinical sample (Goodman *et al.*, 2018). Together, these results imply that weight suppression may impact psychological factors and eating behaviour in a manner associated with greater BWV. However, further research is required to fully elucidate these mechanisms.

The study was the first to provide evidence of a negative effect of BWV on self-reported behaviour and psychological wellbeing. Greater BWV in the first 6 months predicted increases in binge eating and disinhibition and decreases in mental wellbeing and body image acceptance, however, the variance in change explained did not exceed 2.2% and further research is required which aims specifically to investigate the impact of BWV on psychological health. The modest effect sizes observed are likely to be due not only to the fact that the measurement of BWV is not a direct measurement of fluctuations of energy balance (discussed below in limitations), but also the extent to which self-reported questionnaires actually relate to behaviours. Indeed, the extent to which questionnaires measure actual psychological processes and behaviours is unclear, as highlighted recently in nutrition research (Dhurandhar *et al.*, 2015). Recommendations as to how future studies might partially address such limitations are given later in this chapter.

10.2 Strengths of the PhD

Each study has separate strengths and limitations which are discussed as part of each chapter, however there are some overarching themes which should be outlined here. Firstly, the thesis is effectively split into two parts which aimed to (a) take a close look at the predictors of a single weight cycle (i.e. what characteristics of weight loss predict subsequent weight gain) and (b) take a wider look at how instability in body weight actually portrays itself, with specific examination of both its causes and consequences. This joint approach helps to improve the understanding of weight instability at both the macro and micro level.

Many of the PhD strengths are owed to the novelty of the methods used. Most importantly, WiFi connected smart scales were used throughout to measure body weight and therefore estimate BWV. The use of these devices provides 2 advantages: (1) data can be collected frequently, meaning that true body weight patterns can be discerned, and actual BWV can be estimated and (2) the data is objectively measured and date-stamped,

whereas in previous research, body weight data used to estimate BWV is often collected by retrospective or prospective self-report which is subject to recall and social desirability biases. From the studies conducted, it is clear that smart scale devices have the potential to greatly enhance scientific understanding of BWV.

Next, a new method of estimating BWV was devised to overcome the limitations of the most commonly used method, root mean square error (RMSE). When using RMSE, individuals with cyclical (e.g. V-shaped) weight patterns have inflated BWV values because a linear regression does not fit closely to V-shaped data. The new method, termed non-linear mean deviation (NLMD), fits a polynomial LOESS regression to the body weight data, meaning that in individuals with cyclical weight patterns, the regression fits more closely to the body weight data. The result is that BWV estimates are more comparable between individuals with linear and V or M-shaped weight patterns. As such, NLMD is more sensitive to smaller fluctuations in body weight such as those between days and weeks, whereas RMSE is more sensitive to larger weight cycles.

Given that BWV research is in its infancy it is unclear which patterns of body weight might relate to outcomes of interest. Therefore, in some studies including those relating to cardiometabolic health outcomes (chapter 7) and body weight outcomes (chapter 8), multiple methods of estimating BWV were used (4 and 2 respectively). This was an explorative approach which allowed the identification of whether any observed effects were confounded by a single measurement of BWV and was deemed preferable to using a single method alone. The studies conducted sampled from participants in the NoHoW trial. This allowed us to examine the role of BWV in a specific group (i.e. weight loss maintainers who recently lost, on average ~11% body weight) and how it relates to health, weight and psychological outcomes, which has never been examined before.

Numerous physiological measurements were collected which aligned with body weight measurements, including systolic and diastolic blood pressure, lipids (high- and low-density lipoprotein cholesterols and triglycerides) and haemoglobin A1c in addition to body composition measurements made by 2 methods (bioelectrical impedance and dual energy xray absorptiometry in a subsample). Together this allowed a comprehensive examination of the influence of BWV on human physiology. Similarly, a comprehensive array of self-reported variables relating to psychological status, behaviour and weight history were collected. This allowed associations to be assessed between prospectively measured BWV

and many variables which it has yet to be related to. Together, this meant that a large number of novel physiological and psychological relationships were investigated within this PhD in order to improve scientific understanding of BWV.

10.3 Limitations of the PhD

Aside from the specific limitations addressed in each chapter, this PhD has some notable overarching limitations. Most importantly, it is impossible to be certain (under current conditions) what exactly the estimates of BWV are measuring (an issue which has been discussed throughout this thesis). There are two primary reasons for this, which include a lack of information on: (1) the properties of the fluctuating mass and (2) errors relating to the use of smart scales at home. Body weight variability values are generated as a summary of weight changes which are composed of both fat mass (FM) and fat free mass (FFM). As discussed previously, the composition of FFM is heterogeneous as it contains both energy dense tissues (e.g. skeletal muscle) and low or no energy compartments (e.g. gut weight and total body water [TBW]). Bhutani et al assessed the composition of 2-week weight fluctuations in 46 adults with overweight and obesity using repeated stable isotope dilution and dual energy x-ray absorptiometry (Bhutani *et al.*, 2017b), reporting that the changes in body weight were composed of 84% FFM, and that significant changes in TBW were observed with each weight change. Also, the energy content per kg of short-term weight change was ~2380kcal. Together, these results suggest that most of the BWV measured in this study is not related to changes is energy balance, but instead to fluctuations in TBW (and potentially gut weight). Adding further noise, problems with home collection of body weight data using smart scales may arise from factors such as variability in clothing; the time of day; last toilet trip; last meal or the surface on which the scales are placed. Movement of the scales may, if not addressed, decalibrate the scales, adding additional noise. Indeed, participants were advised to maintain consistent weighing conditions but the extent to which this was adhered to cannot be ascertained. Together, these factors add further noise to the estimates of BWV yet cannot be adjusted for. It is primarily the fluctuations in energy balance compartments that are of scientific interest, yet it is likely that this represents only a small signal in highly noisy data. Potential solutions to these problems are discussed below in section 10.5.

Next, the duration of the studies conducted on BWV were limited to 12 or 18 months (i.e. some physiological markers were only collected at 0 and 12 months) due to the pre-defined design of the NoHoW trial. As discussed in chapter 3, epidemiological evidence relating BWV to risk of cardiometabolic diseases and mortality typically span for several years or decades. Indeed, it could be that BWV takes a much greater time to affect health, however it was not possible to examine this presently as data were not available.

Each of the studies conducted used a sample of individuals with overweight and obesity who recently lost >5% body weight (on average ~11% dependent on the sample used) and engaged in a weight loss maintenance intervention. This differentiates them physiologically from the general population because they are likely to have recently benefitted from health improvements which may confound the subsequent associations between BWV and health. Furthermore, it has been hypothesised that instability in body weight has detrimental effects on body composition and cardiometabolic health specifically in lean individuals (Dulloo *et al.*, 2015; Montani, Schutz and Dulloo, 2015b) but we were not able to examine this relationship due to our sample characteristics. The sample characteristics may also confound associations with weight outcomes (as examined in chapter 8) as they were actively engaged in an intervention and are also likely to have developed weight management skills from recently reducing body weight. This also makes them a psychologically and behaviourally distinct group, thus limiting the generalisability of observations made when relating BWV to these factors.

10.4 Implications of the PhD

While this PhD did not generate sufficient evidence for clinical recommendations to be made, there are several implications of the research findings which may impact the future study of BWV. In chapter 2, the first evidence of a potential functional role of proportionate reductions in FFM in relation to increased self-reported appetite was reported and may further contribute to the scientific understanding of the aetiology of weight regain (though this association was inconsistent between genders and requires further study). Moreover, this relationship was hypothesised to operate in lean individuals under extreme conditions (e.g. starvation) (Dulloo, Jacquet and Girardier, 1997b) yet evidence of an association in men with overweight and obesity undergoing therapeutic

weight loss was observed, suggesting extreme conditions may not be required for this effect to operate.

No study to date has considered pre-processing of data collected by electronic smart scales, as has been done with activity tracking devices (Liu *et al.*, 2016; Borghese *et al.*, 2019) including work by our research group (R. O'Driscoll *et al.*, 2020). Novel guidance on how to conservatively remove outliers and validation of the errors and uncertainties associated with univariate and multivariate data imputation was published (Jake Turicchi, O'Driscoll, Finlayson, Duarte, A L Palmeira, *et al.*, 2020) and can be applied in any study using similar devices. Importantly, this information is not specific to the study of BWV. This study also provided an estimate of the errors associated with BWV calculations under different degrees of missing data (and imputed data) and functions to inform future BWV studies using smart scales. It was shown that imputation of body weight data serves to significantly underestimate BWV and recommendations to use raw data were provided.

The hypothesis that early BWV can be used to predict longer-term increased weight suggested by Lowe and colleagues was confirmed for the first time outside of a single research group, in a large sample of individuals engaged in a weight loss maintenance intervention. Furthermore, while the models did not explain >5% of the variance in weight change, when weight change at 18 months was compared between high and low 12-week BWV groups (by RMSE), those with a high BWV gained an additional 5%, suggesting a potential clinical importance of short-term BWV for weight management.

Lastly, while the associations between weight loss and psychological status has been well studied and include improvements to quality of life, body image and self-efficacy (Lasikiewicz *et al.*, 2014), whether BWV influences psychological and behavioural factors had not been investigated. In chapter 9, it was shown that BWV may contribute to a worsening of (a) psychological factors (shown by decreased mental wellbeing and body image acceptance) and (b) control of eating (shown by increased binge eating and disinhibition). This is the first time this effect has ever been observed, thought the effect sizes were modest (< 3% variance explained), nonetheless, further investigation of the psychological impact of BWV is merited.

10.5 New Research Pathways and Future Recommendations

Several potential new directions and recommendations for the future study of BWV can be ascertained from the work conducted in this thesis. In chapter 3, the literature in animal models revealed evidence that weight cycling has a significant impact on immune and inflammatory responses, as well as causing disturbance to glucose and insulin regulation and potentially causing increased visceral fat deposition. These outcomes have not been explored sufficiently in relation to BWV and future studies should investigate if these mechanisms operate in humans as this might potentially offer a pathway linking BWV to risk of disease and mortality.

Next, the use of Wi-Fi connected smart scales to collect body weight data is central to the increased understanding of BWV. Indeed, only one recent study had previously used these devices (Benson *et al.*, 2020) however smart scales are becoming increasingly used in research settings and the data collected by these facilitates appropriate estimations of BWV. Importantly, to overcome a limitation of the present work related to the short measurement period of 12-18 months, longer-term data collection is important and may facilitate more relevant comparison to the epidemiological literature on BWV and health. It is indeed possible to retrospectively acquire consent to study individual's data collected by smart scales over the previous years (as done in Benson et al.), and large companies such as Fitbit store millions of user's data over many years, the use of which could further enhance the study of BWV if access is granted.

From an energy balance and weight management perspective, it is primarily the variability in body weight associated with an energy content (i.e. not water) which are of interest (see limitations above for a full discussion). The only way to determine the composition of BWV is through regular multi-compartment body composition measurements including at least a measure of total body water. With this, a greater idea of the energy content of the variability could be ascertained. This would allow much greater resolution in the ability to measure energy balance variability and relate it to energy balance determinants such as eating behaviour and physical activity. However, the possibility of regular high-quality measurements of body composition (such as by DXA) is low due to the associated costs and burden on researchers and participants.

Tracking of energy balance behaviours may help improve the understanding of determinants of BWV. Indeed, weight changes occur in responses to change in EE and/or EI. The extent to which BWV is attributable to either component of energy balance is unclear, however it is likely that EI is more variable than EE (Chow and Hall, 2014) and therefore may contribute to a greater proportion of BWV. Using remote tracking devices and machine learning methods we have recently evidenced the ability to accurately track EE using machine learning algorithms applied to raw data (Ruairi O'Driscoll *et al.*, 2020). Furthermore, using mathematical models, EI can be estimated if both body weight and EE are continuously tracked by assuming an energy content for the cost of weight change (Hall, 2014; Sanghvi *et al.*, 2015). This energy value of weight change is dependent on the composition of the change, which is largely reliant on the body composition of the individual (Hall, 2007). In our lab, we have been working on developing these models and validating them against a doubly labelled water (DLW) criterion measure. However, due to the Covid-19, the DLW data was delayed by a significant amount of time and thus these models were unable to be validated and used in the present thesis. Future research could use mathematical models to estimate energy balance components and their contribution to BWV, thus increasing scientific understanding of the mechanisms through which BWV occurs.

10.6 Final Conclusions

This thesis used novel data collection techniques and statistical approaches to add unique insights which advance the current scientific understanding of the phenomenon of BWV. Characteristics of weight loss predictive of subsequent weight regain were identified which implicated a potentially functional role of proportionate changes of body composition contributing to appetitive changes and future weight outcomes. The thesis then progressed towards looking at true weight trajectories, first by improving the understanding of BWV calculation, and next by describing temporal patterns and comparing BWV to health, weight and psychological outcomes. Combining continuous tracking of energy balance alongside longitudinally collected biomarkers of health and self-reported measures of psychological factors is critical for advancing understanding in future studies of energy balance and health,

and is likely, in future, to form the basis of personalised behavioural medicine and form the basis upon which interventions can be tailored and baseline and in real time.

List of References

Ades, P. A. and Savage, P. D. (2010) 'The obesity paradox: Perception vs knowledge', *Mayo Clinic Proceedings*. Elsevier Ltd, pp. 112–114. doi: 10.4065/mcp.2009.0777.
Van Aggel-Leijssen, D. P. *et al.* (2002) 'Long-term effects of low-intensity exercise training on fat metabolism in weight-reduced obese men.', *Metabolism: clinical and experimental*, 51(8), pp. 1003–10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12145773 (Accessed: 22 October 2018).
Agha, M. and Agha, R. (2017) 'The rising prevalence of obesity: part A: impact on public health.', *International journal of surgery. Oncology*, 2(7), p. e17. doi: 10.1097/IJ9.0000000000000017.
Al-Goblan, A. S., Al-Alfi, M. A. and Khan, M. Z. (2014) 'Mechanism linking diabetes mellitus and obesity', *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, 7, pp. 587–591. doi: 10.2147/DMSO.S67400.
Alashwal, H. *et al.* (2019) 'The application of unsupervised clustering methods to Alzheimer's disease', *Frontiers in Computational Neuroscience*. Frontiers Media S.A., p. 31. doi: 10.3389/fncom.2019.00031.
Alboukadel, K. (2020) *Package 'Factoextra' - R*. Available at: https://cran.r-project.org/web/packages/factoextra/factoextra.pdf (Accessed: 15 July 2020).
Aller, E. E. J. G. *et al.* (2014) 'Weight loss maintenance in overweight subjects on ad libitum diets with high or low protein content and glycemic index: the DIOGENES trial 12-month results', *International Journal of Obesity*, 38(12), pp. 1511–1517. doi: 10.1038/ijo.2014.52.
Althouse, A. D. (2016) 'Adjust for Multiple Comparisons? It's Not That Simple', *The Annals of Thoracic Surgery*, 101(5), pp. 1644–1645. doi: 10.1016/j.athoracsur.2015.11.024.
Altman, D. G. and Bland, J. M. (2005) 'Treatment allocation by minimisation', *BMJ*, 330(7495), p. 843. doi: 10.1136/bmj.330.7495.843.
An, R. (2016) 'Weekend-weekday differences in diet among U.S. adults, 2003–2012', *Annals of Epidemiology*, 26(1), pp. 57–65. doi: 10.1016/j.annepidem.2015.10.010.
Anderson, E. K. *et al.* (2013) 'Weight Cycling Increases T-Cell Accumulation in Adipose Tissue and Impairs Systemic Glucose Tolerance', *Diabetes*, 62(9), pp. 3180–3188. doi: 10.2337/db12-1076.
Andriessen, C. *et al.* (2018a) 'Weight loss decreases self-reported appetite and alters food preferences in overweight and obese adults: Observational data from the DiOGenes study', *Appetite*, 125, pp. 314–322. doi: 10.1016/j.appet.2018.02.016.
Andriessen, C. *et al.* (2018b) 'Weight loss decreases self-reported appetite and alters food preferences in overweight and obese adults: Observational data from the DiOGenes study', *Appetite*, 125, pp. 314–322. doi: 10.1016/j.appet.2018.02.016.
Di Angelantonio, E. *et al.* (2016) 'Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents', *The Lancet*, 388(10046), pp. 776–786. doi: 10.1016/S0140-6736(16)30175-1.
Antony, M. M. *et al.* (1998) 'Psychometric properties of the 42-item and 21-item versions of the Depression Anxiety Stress Scales in clinical groups and a community sample', *Psychological Assessment*, 10(2), pp. 176–181. doi: 10.1037/1040-3590.10.2.176.
Arnold, A. M. *et al.* (2010) 'Body Weight Dynamics and Their Association With Physical Function and Mortality in Older Adults: The Cardiovascular Health Study', *Journal of Gerontology: MEDICAL SCIENCES Cite journal as J Gerontol A Biol Sci Med Sci All*, 65(1), pp. 63–70. doi: 10.1093/gerona/glp050.
Arnold, T. A. *et al.* (2015) 'Eating in the absence of hunger in college students', *Appetite*, 92, pp. 51–56. doi: 10.1016/j.appet.2015.05.010.
Ashtary-Larky, D. *et al.* (2017) 'Rapid Weight Loss vs. Slow Weight Loss: Which is More Effective on Body Composition and Metabolic Risk Factors?', *International journal of endocrinology and metabolism*, 15(3), p. e13249. doi: 10.5812/ijem.13249.
Aslam, M. *et al.* (2009) 'Assessing Body Fat Changes during Moderate Weight Loss with

Anthropometry and Bioelectrical Impedance.', *Obesity research & clinical practice*, 3(4), p. 209. doi: 10.1016/j.orcp.2009.03.005.
Astrup, A. *et al.* (1999) 'Meta-analysis of resting metabolic rate in formerly obese subjects', *American Journal of Clinical Nutrition*, 69(6), pp. 1117–1122. doi: 10.1093/ajcn/69.6.1117.
Astrup, A. and Rössner, S. (2000) 'Lessons from obesity management programmes: greater initial weight loss improves long-term maintenance.', *Obesity reviews : an official journal of the International Association for the Study of Obesity*, 1(1), pp. 17–9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12119640 (Accessed: 20 July 2018).
Aubuchon, M. *et al.* (2016) 'The impact of supervised weight loss and intentional weight regain on sex hormone binding globulin and testosterone in premenopausal women', *Systems Biology in Reproductive Medicine*, 62(4), pp. 283–289. doi: 10.1080/19396368.2016.1177619.
Aucott, Lorna S *et al.* (2016) 'Patterns of weight change after the diagnosis of type 2 diabetes in Scotland and their relationship with glycaemic control, mortality and cardiovascular outcomes: a retrospective cohort study', *BMJ Open*, 6(7). doi: 10.1136/bmjopen-2015-010836.
Aucott, Lorna S. *et al.* (2016) 'Patterns of weight change after the diagnosis of type 2 diabetes in Scotland and their relationship with glycaemic control, mortality and cardiovascular outcomes: A retrospective cohort study', *BMJ Open*, 6(7), p. e010836. doi: 10.1136/bmjopen-2015-010836.
van Baak, M. A. *et al.* (2003) 'Leisure-time activity is an important determinant of long-term weight maintenance after weight loss in the Sibutramine Trial on Obesity Reduction and Maintenance (STORM trial)', *The American Journal of Clinical Nutrition*, 78(2), pp. 209–214. doi: 10.1093/ajcn/78.2.209.
van Baak, M. A. and Mariman, E. C. M. (2019) 'Mechanisms of weight regain after weight loss — the role of adipose tissue', *Nature Reviews Endocrinology*. Nature Publishing Group, pp. 274–287. doi: 10.1038/s41574-018-0148-4.
Baicus, C. *et al.* (2014) 'Cancer and Involuntary Weight Loss: Failure to Validate a Prediction Score', *PLoS ONE*. Edited by E. von Elm, 9(4), p. e95286. doi: 10.1371/journal.pone.0095286.
Bakker, M. and Wicherts, J. M. (2014) 'Outlier removal and the relation with reporting errors and quality of psychological research', *PLoS ONE*, 9(7). doi: 10.1371/journal.pone.0103360.
Banasik, J. L. *et al.* (2013) 'Low-calorie diet induced weight loss may alter regulatory hormones and contribute to rebound visceral adiposity in obese persons with a family history of type-2 diabetes', *Journal of the American Association of Nurse Practitioners*, 25(8), pp. 440–448. doi: 10.1111/j.1745-7599.2012.00808.x.
Bangalore, S. *et al.* (2017) 'Body-Weight Fluctuations and Outcomes in Coronary Disease', *New England Journal of Medicine*, 376(14), pp. 1332–1340. doi: 10.1056/NEJMoa1606148.
Barbosa-da-Silva, S. *et al.* (2012) 'Weight Cycling Enhances Adipose Tissue Inflammatory Responses in Male Mice', *PLoS ONE*. Edited by M. Federici, 7(7), p. e39837. doi: 10.1371/journal.pone.0039837.
Barnes, R. D. and Tantleff-Dunn, S. (2010) 'A preliminary investigation of sex differences and the mediational role of food thought suppression in the relationship between stress and weight cycling.', *Eating and weight disorders : EWD*, 15(4), pp. e265-9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21406950 (Accessed: 22 June 2018).
Barte, J. C. M. *et al.* (2010) 'Maintenance of weight loss after lifestyle interventions for overweight and obesity, a systematic review', *Obesity Reviews*, 11(12), pp. 899–906. doi: 10.1111/j.1467-789X.2010.00740.x.
Bartlett, S. J., Wadden, T. A. and Vogt, R. A. (1996) 'Psychosocial consequences of weight cycling.', *Journal of consulting and clinical psychology*, 64(3), pp. 587–92. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8698953 (Accessed: 21 June 2018).
Bays, H. E., Chapman, R. H. and Grandy, S. (2007) 'The relationship of body mass index to diabetes mellitus, hypertension and dyslipidaemia: Comparison of data from two national surveys', *International Journal of Clinical Practice*, 61(5), pp. 737–747. doi: 10.1111/j.1742-1241.2007.01336.x.
Beaulieu, K. *et al.* (2016) 'Does Habitual Physical Activity Increase the Sensitivity of the Appetite Control System? A Systematic Review', *Sports Medicine*, 46(12), pp. 1897–1919. doi:

10.1007/s40279-016-0518-9.
Beaulieu, K., Oustric, P. and Finlayson, G. (2020) 'The Impact of Physical Activity on Food Reward: Review and Conceptual Synthesis of Evidence from Observational, Acute, and Chronic Exercise Training Studies', *Current obesity reports*. NLM (Medline), pp. 63–80. doi: 10.1007/s13679-020-00372-3.
Beavers, D. P. *et al.* (2013) 'Cardiometabolic risk after weight loss and subsequent weight regain in overweight and obese postmenopausal women.', *The journals of gerontology. Series A, Biological sciences and medical sciences*, 68(6), pp. 691–8. doi: 10.1093/gerona/gls236.
Beavers, K. M. *et al.* (2011) 'Is lost lean mass from intentional weight loss recovered during weight regain in postmenopausal women?', *The American journal of clinical nutrition*, 94(3), pp. 767–74. doi: 10.3945/ajcn.110.004895.
Beleigoli, A. M. *et al.* (2019) 'Web-based digital health interventions for weight loss and lifestyle habit changes in overweight and obese adults: Systematic review and meta-analysis', *Journal of Medical Internet Research*, 21(1). doi: 10.2196/jmir.9609.
Benini, Z. *et al.* (2001) 'Contribution of weight cycling to serum leptin in human obesity', *International Journal of Obesity*, 25(5), pp. 721–726. doi: 10.1038/sj.ijo.0801587.
Benson, L. *et al.* (2020) 'Weight variability during self-monitored weight loss predicts future weight loss outcome', *International Journal of Obesity*, 44(6), pp. 360–1367. doi: 10.1038/s41366-020-0534-6.
Beretta, L. and Santaniello, A. (2016) 'Nearest neighbor imputation algorithms: a critical evaluation.', *BMC medical informatics and decision making*, 16 Suppl 3(Suppl 3), p. 74. doi: 10.1186/s12911-016-0318-z.
BERNSTEIN, L. M. and GROSSMAN, M. I. (1956) 'An experimental test of the glucostatic theory of regulation of food intake', *The Journal of clinical investigation*, 35(6), pp. 627–633. doi: 10.1172/JCI103318.
Bérubé-Parent, S. *et al.* (2001) 'Obesity treatment with a progressive clinical tri-therapy combining sibutramine and a supervised diet–exercise intervention', *International Journal of Obesity*, 25(8), pp. 1144–1153. doi: 10.1038/sj.ijo.0801677.
Beydoun, M. A. (2014) 'The Interplay of Gender, Mood, and Stress Hormones in the Association between Emotional Eating and Dietary behavior', *The Journal of Nutrition*, 144(8), pp. 1139–1141. doi: 10.3945/jn.114.196717.
Bhaskaran, K. and Smeeth, L. (2014) 'What is the difference between missing completely at random and missing at random?', *International journal of epidemiology*, 43(4), pp. 1336–9. doi: 10.1093/ije/dyu080.
Bhatnagar, P. *et al.* (2016) 'Trends in the epidemiology of cardiovascular disease in the UK.', *Heart (British Cardiac Society)*, 102(24), pp. 1945–1952. doi: 10.1136/heartjnl-2016-309573.
Bhatt, A. A. *et al.* (2017) 'Effect of a Low-Calorie Diet on Restoration of Normoglycemia in Obese subjects with Type 2 Diabetes.', *Indian journal of endocrinology and metabolism*, 21(5), pp. 776–780. doi: 10.4103/ijem.IJEM_206_17.
Bhutani, S. *et al.* (2017a) 'Composition of two-week change in body weight under unrestricted free-living conditions.', *Physiological reports*, 5(13). doi: 10.14814/phy2.13336.
Bhutani, S. *et al.* (2017b) 'Composition of two-week change in body weight under unrestricted free-living conditions', *Physiol Rep*, 5(13). doi: 10.14814/phy2.13336.
Birch, J. *et al.* (2019) 'Clustering of behavioural risk factors for health in UK adults in 2016: a cross-sectional survey', *Journal of public health (Oxford, England)*, 41(3), pp. e226–e236. doi: 10.1093/pubmed/fdy144.
Björvell, H. and Rössner, S. (1992) 'A ten-year follow-up of weight change in severely obese subjects treated in a combined behavioural modification programme.', *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity*, 16(8), pp. 623–5. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1326492 (Accessed: 20 July 2018).
Blackburn, G. L. *et al.* (1989) 'Weight cycling: the experience of human dieters', *The American*

Journal of Clinical Nutrition, 49(5), pp. 1105–1109. doi: 10.1093/ajcn/49.5.1105.
Blair, S. N. *et al.* (1993a) 'Body weight change, all-cause mortality, and cause-specific mortality in the Multiple Risk Factor Intervention Trial.', *Annals of internal medicine*, 119(7 Pt 2), pp. 749–57. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8363210 (Accessed: 21 June 2018).
Blair, S. N. *et al.* (1993b) 'Body weight change, all-cause mortality, and cause-specific mortality in the Multiple Risk Factor Intervention Trial.', *Annals of internal medicine*, 119(7 Pt 2), pp. 749–57. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8363210 (Accessed: 22 December 2017).
Blundell, J. (2018) 'Behaviour, energy balance, obesity and capitalism', *European Journal of Clinical Nutrition*, 72(9), pp. 1305–1309. doi: 10.1038/s41430-018-0231-x.
Blundell, J. E. *et al.* (2012) 'Role of resting metabolic rate and energy expenditure in hunger and appetite control: a new formulation.', *Disease models & mechanisms*, 5(5), pp. 608–13. doi: 10.1242/dmm.009837.
Blundell, J. E. and MacDiarmid, J. I. (1997) 'Passive overconsumption: Fat intake and short-term energy balance', *Annals of the New York Academy of Sciences*, 827, pp. 392–407. doi: 10.1111/j.1749-6632.1997.tb51850.x.
Bohrer, B. K., Forbush, K. T. and Hunt, T. K. (2015) 'Are common measures of dietary restraint and disinhibited eating reliable and valid in obese persons?', *Appetite*, 87, pp. 344–351. doi: 10.1016/j.appet.2014.12.226.
Bonomi, A. G. *et al.* (2013) 'Weight-Loss Induced Changes in Physical Activity and Activity Energy Expenditure in Overweight and Obese Subjects before and after Energy Restriction', *PLoS ONE*. Edited by D. Johannsen, 8(3), p. e59641. doi: 10.1371/journal.pone.0059641.
Booth, H. P. *et al.* (2014) 'Effectiveness of behavioural weight loss interventions delivered in a primary care setting: A systematic review and meta-analysis', *Family Practice*, 31(6), pp. 643–653. doi: 10.1093/fampra/cmu064.
Borel, A.-L. *et al.* (2017) 'Cardiometabolic risk improvement in response to a 3-yr lifestyle modification program in men: contribution of improved cardiorespiratory fitness vs. weight loss', *American Journal of Physiology - Endocrinology And Metabolism*, 312(4), pp. E273–E281. doi: 10.1152/ajpendo.00278.2016.
Borges, M. B. F. *et al.* (2002a) 'Binge-Eating Disorder in Brazilian Women on a Weight-Loss Program', *Obesity Research*, 10(11), pp. 1127–1134. doi: 10.1038/oby.2002.153.
Borges, M. B. F. *et al.* (2002b) 'Binge-Eating Disorder in Brazilian Women on a Weight-Loss Program', *Obesity Research*, 10(11), pp. 1127–1134. doi: 10.1038/oby.2002.153.
Borghese, M. M. *et al.* (2019) 'Imputing accelerometer nonwear time in children influences estimates of sedentary time and its associations with cardiometabolic risk 11 Medical and Health Sciences 1117 Public Health and Health Services', *International Journal of Behavioral Nutrition and Physical Activity*, 16(1), p. 7. doi: 10.1186/s12966-019-0770-0.
Bosch, X. *et al.* (2017) 'Unintentional weight loss: Clinical characteristics and outcomes in a prospective cohort of 2677 patients.', *PloS one*, 12(4), p. e0175125. doi: 10.1371/journal.pone.0175125.
Bosy-Westphal, A. *et al.* (2013) 'Effect of weight loss and regain on adipose tissue distribution, composition of lean mass and resting energy expenditure in young overweight and obese adults', *International Journal of Obesity*, 37(10), pp. 1371–1377. doi: 10.1038/ijo.2013.1.
Bosy-Westphal, A. and Müller, M. J. (2014) 'Measuring the impact of weight cycling on body composition', *Current Opinion in Clinical Nutrition and Metabolic Care*, 17(5), pp. 396–400. doi: 10.1097/MCO.0000000000000092.
Bouchard, C. *et al.* (1993) 'Genetic Influences on Energy Expenditure in Humans', *Critical Reviews in Food Science and Nutrition*, 33(4–5), pp. 345–350. doi: 10.1080/10408399309527631.
Brancati, F. L. *et al.* (1999) 'Body Weight Patterns From 20 to 49 Years of Age and Subsequent Risk for Diabetes Mellitus', *Archives of Internal Medicine*, 159(9), p. 957. doi: 10.1001/archinte.159.9.957.
Brinkworth, G. D. *et al.* (2004) 'Long-term effects of advice to consume a high-protein, low-fat diet, rather than a conventional weight-loss diet, in obese adults with Type 2 diabetes: one-year follow-up

of a randomised trial', *Diabetologia*, 47(10), pp. 1677–1686. doi: 10.1007/s00125-004-1511-7.
Brownell, K. D. *et al.* (1986) 'The effects of repeated cycles of weight loss and regain in rats.', *Physiology & behavior*, 38(4), pp. 459–64. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3823159 (Accessed: 21 June 2018).
Bryant, E. J. *et al.* (2010) 'Interaction between disinhibition and restraint: Implications for body weight and eating disturbance.', *Eating and weight disorders : EWD*, 15(1–2), pp. e43-51. doi: 10.1007/bf03325279.
Burke, L. E., Wang, J. and Sevick, M. A. (2011) 'Self-Monitoring in Weight Loss: A Systematic Review of the Literature', *Journal of the American Dietetic Association*, 111(1), pp. 92–102. doi: 10.1016/j.jada.2010.10.008.
Buuren, S. van, and K. G.-O. (2010) 'mice: Multivariate imputation by chained equations in R', *Journal of statistical software*, pp. 1–68.
Byrne, N. M. *et al.* (2003) 'Influence of distribution of lean body mass on resting metabolic rate after weight loss and weight regain: comparison of responses in white and black women.', *The American journal of clinical nutrition*, 77(6), pp. 1368–73. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12791611 (Accessed: 22 December 2017).
Byrne, N. M. *et al.* (2018) 'Intermittent energy restriction improves weight loss efficiency in obese men: the MATADOR study.', *International journal of obesity (2005)*, 42(2), pp. 129–138. doi: 10.1038/ijo.2017.206.
Calle, E. E. *et al.* (2003) 'Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. Adults', *New England Journal of Medicine*, 348(17), pp. 1625–1638. doi: 10.1056/NEJMoa021423.
Cameron, J. D. *et al.* (2008) 'The effects of prolonged caloric restriction leading to weight-loss on food hedonics and reinforcement', *Physiology and Behavior*, 94(3), pp. 474–480. doi: 10.1016/j.physbeh.2008.02.014.
Cameron, J. D., Sigal, R. J., *et al.* (2016) 'Body composition and energy intake — skeletal muscle mass is the strongest predictor of food intake in obese adolescents: The HEARTY trial', *Applied Physiology, Nutrition, and Metabolism*, 41(6), pp. 611–617. doi: 10.1139/apnm-2015-0479.
Cameron, J. D., Goldfield, G. S., *et al.* (2016) 'Energy depletion by diet or aerobic exercise alone: Impact of energy deficit modality on appetite parameters', *American Journal of Clinical Nutrition*, 103(4), pp. 1008–1016. doi: 10.3945/ajcn.115.115584.
Cameron, J. D., Goldfield, G. S. and Doucet, É. (2012) 'Fasting for 24h improves nasal chemosensory performance and food palatability in a related manner', *Appetite*, 58(3), pp. 978–981. doi: 10.1016/j.appet.2012.02.050.
Camps, S. G., Verhoef, S. P. and Westerterp, K. R. (2013) 'Weight loss, weight maintenance, and adaptive thermogenesis', *The American Journal of Clinical Nutrition*, 97(5), pp. 990–994. doi: 10.3945/ajcn.112.050310.
Capstick, F. *et al.* (1997) 'Very low calorie diet (VLCD): a useful alternative in the treatment of the obese NIDDM patient.', *Diabetes research and clinical practice*, 36(2), pp. 105–11. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9229194 (Accessed: 30 October 2018).
Caria, C. R. e P. *et al.* (2017) 'Extracellular matrix remodeling and matrix metalloproteinase inhibition in visceral adipose during weight cycling in mice', *Experimental Cell Research*, 359(2), pp. 431–440. doi: 10.1016/j.yexcr.2017.08.026.
Carlson, L. E. and Brown, K. W. (2005) 'Validation of the Mindful Attention Awareness Scale in a cancer population', *Journal of Psychosomatic Research*, 58(1), pp. 29–33. doi: 10.1016/j.jpsychores.2004.04.366.
Carmody, T. P., Brunner, R. L. and St Jeor, S. T. (1995) 'Dietary helplessness and disinhibition in weight cyclers and maintainers.', *The International journal of eating disorders*, 18(3), pp. 247–56. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8556020 (Accessed: 21 June 2018).
Casanova, N. *et al.* (2019) 'Metabolic adaptations during negative energy balance and their potential impact on appetite and food intake', in *Proceedings of the Nutrition Society*. Cambridge University

Press, pp. 279–289. doi: 10.1017/S0029665118002811.
Casazza, K. *et al.* (2015) 'Weighing the Evidence of Common Beliefs in Obesity Research', *Critical Reviews in Food Science and Nutrition*, 55(14), pp. 2014–2053. doi: 10.1080/10408398.2014.922044.
Casebeer, K. (1997) 'Differences in Perceptual and Subjective Body Image between Weight Cycling and Noncycling Graduate Students', *Dissertations*. Available at: https://scholarworks.wmich.edu/dissertations/1645 (Accessed: 22 June 2018).
Catellier, D. J. *et al.* (2005) 'Imputation of missing data when measuring physical activity by accelerometry', in *Medicine and Science in Sports and Exercise*. doi: 10.1249/01.mss.0000185651.59486.4e.
Catenacci, V. A. *et al.* (2016) 'A randomized pilot study comparing zero-calorie alternate-day fasting to daily caloric restriction in adults with obesity', *Obesity*, 24(9), pp. 1874–1883. doi: 10.1002/oby.21581.
Cereda, E. *et al.* (2011) 'Weight cycling is associated with body weight excess and abdominal fat accumulation: A cross-sectional study', *Clinical Nutrition*, 30(6), pp. 718–723. doi: 10.1016/j.clnu.2011.06.009.
Charrad, M. *et al.* (2014) 'Nbclust: An R package for determining the relevant number of clusters in a data set', *Journal of Statistical Software*, 61(6), pp. 1–36. doi: 10.18637/jss.v061.i06.
Chaston, T. B., Dixon, J. B. and O'Brien, P. E. (2007) 'Changes in fat-free mass during significant weight loss: a systematic review', *International Journal of Obesity*, 31(5), pp. 743–750. doi: 10.1038/sj.ijo.0803483.
Chen, B. *et al.* (2015) 'Basic psychological need satisfaction, need frustration, and need strength across four cultures', *Motivation and Emotion*, 39(2), pp. 216–236. doi: 10.1007/s11031-014-9450-1.
Chikamoto, K. *et al.* (2016) 'Rapid response of the steatosis-sensing hepatokine LECT2 during diet-induced weight cycling in mice', *Biochemical and Biophysical Research Communications*, 478(3), pp. 1310–1316. doi: 10.1016/j.bbrc.2016.08.117.
Chooi, Y. C., Ding, C. and Magkos, F. (2019) 'The epidemiology of obesity', *Metabolism: Clinical and Experimental*, 92, pp. 6–10. doi: 10.1016/j.metabol.2018.09.005.
Chow, C. C. and Hall, K. D. (2014) 'Short and long-term energy intake patterns and their implications for human body weight regulation', *Physiology and Behavior*, 134(C), pp. 60–65. doi: 10.1016/j.physbeh.2014.02.044.
Christensen, P. *et al.* (2013) 'Comparison of three weight maintenance programs on cardiovascular risk, bone and vitamins in sedentary older adults', *Obesity*, 21(10), pp. 1982–1990. doi: 10.1002/oby.20413.
Clark, J. E. (2015) 'Diet, exercise or diet with exercise: Comparing the effectiveness of treatment options for weight-loss and changes in fitness for adults (18-65 years old) who are overfat, or obese; systematic review and meta-analysis', *Journal of Diabetes and Metabolic Disorders*, 14(1), p. 31. doi: 10.1186/s40200-015-0154-1.
Clifton, P. M. (2019) 'Diet, exercise and weight loss and dyslipidaemia', *Pathology*. Elsevier B.V., pp. 222–226. doi: 10.1016/j.pathol.2018.10.013.
Cohen, S., Kamarck, T. and Mermelstein, R. (1983) 'A global measure of perceived stress.', *Journal of health and social behavior*, 24(4), pp. 385–396. doi: 10.2307/2136404.
Cologne, J. *et al.* (2019) 'Association of Weight Fluctuation With Mortality in Japanese Adults', *JAMA Network Open*, 2(3), p. e190731. doi: 10.1001/jamanetworkopen.2019.0731.
Conry, M. C. *et al.* (2011) 'The clustering of health behaviours in Ireland and their relationship with mental health, self-rated health and quality of life', *BMC Public Health*, 11. doi: 10.1186/1471-2458-11-692.
Considine, R. V. *et al.* (1996) 'Serum immunoreactive-leptin concentrations in normal-weight and obese humans', *New England Journal of Medicine*, 334(5), pp. 292–295. doi: 10.1056/NEJM199602013340503.
Coupe, N. *et al.* (2019) 'The effect of commitment-making on weight loss and behaviour change in adults with obesity/overweight; A systematic review', *BMC Public Health*. BioMed Central Ltd., p.

816. doi: 10.1186/s12889-019-7185-3.
Craig, C. L. *et al.* (2003) 'International physical activity questionnaire: 12-Country reliability and validity', *Medicine and Science in Sports and Exercise*, 35(8), pp. 1381–1395. doi: 10.1249/01.MSS.0000078924.61453.FB.
Crane, T. E. *et al.* (2019) 'Does Season of Reported Dietary Intake Influence Diet Quality? Analysis From the Women's Health Initiative', *American Journal of Epidemiology*, 188(7), pp. 1304–1310. doi: 10.1093/aje/kwz087.
Crow, R. S. *et al.* (2018) 'Mortality Risk Along the Frailty Spectrum: Data from the National Health and Nutrition Examination Survey 1999 to 2004', *Journal of the American Geriatrics Society*, 66(3), pp. 496–502. doi: 10.1111/jgs.15220.
Czlapka-Matyasik, M. *et al.* (2018) '"Cutting Down on Sugar" by Non-Dieting Young Women: An Impact on Diet Quality on Weekdays and the Weekend.', *Nutrients*, 10(10). doi: 10.3390/nu10101463.
DA, S. (2014) 'The effect of holiday weight gain on body weight', *Physiology & behavior*, 134. doi: 10.1016/J.PHYSBEH.2014.03.018.
Dandanell, S. *et al.* (2017) 'Maintaining a clinical weight loss after intensive lifestyle intervention is the key to cardiometabolic health', *Obesity Research & Clinical Practice*, 11(4), pp. 489–498. doi: 10.1016/j.orcp.2016.09.009.
Dankel, S. N. *et al.* (2014) 'Weight cycling promotes fat gain and altered clock gene expression in adipose tissue in C57BL/6J mice', *American Journal of Physiology-Endocrinology and Metabolism*, 306(2), pp. E210–E224. doi: 10.1152/ajpendo.00188.2013.
Dassen, F. C. M. *et al.* (2018) 'Self-regulation and obesity: The role of executive function and delay discounting in the prediction of weight loss', *Journal of Behavioral Medicine*, 41(6), pp. 806–818. doi: 10.1007/s10865-018-9940-9.
Davis, L. M. *et al.* (2010) 'Efficacy of a meal replacement diet plan compared to a food-based diet plan after a period of weight loss and weight maintenance: a randomized controlled trial', *Nutrition Journal*, 9(1), p. 11. doi: 10.1186/1475-2891-9-11.
De'riaz, O., Tremblay, A. and Bouchard, C. (1993) 'Non Linear Weight Gain with Long Term Overfeeding in Man', *Obesity Research*, 1(3), p. 179. doi: 10.1002/j.1550-8528.1993.tb00609.x.
Deaner, R. O. *et al.* (2012) 'A Sex Difference in the Predisposition for Physical Competition: Males Play Sports Much More than Females Even in the Contemporary U.S', *PLoS ONE*. Edited by M. Hayward, 7(11), p. e49168. doi: 10.1371/journal.pone.0049168.
DeBenedictis, J. N. *et al.* (2020) 'Changes in the Homeostatic Appetite System After Weight Loss Reflect a Normalization Toward a Lower Body Weight', *The Journal of clinical endocrinology and metabolism*, 105(7), pp. 2538–2546. doi: 10.1210/clinem/dgaa202.
Deeks, J. J. *et al.* (2003) 'Evaluating non-randomised intervention studies.', *Health technology assessment (Winchester, England)*, 7(27), pp. iii–x, 1–173. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14499048 (Accessed: 10 June 2018).
Deighton, K. *et al.* (2019) 'A single day of mixed-macronutrient overfeeding does not elicit compensatory appetite or energy intake responses but exaggerates postprandial lipaemia during the next day in healthy young men', *British Journal of Nutrition*, 121(8), pp. 945–954. doi: 10.1017/S0007114519000205.
Delahanty, L. M. *et al.* (2014) 'Effects of weight loss, weight cycling, and weight loss maintenance on diabetes incidence and change in cardiometabolic traits in the Diabetes Prevention Program.', *Diabetes care*, 37(10), pp. 2738–45. doi: 10.2337/dc14-0018.
DelParigi, A. *et al.* (2004) 'Persistence of abnormal neural responses to a meal in postobese individuals', *International Journal of Obesity*, 28(3), pp. 370–377. doi: 10.1038/sj.ijo.0802558.
Deurenberg, P., Weststrate, J. A. and Hautvast, J. G. (1989) 'Changes in fat-free mass during weight loss measured by bioelectrical impedance and by densitometry', *The American Journal of Clinical Nutrition*, 49(1), pp. 33–36. doi: 10.1093/ajcn/49.1.33.
Dhurandhar, N. V. *et al.* (2015) 'Energy balance measurement: When something is not better than

nothing', *International Journal of Obesity*, 39(7), pp. 1109–1113. doi: 10.1038/ijo.2014.199.
Diabetes Prevention Program Research Group (2002) 'Reduction in the Incidence of Type 2 Diabetes with Lifestyle Intervention or Metformin', *New England Journal of Medicine*, 346(6), pp. 393–403. doi: 10.1056/NEJMoa012512.
Díaz-Zavala, R. G. *et al.* (2017) 'Effect of the Holiday Season on Weight Gain: A Narrative Review', *Journal of Obesity*, 2017, pp. 1–13. doi: 10.1155/2017/2085136.
Diaz, K. M. *et al.* (2014) 'Visit-to-visit variability of blood pressure and cardiovascular disease and all-cause mortality a systematic review and meta-analysis', *Hypertension*, 64(5), pp. 965–982. doi: 10.1161/HYPERTENSIONAHA.114.03903.
Diaz, V. A., Mainous, A. G. and Everett, C. J. (2005) 'THE ASSOCIATION BETWEEN WEIGHT FLUCTUATION AND MORTALITY: RESULTS FROM A POPULATION-BASED COHORT STUDY', *Journal of Community Health*, 30(3), pp. 153–165. doi: 10.1007/s10900-004-1955-1.
Diepvens, K. *et al.* (2007) 'Long-term effects of consumption of a novel fat emulsion in relation to body-weight management', *International Journal of Obesity*, 31(6), pp. 942–949. doi: 10.1038/sj.ijo.0803532.
Dietitians Association of Australia (2012) *DAA Best Practice Guidelines for the Treatment of Overweight and Obesity in Adults*. Available at: https://www.pennutrition.com/resources/PEN_resources/DAA PDFs/FINAL-DAA-obesity-guidelines-report-25th-January-2011-2.pdf (Accessed: 22 October 2018).
Dimitrov, D. V (2016) 'Medical Internet of Things and Big Data in Healthcare.', *Healthcare informatics research*, 22(3), pp. 156–63. doi: 10.4258/hir.2016.22.3.156.
Dombrowski, S. U., O'Carroll, R. E. and Williams, B. (2016) 'Form of delivery as a key "active ingredient" in behaviour change interventions', *British Journal of Health Psychology*, 21(4), pp. 733–740. doi: 10.1111/bjhp.12203.
Doucet, E. *et al.* (2000) 'Appetite after weight loss by energy restriction and a low-fat diet-exercise follow-up.', *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity*, 24(7), pp. 906–14. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10918539 (Accessed: 9 May 2019).
Drenowatz, C. *et al.* (2016) 'The Association of Physical Activity during Weekdays and Weekend with Body Composition in Young Adults.', *Journal of obesity*, 2016, p. 8236439. doi: 10.1155/2016/8236439.
Duarte, C. *et al.* (2017) 'The impact of shame, self-criticism and social rank on eating behaviours in overweight and obese women participating in a weight management programme', *PLoS ONE*, 12(1). doi: 10.1371/journal.pone.0167571.
Duarte, C. *et al.* (2019) 'The Weight-Focused Forms of Self-Criticising/Attacking and Self-Reassuring Scale: Confirmatory Factor Analysis and associations with control, loss of control of eating and weight in overweight and obese women', *Psychology and Psychotherapy: Theory, Research and Practice*, 92(4), pp. 539–553. doi: 10.1111/papt.12196.
Duarte, C., Pinto-Gouveia, J. and Ferreira, C. (2014) 'Escaping from body image shame and harsh self-criticism: Exploration of underlying mechanisms of binge eating', *Eating Behaviors*, 15(4), pp. 638–643. doi: 10.1016/j.eatbeh.2014.08.025.
Duarte, C., Pinto-Gouveia, J. and Ferreira, C. (2015) 'Expanding binge eating assessment: Validity and screening value of the Binge Eating Scale in women from the general population', *Eating Behaviors*, 18, pp. 41–47. doi: 10.1016/j.eatbeh.2015.03.007.
Duarte, C., Pinto-Gouveia, J. and Ferreira, C. (2017) 'Ashamed and Fused with Body Image and Eating: Binge Eating as an Avoidance Strategy', *Clinical Psychology & Psychotherapy*, 24(1), pp. 195–202. doi: 10.1002/cpp.1996.
Dubois (1927) 'Basal Metabolism in Health and Disease', *Can Med Assoc J.* 7th edn. Edited by Can Med Assoc J, 17(7), pp. 10–12. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC407460/ (Accessed: 18 August 2020).
Due, A. *et al.* (2004) 'Effect of normal-fat diets, either medium or high in protein, on body weight in

overweight subjects: a randomised 1-year trial', *International Journal of Obesity*, 28(10), pp. 1283–1290. doi: 10.1038/sj.ijo.0802767.
Dulloo, A. G. *et al.* (2015) 'How dieting makes the lean fatter: from a perspective of body composition autoregulation through adipostats and proteinstats awaiting discovery', *Obesity Reviews*, 16, pp. 25–35. doi: 10.1111/obr.12253.
Dulloo, A. G. (2017) 'Collateral fattening: When a deficit in lean body mass drives overeating', *Obesity*, 25(2), pp. 277–279. doi: 10.1002/oby.21734.
Dulloo, A. G. *et al.* (2017) 'Passive and active roles of fat-free mass in the control of energy intake and body composition regulation', *European Journal of Clinical Nutrition*, 71(3), pp. 353–357. doi: 10.1038/ejcn.2016.256.
Dulloo, A. G., Jacquet, J. and Girardier, L. (1996) 'Autoregulation of body composition during weight recovery in human: the Minnesota Experiment revisited.', *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity*, 20(5), pp. 393–405. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8696417 (Accessed: 10 June 2018).
Dulloo, A. G., Jacquet, J. and Girardier, L. (1997a) 'Poststarvation hyperphagia and body fat overshooting in humans: a role for feedback signals from lean and fat tissues', *The American Journal of Clinical Nutrition*, 65(3), pp. 717–723. doi: 10.1093/ajcn/65.3.717.
Dulloo, A. G., Jacquet, J. and Girardier, L. (1997b) 'Poststarvation hyperphagia and body fat overshooting in humans: a role for feedback signals from lean and fat tissues', *The American Journal of Clinical Nutrition*, 65(3), pp. 717–723. doi: 10.1093/ajcn/65.3.717.
Dulloo, A. G., Miles-Chan, J. L. and Schutz, Y. (2018) 'Collateral fattening in body composition autoregulation: its determinants and significance for obesity predisposition', *European Journal of Clinical Nutrition*, 72(5), pp. 657–664. doi: 10.1038/s41430-018-0138-6.
Dulloo, A. G. and Montani, J.-P. (2015) 'Pathways from dieting to weight regain, to obesity and to the metabolic syndrome: an overview', *Obesity Reviews*, 16, pp. 1–6. doi: 10.1111/obr.12250.
Dyer, A. R., Stamler, J. and Greenland, P. (2000) 'Associations of Weight Change and Weight Variability with Cardiovascular and All-Cause Mortality in the Chicago Western Electric Company Study', *American Journal of Epidemiology*, 152(4), pp. 324–333. doi: 10.1093/aje/152.4.324.
Edholm, O. G. *et al.* (1955) 'The Energy Expenditure and Food Intake of Individual Men', *British Journal of Nutrition*, 9(3), pp. 286–300. doi: 10.1079/bjn19550040.
Edholm, O. G. *et al.* (1970) 'Food intake and energy expenditure of army recruits', *British Journal of Nutrition*, 24(4), pp. 1091–1107. doi: 10.1079/bjn19700112.
Elder, K. A. *et al.* (2008) 'Loss of control over eating is associated with eating disorder psychopathology in a community sample of Latinas', *Eating Behaviors*, 9(4), pp. 501–503. doi: 10.1016/j.eatbeh.2008.04.003.
Elfhag, K. and Rossner, S. (2005) 'Who succeeds in maintaining weight loss? A conceptual review of factors associated with weight loss maintenance and weight regain', *Obesity Reviews*, 6(1), pp. 67–85. doi: 10.1111/j.1467-789X.2005.00170.x.
Eston, R. G. *et al.* (1992) 'Effect of very low calorie diet on body composition and exercise response in sedentary women.', *European journal of applied physiology and occupational physiology*, 65(5), pp. 452–8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1425652 (Accessed: 9 May 2019).
Evenson, K. R. *et al.* (2015) 'Physical activity and sedentary behavior patterns using accelerometry from a national sample of United States adults', *International Journal of Behavioral Nutrition and Physical Activity*, 12(1), p. 20. doi: 10.1186/s12966-015-0183-7.
Fahey, M. C., Klesges, R. C., Kocak, M., Wang, J., *et al.* (2019) 'Do the holidays impact weight and self-weighing behaviour among adults engaged in a behavioural weight loss intervention?', *Obesity Research & Clinical Practice*. doi: 10.1016/j.orcp.2019.05.001.
Fahey, M. C., Klesges, R. C., Kocak, M., Talcott, G. W., *et al.* (2019a) 'Seasonal fluctuations in weight and self-weighing behavior among adults in a behavioral weight loss intervention', *Eating and Weight Disorders - Studies on Anorexia, Bulimia and Obesity*. doi: 10.1007/s40519-019-00707-7.

Fahey, M. C., Klesges, R. C., Kocak, M., Talcott, G. W., *et al.* (2019b) 'Seasonal fluctuations in weight and self-weighing behavior among adults in a behavioral weight loss intervention', *Eating and Weight Disorders - Studies on Anorexia, Bulimia and Obesity*, pp. 1–8. doi: 10.1007/s40519-019-00707-7.
Faust, L. *et al.* (2019) 'Physical activity trend extraction: A framework for extracting moderate-vigorous physical activity trends from wearable fitness tracker data', *Journal of Medical Internet Research*, 21(3). doi: 10.2196/11075.
Fazzino, T. L. *et al.* (2017) 'Weight fluctuation during adulthood and weight gain since breast cancer diagnosis predict multiple dimensions of body image among rural breast cancer survivors.', *Psycho-oncology*, 26(3), pp. 392–399. doi: 10.1002/pon.4035.
Feehan, L. M. *et al.* (2018) 'Accuracy of fitbit devices: Systematic review and narrative syntheses of quantitative data', *JMIR mHealth and uHealth*. JMIR Publications. doi: 10.2196/10527.
Feig, E. H. and Lowe, M. R. (2017) 'Variability in Weight Change Early in Behavioral Weight Loss Treatment: Theoretical and Clinical Implications', *Obesity*, 25(9), pp. 1509–1515. doi: 10.1002/oby.21925.
Ferreira, C., Pinto-Gouveia, J. and Duarte, C. (2011) 'The Validation of the Body Image Acceptance and Action Questionnaire: Exploring the Moderator Effect of Acceptance on Disordered Eating', *InternatIonal Journal of Psychology and PsychologIcal theraPy*, 11(3), pp. 327–345. Available at: http://www.ijpsy.com/volumen11/num3/302/the-validation-of-the-body-image-acceptance-EN.pdf (Accessed: 22 June 2018).
Field, A. E. *et al.* (1999) 'Weight cycling, weight gain, and risk of hypertension in women.', *American journal of epidemiology*, 150(6), pp. 573–9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10489996 (Accessed: 6 April 2018).
Field, A. E. *et al.* (2004) 'Association of weight change, weight control practices, and weight cycling among women in the Nurses' Health Study II', *International Journal of Obesity*, 28(9), pp. 1134–1142. doi: 10.1038/sj.ijo.0802728.
Field, Alison E. *et al.* (2004) 'Weight Cycling and the Risk of Developing Type 2 Diabetes among Adult Women in the United States', *Obesity Research*, 12(2), pp. 267–274. doi: 10.1038/oby.2004.34.
Field, A. E., Malspeis, S. and Willett, W. C. (2009) 'Weight cycling and mortality among middle-aged or older women.', *Archives of internal medicine*, 169(9), pp. 881–6. doi: 10.1001/archinternmed.2009.67.
Fischer, I. P. *et al.* (2018) 'A history of obesity leaves an inflammatory fingerprint in liver and adipose tissue', *International Journal of Obesity*, 42(3), pp. 507–517. doi: 10.1038/ijo.2017.224.
Flint, A. *et al.* (2000) 'Reproducibility, power and validity of visual analogue scales in assessment of appetite sensations in single test meal studies.', *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity*, 24(1), pp. 38–48. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10702749 (Accessed: 12 April 2019).
Fogelholm, M. *et al.* (1998) 'Additive Effects of the Mutations in theβ_3-Adrenergic Receptor and Uncoupling Protein-1 Genes on Weight Loss and Weight Maintenance in Finnish Women [1]', *The Journal of Clinical Endocrinology & Metabolism*, 83(12), pp. 4246–4250. doi: 10.1210/jcem.83.12.5339.
Folsom, A. R. *et al.* (1996) 'Weight variability and mortality: the Iowa Women's Health Study.', *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity*, 20(8), pp. 704–9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8856391 (Accessed: 7 January 2019).
Forbes, G. B. (1987) 'Lean body mass-body fat interrelationships in humans.', *Nutrition reviews*, 45(8), pp. 225–31. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3306482 (Accessed: 16 July 2018).
Foreyt, J. P. *et al.* (1995) 'Psychological correlates of weight fluctuation.', *The International journal of eating disorders*, 17(3), pp. 263–75. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7773263 (Accessed: 22 June 2018).

Forouhi, N. G. and Wareham, N. J. (2019) 'Epidemiology of diabetes', *Medicine (United Kingdom)*. Elsevier Ltd, pp. 22–27. doi: 10.1016/j.mpmed.2018.10.004.
Fortenberry, M. (2012) 'Assessing the effects of the holiday season on body weight, body fat percentage, and blood pressure', *MSc Thesis, Texas Tech University*. Available at: https://ttu-ir.tdl.org/handle/2346/45173 (Accessed: 16 July 2019).
Foster-Schubert, K. E. *et al.* (2012) 'Effect of diet and exercise, alone or combined, on weight and body composition in overweight-to-obese postmenopausal women.', *Obesity (Silver Spring, Md.)*, 20(8), pp. 1628–38. doi: 10.1038/oby.2011.76.
Foster, G. D. (1997) 'Psychological effects of weight cycling in obese persons: A review and research agenda', *Obesity Research*, 5(5), pp. 474–488. doi: 10.1002/j.1550-8528.1997.tb00674.x.
Foster, G. D. *et al.* (1997) 'What is a reasonable weight loss? Patients' expectations and evaluations of obesity treatment outcomes.', *Journal of consulting and clinical psychology*, 65(1), pp. 79–85. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9103737 (Accessed: 20 July 2018).
Fothergill, E., Guo, J., Howard, L., Kerns, Jennifer C, *et al.* (2016) 'Persistent metabolic adaptation 6 years after "The Biggest Loser" competition.', *Obesity (Silver Spring, Md.)*, 24(8), pp. 1612–9. doi: 10.1002/oby.21538.
Fothergill, E., Guo, J., Howard, L., Kerns, Jennifer C., *et al.* (2016a) 'Persistent metabolic adaptation 6 years after "The Biggest Loser" competition', *Obesity*, 24(8), pp. 1612–1619. doi: 10.1002/oby.21538.
Fothergill, E., Guo, J., Howard, L., Kerns, Jennifer C., *et al.* (2016b) 'Persistent metabolic adaptation 6 years after "The Biggest Loser" competition', *Obesity*, 24(8), pp. 1612–1619. doi: 10.1002/oby.21538.
Franz, M. J. *et al.* (2007a) 'Weight-Loss Outcomes: A Systematic Review and Meta-Analysis of Weight-Loss Clinical Trials with a Minimum 1-Year Follow-Up', *Journal of the American Dietetic Association*, 107(10), pp. 1755–1767. doi: 10.1016/j.jada.2007.07.017.
Franz, M. J. *et al.* (2007b) 'Weight-Loss Outcomes: A Systematic Review and Meta-Analysis of Weight-Loss Clinical Trials with a Minimum 1-Year Follow-Up', *Journal of the American Dietetic Association*, 107(10), pp. 1755–1767. doi: 10.1016/j.jada.2007.07.017.
French, S. A. *et al.* (1997) 'Weight variability and incident disease in older women: the Iowa Women's Health Study.', *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity*, 21(3), pp. 217–23. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9080261 (Accessed: 7 January 2019).
Fresco, D. M. *et al.* (2007) 'Initial Psychometric Properties of the Experiences Questionnaire: Validation of a Self-Report Measure of Decentering', *Behavior Therapy*, 38(3), pp. 234–246. doi: 10.1016/j.beth.2006.08.003.
Friedl, K. E. *et al.* (2000) 'Endocrine markers of semistarvation in healthy lean men in a multistressor environment', *Journal of Applied Physiology*, 88(5), pp. 1820–1830. doi: 10.1152/jappl.2000.88.5.1820.
Friedman, J. M. (2011) 'Leptin and the regulation of body weigh.', *The Keio journal of medicine*, 60(1), pp. 1–9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21460597 (Accessed: 12 April 2019).
Friedman, M. A., Schwartz, M. B. and Brownell, K. D. (1998) 'Differential relation of psychological functioning with the history and experience of weight cycling.', *Journal of consulting and clinical psychology*, 66(4), pp. 646–50. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9735581 (Accessed: 22 June 2018).
Gaddey, H. L. and Holder, K. (2014) 'Unintentional weight loss in older adults.', *American family physician*, 89(9), pp. 718–22. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24784334 (Accessed: 7 January 2019).
Galgani, J. E. *et al.* (2010) 'Leptin replacement prevents weight loss-induced metabolic adaptation in congenital leptin-deficient patients', *Journal of Clinical Endocrinology and Metabolism*, 95(2), pp. 851–855. doi: 10.1210/jc.2009-1739.

Gallagher, D. *et al.* (2000) 'Weight loss in postmenopausal obesity: no adverse alterations in body composition and protein metabolism', *American Journal of Physiology-Endocrinology and Metabolism*, 279(1), pp. E124–E131. doi: 10.1152/ajpendo.2000.279.1.E124.
Ganz, M. L. *et al.* (2014) 'The association of body mass index with the risk of type 2 diabetes: a case–control study nested in an electronic health records system in the United States', *Diabetology & Metabolic Syndrome*, 6(1), p. 50. doi: 10.1186/1758-5996-6-50.
García-Hermoso, A. *et al.* (2018) 'Muscular Strength as a Predictor of All-Cause Mortality in an Apparently Healthy Population: A Systematic Review and Meta-Analysis of Data From Approximately 2 Million Men and Women', *Archives of Physical Medicine and Rehabilitation*. W.B. Saunders, pp. 2100-2113.e5. doi: 10.1016/j.apmr.2018.01.008.
García, C. G. *et al.* (2013) '[Prospective study on the effect of the influence of holiday periods in the weight during a low-calory dietetic treatment].', *Nutricion hospitalaria*, 28(6), pp. 2246–51. doi: 10.3305/nutr hosp.v28in06.6880.
Genell, A. *et al.* (2010) 'Model selection in Medical Research: A simulation study comparing Bayesian Model Averaging and Stepwise Regression', *BMC Medical Research Methodology*, 10(1), p. 108. doi: 10.1186/1471-2288-10-108.
Ghasemi, A. and Zahediasl, S. (2012) 'Normality tests for statistical analysis: a guide for non-statisticians.', *International journal of endocrinology and metabolism*, 10(2), pp. 486–9. doi: 10.5812/ijem.3505.
Gibson, A. A. and Sainsbury, A. (2017) 'Strategies to improve adherence to dietaryweight loss interventions in research and real-world settings', *Behavioral Sciences*. MDPI Multidisciplinary Digital Publishing Institute. doi: 10.3390/bs7030044.
Gilbert, P. *et al.* (2017) 'The development of compassionate engagement and action scales for self and others', *Journal of Compassionate Health Care*, 4(1), p. 4. doi: 10.1186/s40639-017-0033-3.
Gilden Tsai, A. and Wadden, T. A. (2006) 'The Evolution of Very-Low-Calorie Diets: An Update and Meta-analysis*', *Obesity*, 14(8), pp. 1283–1293. doi: 10.1038/oby.2006.146.
Gilis-Januszewska, A. *et al.* (2018) 'Predictors of long term weight loss maintenance in patients at high risk of type 2 diabetes participating in a lifestyle intervention program in primary health care: The DE-PLAN study', *PLoS ONE*, 13(3). doi: 10.1371/journal.pone.0194589.
Gill, R. S. *et al.* (2012) 'Predictors of attrition in a multidisciplinary adult weight management clinic', *Canadian Journal of Surgery*, 55(4), pp. 239–243. doi: 10.1503/cjs.035710.
De Gonzalez, A. B. *et al.* (2010) 'Body-mass index and mortality among 1.46 million white adults', *New England Journal of Medicine*, 363(23), pp. 2211–2219. doi: 10.1056/NEJMoa1000367.
Goodenough, A. E., Hart, A. G. and Stafford, R. (2012) 'Regression with empirical variable selection: Description of a new method and application to ecological datasets', *PLoS ONE*, 7(3), p. 34338. doi: 10.1371/journal.pone.0034338.
Goodman, E. L. *et al.* (2018) 'Weight suppression and weight elevation are associated with eating disorder symptomatology in women age 50 and older: Results of the gender and body image study', *International Journal of Eating Disorders*, 51(8), pp. 835–841. doi: 10.1002/eat.22869.
Gormally, J. *et al.* (1982) 'The assessment of binge eating severity among obese persons', *Addictive Behaviors*, 7(1), pp. 47–55. doi: 10.1016/0306-4603(82)90024-7.
Goyenechea, E. *et al.* (2009) 'Expression of Two Inflammation-Related Genes (RIPK3 and RNF216) in Mononuclear Cells Is Associated with Weight-Loss Regain in Obese Subjects', *Journal of Nutrigenetics and Nutrigenomics*, 2(2), pp. 78–84. doi: 10.1159/000210452.
Graci, S. *et al.* (2004) 'Weight cycling and cardiovascular risk factors in obesity', *International Journal of Obesity*, 28(1), pp. 65–71. doi: 10.1038/sj.ijo.0802537.
Gratz, K. L. and Roemer, L. (2004) 'Multidimensional Assessment of Emotion Regulation and Dysregulation: Development, Factor Structure, and Initial Validation of the Difficulties in Emotion Regulation Scale', in *Journal of Psychopathology and Behavioral Assessment*. Kluwer Academic/Plenum Publishers, pp. 41–54. doi: 10.1023/B:JOBA.0000007455.08539.94.
Grave, R. D. *et al.* (1996) 'Binge eating disorder and weight cycling in obese women', *Eating*

Disorders, 4(1), pp. 67–73. doi: 10.1080/10640269608250077.
Greenway, F. L. (2015) 'Physiological adaptations to weight loss and factors favouring weight regain', *International Journal of Obesity*, 39(8), pp. 1188–1196. doi: 10.1038/ijo.2015.59.
Gu, J. *et al.* (2019) 'Visit-to-visit variability in low-density lipoprotein cholesterol is associated with adverse events in non-obstructive coronary artery disease', *Anatolian Journal of Cardiology*, 22(3), pp. 117–124. doi: 10.14744/AnatolJCardiol.2019.26428.
Guagnano, M. T. *et al.* (1999) 'Weight fluctuations could increase blood pressure in android obese women.', *Clinical science (London, England : 1979)*, 96(6), pp. 677–80. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10334976 (Accessed: 12 December 2019).
Guagnano, M. T. *et al.* (2000) 'Risk factors for hypertension in obese women. The role of weight cycling', *European Journal of Clinical Nutrition*, 54(4), pp. 356–360. doi: 10.1038/sj.ejcn.1600963.
Guerdjikova, A. I. *et al.* (2012) 'Binge eating disorder in elderly individuals', *International Journal of Eating Disorders*, 45(7), pp. 905–908. doi: 10.1002/eat.22028.
Hainer, V. and Aldhoon-Hainerová, I. (2013) 'Obesity paradox does exist', *Diabetes Care*, 36(SUPPL.2), pp. S276–S281. doi: 10.2337/dcS13-2023.
Halaas, J. L. *et al.* (1995) 'Weight-reducing effects of the plasma protein encoded by the obese gene.', *Science (New York, N.Y.)*, 269(5223), pp. 543–6. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7624777 (Accessed: 21 July 2018).
Halaas, J. L. *et al.* (1997) 'Physiological response to long-term peripheral and central leptin infusion in lean and obese mice', *Proceedings of the National Academy of Sciences of the United States of America*, 94(16), pp. 8878–8883. doi: 10.1073/pnas.94.16.8878.
Hall, K. D. (2007) 'Body fat and fat-free mass inter-relationships: Forbes's theory revisited.', *The British journal of nutrition*, 97(6), pp. 1059–63. doi: 10.1017/S0007114507691946.
Hall, K. D. (2010) 'Predicting metabolic adaptation, body weight change, and energy intake in humans.', *American journal of physiology. Endocrinology and metabolism*, 298(3), pp. E449-66. doi: 10.1152/ajpendo.00559.2009.
Hall, K. D. *et al.* (2011) 'Quantification of the effect of energy imbalance on bodyweight', *The Lancet*. Lancet Publishing Group, pp. 826–837. doi: 10.1016/S0140-6736(11)60812-X.
Hall, K. D. *et al.* (2012) 'Energy balance and its components: Implications for body weight regulation', *American Journal of Clinical Nutrition*. American Society for Nutrition, pp. 989–994. doi: 10.3945/ajcn.112.036350.
Hall, K. D. (2014) 'Estimating human energy intake using mathematical models', *American Journal of Clinical Nutrition*. American Society for Nutrition, pp. 744–745. doi: 10.3945/ajcn.114.094441.
Hall, K. D. and Guo, J. (2017) 'Obesity Energetics: Body Weight Regulation and the Effects of Diet Composition.', *Gastroenterology*, 152(7), pp. 1718-1727.e3. doi: 10.1053/j.gastro.2017.01.052.
Hall, K. D. and Kahan, S. (2018) 'Maintenance of Lost Weight and Long-Term Management of Obesity', *Medical Clinics of North America*. W.B. Saunders, pp. 183–197. doi: 10.1016/j.mcna.2017.08.012.
Hallion, L. S. *et al.* (2018) 'Psychometric Properties of the Difficulties in Emotion Regulation Scale (DERS) and Its Short Forms in Adults With Emotional Disorders', *Frontiers in Psychology*, 9(APR), p. 539. doi: 10.3389/fpsyg.2018.00539.
Hamman, Richard F *et al.* (2006) 'Effect of weight loss with lifestyle intervention on risk of diabetes.', *Diabetes care*, 29(9), pp. 2102–7. doi: 10.2337/dc06-0560.
Hamman, Richard F. *et al.* (2006a) 'Effect of weight loss with lifestyle intervention on risk of diabetes', *Diabetes Care*, 29(9), pp. 2102–2107. doi: 10.2337/dc06-0560.
Hamman, Richard F. *et al.* (2006b) 'Effect of weight loss with lifestyle intervention on risk of diabetes', *Diabetes Care*, 29(9), pp. 2102–2107. doi: 10.2337/dc06-0560.
Handjieva-Darlenska, T. *et al.* (2010a) 'Initial weight loss on an 800-kcal diet as a predictor of weight loss success after 8 weeks: The Diogenes study', *European Journal of Clinical Nutrition*, 64(9), pp. 994–999. doi: 10.1038/ejcn.2010.110.
Handjieva-Darlenska, T. *et al.* (2010b) 'Initial weight loss on an 800-kcal diet as a predictor of weight

loss success after 8 weeks: The Diogenes study', *European Journal of Clinical Nutrition*, 64(9), pp. 994–999. doi: 10.1038/ejcn.2010.110.
Hanson, R. L. *et al.* (1995) 'Rate of weight gain, weight fluctuation, and incidence of NIDDM.', *Diabetes*, 44(3), pp. 261–6. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7883111 (Accessed: 22 December 2017).
Hanson, R. L. *et al.* (1996) 'Weight fluctuation, mortality and vascular disease in Pima Indians.', *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity*, 20(5), pp. 463–71. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8696426 (Accessed: 10 June 2018).
Hart, K. E. and Warriner, E. M. (2005) 'Weight loss and biomedical health improvement on a very low calorie diet: The moderating role of history of weight cycling', *Behavioral Medicine*, 30(4), pp. 161–172. doi: 10.3200/BMED.30.4.161-172.
Hasler, G. *et al.* (2005) 'Major Depression Predicts an Increase in Long-Term Body Weight Variability in Young Adults', *Obesity Research*, 13(11), pp. 1991–1998. doi: 10.1038/oby.2005.244.
Heinze, G., Wallisch, C. and Dunkler, D. (2018) 'Variable selection – A review and recommendations for the practicing statistician', *Biometrical Journal*. Wiley-VCH Verlag, pp. 431–449. doi: 10.1002/bimj.201700067.
Helander, E. *et al.* (2015) 'Time-series modeling of long-term weight self-monitoring data', in *2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*. IEEE, pp. 1616–1620. doi: 10.1109/EMBC.2015.7318684.
Helander, E. E. *et al.* (2014) 'Are breaks in daily self-weighing associated with weight gain?', *PloS one*, 9(11), p. e113164. doi: 10.1371/journal.pone.0113164.
Helander, E. E., Wansink, B. and Chieh, A. (2016) 'Weight Gain over the Holidays in Three Countries', *New England Journal of Medicine*, 375(12), pp. 1200–1202. doi: 10.1056/NEJMc1602012.
Herdman, M. *et al.* (2011) 'Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L)', *Quality of Life Research*, 20(10), pp. 1727–1736. doi: 10.1007/s11136-011-9903-x.
Hex, N. *et al.* (2012) 'Estimating the current and future costs of Type 1 and Type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs', *Diabet Med*, 29(7), pp. 855–62. doi: 10.1111/j.1464-5491.2012.03698.x.
Heymsfield, S. B. *et al.* (2011) 'Voluntary weight loss: systematic review of early phase body composition changes', *Obesity Reviews*, 12(5), pp. e348–e361. doi: 10.1111/j.1467-789X.2010.00767.x.
Heymsfield, S. B. *et al.* (2014) 'Weight loss composition is one-fourth fat-free mass: a critical review and critique of this widely cited rule', *Obesity Reviews*, 15(4), pp. 310–321. doi: 10.1111/obr.12143.
Higgins, J. P. T. (2008) 'Commentary: Heterogeneity in meta-analysis should be expected and appropriately quantified', *International Journal of Epidemiology*. Oxford Academic, pp. 1158–1160. doi: 10.1093/ije/dyn204.
Higgins JPT, Green S, editors. (2011) *Cochrane handbook for systematic reviews of interventions: Section 16.1.3.2 Imputing standard deviations for changes from baseline*. Version 5. Available at: http://handbook-5-1.cochrane.org/chapter_16/16_1_3_2_imputing_standard_deviations_for_changes_from_baseline.htm (Accessed: 20 November 2018).
Hintze, L. J. *et al.* (2017) 'Weight Loss and Appetite Control in Women', *Current Obesity Reports*, 6(3), pp. 334–351. doi: 10.1007/s13679-017-0273-8.
Hoie, L. H., Bruusgaard, D. and Thom, E. (1993) 'Reduction of body mass and change in body composition on a very low calorie diet.', *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity*, 17(1), pp. 17–20. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8383636 (Accessed: 9 May 2019).
Holt, G. M. *et al.* (2017) 'Systematic literature review shows that appetite rating does not predict energy intake', *Critical Reviews in Food Science and Nutrition*, 57(16), pp. 3577–3582. doi: 10.1080/10408398.2016.1246414.

Hopkins, M. *et al.* (2016) 'Modelling the associations between fat-free mass, resting metabolic rate and energy intake in the context of total energy balance', *International Journal of Obesity*, 40(2), pp. 312–318. doi: 10.1038/ijo.2015.155.
Horgan, G. W. (2011) 'The behaviour of a neutral model of weight regulated only by body mass', *Journal of Theoretical Biology*, 270(1), pp. 1–6. doi: 10.1016/j.jtbi.2010.11.001.
Houston, M. C. *et al.* (2005) 'Addressing the global cardiovascular risk of hypertension, dyslipidemia, and insulin resistance in the Southeastern United States', in *American Journal of the Medical Sciences*. Lippincott Williams and Wilkins, pp. 276–291. doi: 10.1097/00000441-200506000-00008.
Hubert, P., King, N. A. and Blundell, J. E. (1998) 'Uncoupling the effects of energy expenditure and energy intake: Appetite response to short-term energy deficit induced by meal omission and physical activity', *Appetite*, 31(1), pp. 9–19. doi: 10.1006/appe.1997.0148.
Hussain, Z. and Khan, J. A. (2017) 'Food intake regulation by leptin: Mechanisms mediating gluconeogenesis and energy expenditure', *Asian Pacific Journal of Tropical Medicine*. Wolters Kluwer Medknow Publications, pp. 940–944. doi: 10.1016/j.apjtm.2017.09.003.
Hyndman, R. *et al.* (2019) *Package 'forecast' Title Forecasting Functions for Time Series and Linear Models Description Methods and tools for displaying and analysing univariate time series forecasts including exponential smoothing via state space models and automatic ARIMA modelli*. Available at: https://cran.r-project.org/web/packages/forecast/forecast.pdf (Accessed: 20 June 2019).
Iepsen, E. W. *et al.* (2016) 'Successful weight loss maintenance includes long-term increased meal responses of GLP-1 and PYY3–36', *European Journal of Endocrinology*, 174(6), pp. 775–784. doi: 10.1530/EJE-15-1116.
Ing, C. T. *et al.* (2018) 'Comparing Weight Loss–Maintenance Outcomes of a Worksite-Based Lifestyle Program Delivered via DVD and Face-to-Face: A Randomized Trial', *Health Education & Behavior*, 45(4), pp. 569–580. doi: 10.1177/1090198118757824.
IntHout, J., Ioannidis, J. P. and Borm, G. F. (2014) 'The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method', *BMC Medical Research Methodology*, 14(1), p. 25. doi: 10.1186/1471-2288-14-25.
Iribarren, C. *et al.* (1995) 'Association of Weight Loss and Weight Fluctuation with Mortality among Japanese American Men', *New England Journal of Medicine*, 333(11), pp. 686–692. doi: 10.1056/NEJM199509143331102.
Islam, M. *et al.* (2018) 'A Systematic Review on Healthcare Analytics: Application and Theoretical Perspective of Data Mining', *Healthcare*, 6(2), p. 54. doi: 10.3390/healthcare6020054.
VAN ITALLIE, T. B., BEAUDOIN, R. and MAYER, J. (1953) 'Arteriovenous glucose differences, metabolic hypoglycemia and food intake in man.', *The American journal of clinical nutrition*, 1(3), pp. 208–217. doi: 10.1093/ajcn/1.3.208.
Jacoby, W. G. (2000) *Electoral inquiry section Loess: a nonparametric, graphical tool for depicting relationships between variables*, *Electoral Studies*. Available at: www.elsevier.com/locate/electstud (Accessed: 27 June 2019).
Jahns, L. *et al.* (2017) 'Diet Quality Is Lower and Energy Intake Is Higher on Weekends Compared with Weekdays in Midlife Women: A 1-Year Cohort Study', *Journal of the Academy of Nutrition and Dietetics*, 117(7), pp. 1080-1086.e1. doi: 10.1016/j.jand.2017.01.012.
James, B. L. *et al.* (2018) 'Early predictors of weight loss in a 1-year behavioural weight-loss programme', *Obesity Science and Practice*, 4(1), pp. 20–28. doi: 10.1002/osp4.149.
Jamshidian, M., Jalal, S. and Jansen, C. (2014) '**MissMech** : An *R* Package for Testing Homoscedasticity, Multivariate Normality, and Missing Completely at Random (MCAR)', *Journal of Statistical Software*, 56(6), pp. 1–31. doi: 10.18637/jss.v056.i06.
Jang, B. Y. and Bu, S. Y. (2018) 'Total energy intake according to the level of skeletal muscle mass in Korean adults aged 30 years and older: an analysis of the Korean National Health and Nutrition Examination Surveys (KNHANES) 2008–2011', *Nutrition Research and Practice*, 12(3), p. 222. doi: 10.4162/nrp.2018.12.3.222.

Janssen, I. and Ross, R. (1999) 'Effects of sex on the change in visceral, subcutaneous adipose tissue and skeletal muscle in response to weight loss', *Int J Obes Relat Metab Disord*, 23(10), pp. 1035–46. Available at: http://www.stockton-press.co.uk/ijo (Accessed: 9 May 2019).
Javaras, K. N. *et al.* (2008) 'Co-occurrence of binge eating disorder with psychiatric and medical disorders', *Journal of Clinical Psychiatry*, 69(2), pp. 266–273. doi: 10.4088/JCP.v69n0213.
Jebb, S. A. *et al.* (2007) 'Validity of the leg-to-leg bioimpedance to estimate changes in body fat during weight loss and regain in overweight women: a comparison with multi-compartment models', *International Journal of Obesity*, 31(5), pp. 756–762. doi: 10.1038/sj.ijo.0803475.
Jeffery, R. W., Wing, R. R. and Mayer, R. R. (1998) 'Are smaller weight losses or more achievable weight loss goals better in the long term for obese patients?', *Journal of consulting and clinical psychology*, 66(4), pp. 641–5. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9735580 (Accessed: 20 July 2018).
Jensen, M. D. *et al.* (2014) '2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: A report of the American College of cardiology/American Heart Association task force on practice guidelines and the obesity society', *Circulation*. Lippincott Williams and Wilkins, pp. S102–S138. doi: 10.1161/01.cir.0000437739.71477.ee.
Jiandani, D. *et al.* (2016) 'Predictors of early attrition and successful weight loss in patients attending an obesity management program', *BMC Obesity*, 3(1), pp. 1–9. doi: 10.1186/S40608-016-0098-0.
Johnson, F., Pratt, M. and Wardle, J. (2012) 'Dietary restraint and self-regulation in eating behavior', *International Journal of Obesity*, pp. 665–674. doi: 10.1038/ijo.2011.156.
Johnston, B. C. *et al.* (2014) 'Comparison of weight loss among named diet programs in overweight and obese adults: A meta-analysis', *JAMA - Journal of the American Medical Association*, 312(9), pp. 923–933. doi: 10.1001/jama.2014.10397.
Johnstone, A. M. *et al.* (1998) 'Overfeeding fat as monoglyceride or triglyceride: Effect on appetite, nutrient balance and the subsequent day's energy intake', *European Journal of Clinical Nutrition*, 52(8), pp. 610–618. doi: 10.1038/sj.ejcn.1600615.
Jornayvaz, F. R. *et al.* (2010) 'A high-fat, ketogenic diet causes hepatic insulin resistance in mice, despite increasing energy expenditure and preventing weight gain.', *American journal of physiology. Endocrinology and metabolism*, 299(5), pp. E808-15. doi: 10.1152/ajpendo.00361.2010.
Jung, S. H., Ha, K. H. and Kim, D. J. (2016) 'Visceral fat mass has stronger associations with diabetes and prediabetes than other anthropometric obesity indicators among Korean adults', *Yonsei Medical Journal*, 57(3), pp. 674–680. doi: 10.3349/ymj.2016.57.3.674.
Jung, Y. G., Kang, M. S. and Heo, J. (2014) 'Clustering performance comparison using K-means and expectation maximization algorithms', *Biotechnology and Biotechnological Equipment*, 28(sup1), pp. S44–S48. doi: 10.1080/13102818.2014.949045.
Justice, M. J. and Dhillon, P. (2016) 'Using the mouse to model human disease: increasing validity and reproducibility.', *Disease models & mechanisms*, 9(2), pp. 101–3. doi: 10.1242/dmm.024547.
Kajioka, T. *et al.* (2002) 'Effects of intentional weight cycling on non-obese young women.', *Metabolism: clinical and experimental*, 51(2), pp. 149–54. doi: 10.1053/META.2002.29976.
Kaptoge, S. *et al.* (2019) 'World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions', *The Lancet Global Health*, 7(10), pp. e1332–e1345. doi: 10.1016/S2214-109X(19)30318-3.
Kataja-Tuomola, M. *et al.* (2010) 'Short-term weight change and fluctuation as risk factors for type 2 diabetes in Finnish male smokers', *European Journal of Epidemiology*, 25(5), pp. 333–339. doi: 10.1007/s10654-010-9444-6.
Keim, N. L., Stern, J. S. and Havel, P. J. (1998) 'Relation between circulating leptin concentrations and appetite during a prolonged, moderate energy deficit in women', *The American Journal of Clinical Nutrition*, 68(4), pp. 794–801. doi: 10.1093/ajcn/68.4.794.
Keller, C. and Siegrist, M. (2015) 'Ambivalence toward palatable food and emotional eating predict weight fluctuations. Results of a longitudinal study with four waves', *Appetite*, 85, pp. 138–145. doi: 10.1016/j.appet.2014.11.024.

KENNEDY, G. C. (1953) 'The role of depot fat in the hypothalamic control of food intake in the rat.', *Proceedings of the Royal Society of London. Series B, Biological sciences*, 140(901), pp. 578–96. doi: 10.1098/RSPB.1953.0009.
Keto, J. *et al.* (2016) 'Cardiovascular disease risk factors in relation to smoking behaviour and history: a population-based cohort study', *Open Heart*, 3(2), p. e000358. doi: 10.1136/openhrt-2015-000358.
Keys, A. *et al.* (1950) *The Biology of Human Starvation.* Minnesota: University of Minnesota.
Khan, S. S. *et al.* (2018) 'Association of body mass index with lifetime risk of cardiovascular disease and compression of morbidity', *JAMA Cardiology*, 3(4), pp. 280–287. doi: 10.1001/jamacardio.2018.0022.
Kim, J. E. *et al.* (2016) 'Effects of dietary protein intake on body composition changes after weight loss in older adults: a systematic review and meta-analysis', *Nutrition Reviews*, 74(3), pp. 210–224. doi: 10.1093/nutrit/nuv065.
Kim, M. K. *et al.* (2018) 'Associations of Variability in Blood Pressure, Glucose and Cholesterol Concentrations, and Body Mass Index With Mortality and Cardiovascular Outcomes in the General Population', *Circulation*, 138(23), pp. 2627–2637. doi: 10.1161/CIRCULATIONAHA.118.034978.
Kim, W. W. *et al.* (1984) 'Evaluation of long-term dietary intakes of adults consuming self-selected diets', *American Journal of Clinical Nutrition*, 40(6 SUPPL.), pp. 1327–1332. doi: 10.1093/ajcn/40.6.1327.
Kivimäki, M. *et al.* (2017) 'Overweight, obesity, and risk of cardiometabolic multimorbidity: pooled analysis of individual-level data for 120 813 adults from 16 cohort studies from the USA and Europe', *The Lancet Public Health*, 2(6), pp. e277–e285. doi: 10.1016/S2468-2667(17)30074-9.
Kliemann, N. *et al.* (2016) 'Development and validation of the Self-Regulation of Eating Behaviour Questionnaire for adults', *International Journal of Behavioral Nutrition and Physical Activity*, 13(1), p. 87. doi: 10.1186/s12966-016-0414-6.
Kodama, S. *et al.* (2017) 'Unstable bodyweight and incident type 2 diabetes mellitus: A meta-analysis', *Journal of Diabetes Investigation*, 8(4), pp. 501–509. doi: 10.1111/jdi.12623.
Konopka, B. M. *et al.* (2018) 'Exploratory data analysis of a clinical study group: Development of a procedure for exploring multidimensional data', *PLoS ONE*, 13(8). doi: 10.1371/journal.pone.0201950.
van der Kooy, K. *et al.* (1993) 'Effect of a weight cycle on visceral fat accumulation', *The American Journal of Clinical Nutrition*, 58(6), pp. 853–857. doi: 10.1093/ajcn/58.6.853.
Kraschnewski, J. L. *et al.* (2010) 'Long-term weight loss maintenance in the United States', *International Journal of Obesity*, 34(11), pp. 1644–1654. doi: 10.1038/ijo.2010.94.
Kritchevsky, S. B. *et al.* (2015) 'Intentional weight loss and all-cause mortality: a meta-analysis of randomized clinical trials.', *PloS one*, 10(3), p. e0121993. doi: 10.1371/journal.pone.0121993.
Kroeger, C. M., Hoddy, K. K. and Varady, K. A. (2014) 'Impact of weight regain on metabolic disease risk: a review of human trials.', *Journal of obesity*, 2014, p. 614519. doi: 10.1155/2014/614519.
Kroke, A. *et al.* (2002) 'Recent weight changes and weight cycling as predictors of subsequent two year weight change in a middle-aged cohort', *International Journal of Obesity*, 26(3), pp. 403–409. doi: 10.1038/sj.ijo.0801920.
Krotkiewski, M. (2001) 'Value of VLCD supplementation with medium chain triglycerides', *International Journal of Obesity*, 25(9), pp. 1393–1400. doi: 10.1038/sj.ijo.0801682.
Kuhl, J. (1994) 'Action versus state orientation: Psychometric properties of the action control scale (ACS-90).', in *In J. Kuhl & J. Beckmann (Eds.)*. Seattle, WA: Hogrefe & Huber., pp. 47–59.
Kyung, D. S. *et al.* (2018) 'Global transcriptome analysis identifies weight regain-induced activation of adaptive immune responses in white adipose tissue of mice.', *International journal of obesity (2005)*, 42(4), pp. 755–764. doi: 10.1038/ijo.2017.297.
Lahti-Koski, M. *et al.* (2005) 'Prevalence of Weight Cycling and its Relation to Health Indicators in Finland', *Obesity Research*, 13(2), pp. 333–341. doi: 10.1038/oby.2005.45.
Lankisch, P. *et al.* (2001) 'Unintentional weight loss: diagnosis and prognosis. The first prospective follow-up study from a secondary referral centre.', *Journal of internal medicine*, 249(1), pp. 41–6.

Available at: http://www.ncbi.nlm.nih.gov/pubmed/11168783 (Accessed: 7 January 2019).
Larsen, T. M. *et al.* (2010) *Diets with High or Low Protein Content and Glycemic Index for Weight-Loss Maintenance A bs tr ac t*, *N Engl J Med*. Available at: http://www.diogenes-eu.org/Voorvertoning van 'Larsen et al Diogenes NEJM online 2010.PDF'.pdf (Accessed: 27 March 2019).
Lasikiewicz, N. *et al.* (2014) 'Psychological benefits of weight loss following behavioural and/or dietary weight loss interventions. A systematic research review', *Appetite*. Appetite, pp. 123–137. doi: 10.1016/j.appet.2013.09.017.
Leaf, A. and Antonio, J. (2017) 'The Effects of Overfeeding on Body Composition: The Role of Macronutrient Composition - A Narrative Review.', *International journal of exercise science*, 10(8), pp. 1275–1296. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29399253 (Accessed: 25 June 2019).
Lee, E. Y. *et al.* (2018) 'Effect of visit-to-visit LDL-, HDL-, and non-HDL-cholesterol variability on mortality and cardiovascular outcomes after percutaneous coronary intervention', *Atherosclerosis*, 279, pp. 1–9. doi: 10.1016/j.atherosclerosis.2018.10.012.
Lee, J. J. *et al.* (2016) 'Association of Changes in Abdominal Fat Quantity and Quality With Incident Cardiovascular Disease Risk Factors', *Journal of the American College of Cardiology*, 68(14), pp. 1509–1521. doi: 10.1016/j.jacc.2016.06.067.
Lee, O. *et al.* (2016) 'Associations between Physical Activity and Obesity Defined by Waist-To-Height Ratio and Body Mass Index in the Korean Population.', *PloS one*, 11(7), p. e0158245. doi: 10.1371/journal.pone.0158245.
Leibel, R. L. (2002) 'The role of leptin in the control of body weight', in *Nutrition Reviews*. International Life Sciences Institute. doi: 10.1301/002966402320634788.
Leibel, R. L. (2008) 'Molecular physiology of weight regulation in mice and humans', *International Journal of Obesity*. Int J Obes (Lond), pp. S98–S108. doi: 10.1038/ijo.2008.245.
Lejeune, M. P. G. M., Kovacs, E. M. R. and Westerterp-Plantenga, M. S. (2005) 'Additional protein intake limits weight regain after weight loss in humans.', *The British journal of nutrition*, 93(2), pp. 281–9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15788122 (Accessed: 20 November 2018).
Lele, S. and Richtsmeier, J. T. (1991) 'Euclidean distance matrix analysis: A coordinate-free approach for comparing biological shapes using landmark data', *American Journal of Physical Anthropology*, 86(3), pp. 415–427. doi: 10.1002/ajpa.1330860307.
Lemstra, M. *et al.* (2016) 'Weight loss intervention adherence and factors promoting adherence: a meta-analysis', *Patient Preference and Adherence*, 10, pp. 1547–1559. doi: 10.2147/PPA.S103649.
Li, S. *et al.* (2020) 'Visit-to-visit HbA1c variability is associated with cardiovascular disease and microvascular complications in patients with newly diagnosed type 2 diabetes', *Diabetes Care*, 43(2), pp. 426–432. doi: 10.2337/dc19-0823.
Li, X. *et al.* (2018) 'Impact of weight cycling on CTRP3 expression, adipose tissue inflammation and insulin sensitivity in C57BL/6J mice.', *Experimental and therapeutic medicine*, 16(3), pp. 2052–2059. doi: 10.3892/etm.2018.6399.
Li, Y.-C. *et al.* (2013) 'Percentage of Body Fat Assessment Using Bioelectrical Impedance Analysis and Dual-Energy X-ray Absorptiometry in a Weight Loss Program for Obese or Overweight Chinese Adults', *PLoS ONE*. Edited by T. Behrens, 8(4), p. e58272. doi: 10.1371/journal.pone.0058272.
Li, Z. *et al.* (2007) 'Weight cycling in a very low-calorie diet programme has no effect on weight loss velocity, blood pressure and serum lipid profile', *Diabetes, Obesity and Metabolism*, 9(3), pp. 379–385. doi: 10.1111/j.1463-1326.2006.00621.x.
Lien, L. F. *et al.* (2009) 'The STEDMAN Project: Biophysical, Biochemical and Metabolic Effects of a Behavioral Weight Loss Intervention during Weight Loss, Maintenance, and Regain', *OMICS A Journal of Integrative Biology*, 13(1). doi: 10.1089/omi.2008.0035.
Lillis, J. and Kendra, K. E. (2014) 'Acceptance and commitment therapy for weight control: Model, evidence, and future directions', *Journal of Contextual Behavioral Science*, 3(1), pp. 1–7. doi: 10.1016/j.jcbs.2013.11.005.

Linna, M. S. *et al.* (2007) 'Successful weight maintenance preserves lower levels of oxidized LDL achieved by weight reduction in obese men', *International Journal of Obesity*, 31(2), pp. 245–253. doi: 10.1038/sj.ijo.0803413.
Lissner, L. *et al.* (1989) 'Body composition and energy intake: do overweight women overeat and underreport?', *The American Journal of Clinical Nutrition*, 49(2), pp. 320–325. doi: 10.1093/ajcn/49.2.320.
Lissner, L. *et al.* (1990) 'Body weight variability in men: metabolic rate, health and longevity.', *International journal of obesity*, 14(4), pp. 373–83. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2361814 (Accessed: 21 June 2018).
List, E. O. *et al.* (2013) 'The effects of weight cycling on lifespan in male C57BL/6J mice', *International Journal of Obesity*, 37(8), pp. 1088–1094. doi: 10.1038/ijo.2012.203.
Liu, B. *et al.* (2016) 'Multiple imputation of completely missing repeated measures data within person from a complex sample: application to accelerometer data in the National Health and Nutrition Examination Survey', *Statistics in Medicine*, 35(28), pp. 5170–5188. doi: 10.1002/sim.7049.
Lovibond, P. F. and Lovibond, S. H. (1995) *The Structure Of Negative Emotional States: Comparison Of The Depression Anxiety Stress Scales (Dass) With The Beck Depression And Anxiety Inventories*, *BehaP. Res. Ther*.
Lowe, M. R. *et al.* (2006) 'Multiple types of dieting prospectively predict weight gain during the freshman year of college', *Appetite*, 47(1), pp. 83–90. doi: 10.1016/j.appet.2006.03.160.
Lowe, M. R. *et al.* (2007) 'The relationship of weight suppression and dietary restraint to binge eating in bulimia nervosa', *International Journal of Eating Disorders*, 40(7), pp. 640–644. doi: 10.1002/eat.20405.
Lowe, M. R. (2015) 'Dieting: proxy or cause of future weight gain?', *Obesity Reviews*, 16, pp. 19–24. doi: 10.1111/obr.12252.
Lowe, M. R. *et al.* (2015) 'Short-term variability in body weight predicts long-term weight gain', *The American Journal of Clinical Nutrition*, 102(5), pp. 995–999. doi: 10.3945/ajcn.115.115402.
Lowe, M. R. *et al.* (2019) 'Weight suppression uniquely predicts body fat gain in first-year female college students', *Eating Behaviors*, 32, pp. 60–64. doi: 10.1016/j.eatbeh.2018.11.005.
Lowe, M. R. *et al.* (2020) 'Weight Dysregulation, Positive Energy Balance, and Binge Eating in Eating Disorders', in *Binge Eating*. Springer International Publishing, pp. 59–67. doi: 10.1007/978-3-030-43562-2_5.
Lowe, M. R., Benson, L. and Singh, S. (2020) 'Individual differences in within-subject weight variability: There's a signal in the noise', *Physiology and Behavior*. Elsevier Inc., p. 113112. doi: 10.1016/j.physbeh.2020.113112.
Luppino, F. S. *et al.* (2010) 'Overweight, obesity, and depression: A systematic review and meta-analysis of longitudinal studies', *Archives of General Psychiatry*. Arch Gen Psychiatry, pp. 220–229. doi: 10.1001/archgenpsychiatry.2010.2.
Luscombe, N. D. *et al.* (2002) 'Effects of energy-restricted diets containing increased protein on weight loss, resting energy expenditure, and the thermic effect of feeding in type 2 diabetes', *Diabetes Care*, 25(4), pp. 652–657. doi: 10.2337/diacare.25.4.652.
Lutes, L. D. *et al.* (2008) 'Small Changes in Nutrition and Physical Activity Promote Weight Loss and Maintenance: 3-Month Evidence from the ASPIRE Randomized Trial', *Annals of Behavioral Medicine*, 35(3), pp. 351–357. doi: 10.1007/s12160-008-9033-z.
Ma, C. *et al.* (2017a) 'Effects of weight loss interventions for adults who are obese on mortality, cardiovascular disease, and cancer: systematic review and meta-analysis', *BMJ (Clinical research ed.)*, 359, p. j4849. doi: 10.1136/bmj.j4849.
Ma, C. *et al.* (2017b) 'Effects of weight loss interventions for adults who are obese on mortality, cardiovascular disease, and cancer: systematic review and meta-analysis', *BMJ (Clinical research ed.)*, 359, p. j4849. doi: 10.1136/bmj.j4849.
Ma, Y. *et al.* (2006) 'Seasonal variation in food intake, physical activity, and body weight in a predominantly overweight population', *European Journal of Clinical Nutrition*, 60(4), pp. 519–528.

doi: 10.1038/sj.ejcn.1602346.
Mackie, G. M., Samocha-Bonet, D. and Tam, C. S. (2017) 'Does weight cycling promote obesity and metabolic risk factors?', *Obesity Research & Clinical Practice*, 11(2), pp. 131–139. doi: 10.1016/j.orcp.2016.10.284.
MacLean, P. S. *et al.* (2011) 'Biology's response to dieting: the impetus for weight regain', *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, 301(3), pp. R581–R600. doi: 10.1152/ajpregu.00755.2010.
Madigan, C. D. *et al.* (2015a) 'Is self-weighing an effective tool for weight loss: a systematic literature review and meta-analysis', *International Journal of Behavioral Nutrition and Physical Activity*, 12(1), p. 104. doi: 10.1186/s12966-015-0267-4.
Madigan, C. D. *et al.* (2015b) 'Is self-weighing an effective tool for weight loss: a systematic literature review and meta-analysis', *International Journal of Behavioral Nutrition and Physical Activity*, 12(1), p. 104. doi: 10.1186/s12966-015-0267-4.
Mandviwala, T., Khalid, U. and Deswal, A. (2016) 'Obesity and Cardiovascular Disease: a Risk Factor or a Risk Marker?', *Current Atherosclerosis Reports*, 18(5), p. 21. doi: 10.1007/s11883-016-0575-4.
Marchesini, G. *et al.* (2004) 'Weight cycling in treatment-seeking obese persons: data from the QUOVADIS study', *International Journal of Obesity*, 28(11), pp. 1456–1462. doi: 10.1038/sj.ijo.0802741.
Markland, D. and Tobin, V. (2004) 'A modification to the behavioural regulation in exercise questionnaire to include an assessment of amotivation', *Journal of Sport and Exercise Psychology*, 26(2), pp. 191–196. doi: 10.1123/jsep.26.2.191.
Márquez-Quiñones, A. *et al.* (2010) 'Adipose tissue transcriptome reflects variations between subjects with continued weight loss and subjects regaining weight 6 mo after caloric restriction independent of energy intake', *The American Journal of Clinical Nutrition*, 92(4), pp. 975–984. doi: 10.3945/ajcn.2010.29808.
Mars, M. *et al.* (2006) 'Fasting leptin and appetite responses induced by a 4-day 65%-energy-restricted diet', *International Journal of Obesity*, 30, pp. 122–128. doi: 10.1038/sj.ijo.0803070.
Martin, C. L., Tate, D. F. and Valle, C. G. (2018) 'Nonadherence to daily self-weighing and activity tracking is associated with weight fluctuations among African American breast cancer survivors.', *PloS one*, 13(6), p. e0199751. doi: 10.1371/journal.pone.0199751.
Martins, C. *et al.* (2020) 'Metabolic adaptation is not a major barrier to weight-loss maintenance', *The American journal of clinical nutrition*, 112(3), pp. 558–565. doi: 10.1093/ajcn/nqaa086.
Mason, F. *et al.* (2018) 'Effectiveness of a brief behavioural intervention to prevent weight gain over the Christmas holiday period: randomised controlled trial.', *BMJ (Clinical research ed.)*, 363, p. k4867. doi: 10.1136/bmj.k4867.
Mateo, G. F. *et al.* (2015) 'Mobile phone apps to promote weight loss and increase physical activity: A systematic review and meta-analysis', *Journal of Medical Internet Research*. Journal of Medical Internet Research, p. e253. doi: 10.2196/jmir.4836.
Matsuo, T. *et al.* (2010) 'An increase in high-density lipoprotein cholesterol after weight loss intervention is associated with long-term maintenance of reduced visceral abdominal fat', *International Journal of Obesity*, 34(12), pp. 1742–1751. doi: 10.1038/ijo.2010.95.
Matsuzaka, T. and Shimano, H. (2011) 'Molecular mechanisms involved in hepatic steatosis and insulin resistance.', *Journal of diabetes investigation*, 2(3), pp. 170–5. doi: 10.1111/j.2040-1124.2011.00111.x.
Mayer, J. (1955) 'REGULATION OF ENERGY INTAKE AND THE BODY WEIGHT: THE GLUCOSTATIC THEORY AND THE LIPOSTATIC HYPOTHESIS', *Annals of the New York Academy of Sciences*, 63(1), pp. 15–43. doi: 10.1111/j.1749-6632.1955.tb36543.x.
McAuley, K. A. *et al.* (2006) 'Long-term effects of popular dietary approaches on weight loss and features of insulin resistance', *International Journal of Obesity*, 30(2), pp. 342–349. doi: 10.1038/sj.ijo.0803075.
McConnon, A. *et al.* (2012) 'Application of the Theory of Planned Behaviour to weight control in an

overweight cohort. Results from a pan-European dietary intervention trial (DiOGenes)', *Appetite*, 58(1), pp. 313–318. doi: 10.1016/j.appet.2011.10.017.
McDuffie, J. R. *et al.* (2004) 'Effects of exogenous leptin on satiety and satiation in patients with lipodystrophy and leptin insufficiency', *Journal of Clinical Endocrinology and Metabolism*, 89(9), pp. 4258–4263. doi: 10.1210/jc.2003-031868.
McGuire, M. T. *et al.* (1999) 'What predicts weight regain in a group of successful weight losers? .', *Journal of consulting and clinical psychology*, 67(2), pp. 177–85. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10224727 (Accessed: 20 July 2018).
McMillen, T. S., Minami, E. and Leboeuf, R. C. (2013) 'Atherosclerosis and cardiac function assessment in low-density lipoprotein receptor-deficient mice undergoing body weight cycling.', *Nutrition & diabetes*, 3(6), p. e79. doi: 10.1038/nutd.2013.19.
McNeil, J. *et al.* (2017) 'Investigating predictors of eating: is resting metabolic rate really the strongest proxy of energy intake?', *The American Journal of Clinical Nutrition*, 106(5), p. ajcn153718. doi: 10.3945/ajcn.117.153718.
Mehrang, S. *et al.* (2016a) 'Seasonal weight variation patterns in seven countries located in northern and southern hemispheres', in *2016 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*. IEEE, pp. 2475–2478. doi: 10.1109/EMBC.2016.7591232.
Mehrang, S. *et al.* (2016b) 'Seasonal weight variation patterns in seven countries located in northern and southern hemispheres', in *2016 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*. IEEE, pp. 2475–2478. doi: 10.1109/EMBC.2016.7591232.
Mehta, T. *et al.* (2014) 'Impact of weight cycling on risk of morbidity and mortality', *Obesity Reviews*, 15(11), pp. 870–881. doi: 10.1111/obr.12222.
MELLINKOFF, S. M. *et al.* (1956) 'Relationship between serum amino acid concentration and fluctuations in appetite.', *Journal of applied physiology*, 8(5), pp. 535–538. doi: 10.1152/jappl.1956.8.5.535.
Meyer, H. E., Tverdal, A. and Selmer, R. (1998) 'Weight variability, weight change and the incidence of hip fracture: A prospective study of 39000 middle-aged Norwegians', *Osteoporosis International*, 8(4), pp. 373–378. doi: 10.1007/s001980050077.
Miller, C. K., Nagaraja, H. N. and Weinhold, K. R. (2015) 'Early Weight-Loss Success Identifies Nonresponders after a Lifestyle Intervention in a Worksite Diabetes Prevention Trial', *Journal of the Academy of Nutrition and Dietetics*, 115(9), pp. 1464–1471. doi: 10.1016/j.jand.2015.04.022.
Moissl, U. M. *et al.* (2006) 'Body fluid volume determination via body composition spectroscopy in health and disease', *Physiological Measurement*, 27(9), pp. 921–933. doi: 10.1088/0967-3334/27/9/012.
Monesi, L. *et al.* (2012) 'Prevalence, incidence and mortality of diagnosed diabetes: evidence from an Italian population-based study', *Diabetic Medicine*, 29(3), pp. 385–392. doi: 10.1111/j.1464-5491.2011.03446.x.
Montani, J.-P., Schutz, Y. and Dulloo, A. G. (2015a) 'Dieting and weight cycling as risk factors for cardiometabolic diseases: who is really at risk?', *Obesity Reviews*, 16, pp. 7–18. doi: 10.1111/obr.12251.
Montani, J.-P., Schutz, Y. and Dulloo, A. G. (2015b) 'Dieting and weight cycling as risk factors for cardiometabolic diseases: who is really at risk?', *Obesity Reviews*, 16, pp. 7–18. doi: 10.1111/obr.12251.
Moore, C. S. *et al.* (2010) 'Dietary strategy to manipulate *ad libitum* macronutrient intake, and glycaemic index, across eight European countries in the Diogenes Study', *Obesity Reviews*, 11(1), pp. 67–75. doi: 10.1111/j.1467-789X.2009.00602.x.
Moritz, S. *et al.* (2015) 'Comparison of different Methods for Univariate Time Series Imputation in R'. Available at: http://arxiv.org/abs/1510.03924 (Accessed: 20 June 2019).
Moritz, S. and Bartz-Beielstein, T. (2017) *imputeTS: Time Series Missing Value Imputation in R*. Available at: https://journal.r-project.org/archive/2017/RJ-2017-009/RJ-2017-009.pdf (Accessed: 26 June 2019).

Morland, K. *et al.* (2002) 'Neighborhood characteristics associated with the location of food stores and food service places', *American Journal of Preventive Medicine*, 22(1), pp. 23–29. doi: 10.1016/S0749-3797(01)00403-2.
Morris, R. D. and Rimm, A. A. (1992) 'Long-term weight fluctuation and non-insulin-dependent diabetes mellitus in white women.', *Annals of epidemiology*, 2(5), pp. 657–64. doi: 10.1016/1047-2797(92)90010-N.
Morton, G. J. (2007) 'Hypothalamic leptin regulation of energy homeostasis and glucose metabolism', *The Journal of Physiology*, 583(2), pp. 437–443. doi: 10.1113/jphysiol.2007.135590.
Mullen, S. P. *et al.* (2016) 'Initial Validation of the Activity Choice Index Among Overweight Women', *Research Quarterly for Exercise and Sport*, 87(2), pp. 174–181. doi: 10.1080/02701367.2016.1152349.
Müller, M. J., Geisler, C., Hübers, M., *et al.* (2018) 'Body composition-related functions: a problem-oriented approach to phenotyping', *European Journal of Clinical Nutrition*, p. 1. doi: 10.1038/s41430-018-0340-6.
Müller, M. J., Geisler, C., Heymsfield, S. B., *et al.* (2018) 'Recent advances in understanding body weight homeostasis in humans', *F1000Research*, 7, p. 1025. doi: 10.12688/f1000research.14151.1.
Müller, M. J. and Bosy-Westphal, A. (2013) 'Adaptive thermogenesis with weight loss in humans', *Obesity*, pp. 218–228. doi: 10.1002/oby.20027.
Müller, M. J., Bosy-Westphal, A. and Heymsfield, S. B. (2010) 'Is there evidence for a set point that regulates human body weight?', *F1000 Medicine Reports*. Faculty of 1000 Ltd. doi: 10.3410/M2-59.
Müller, M. J., Enderle, J. and Bosy-Westphal, A. (2016) 'Changes in Energy Expenditure with Weight Gain and Weight Loss in Humans.', *Current obesity reports*, 5(4), pp. 413–423. doi: 10.1007/s13679-016-0237-4.
Murphy, R. A. *et al.* (2014) 'Weight change, body composition, and risk of mobility disability and mortality in older adults: a population-based cohort study.', *Journal of the American Geriatrics Society*, 62(8), pp. 1476–1483. doi: 10.1111/jgs.12954.
Mushengezi, B. and Chillo, P. (2014) 'Association between body fat composition and blood pressure level among secondary school adolescents in Dar es Salaam, Tanzania', *Pan African Medical Journal*, 19. doi: 10.11604/pamj.2014.19.327.5222.
Nackers, L. M., Ross, K. M. and Perri, M. G. (2010) 'The association between rate of initial weight loss and long-term success in obesity treatment: does slow and steady win the race?', *International journal of behavioral medicine*, 17(3), pp. 161–7. doi: 10.1007/s12529-010-9092-y.
Nagy, T. R. *et al.* (1998) 'Serum leptin concentrations and weight gain in postobese, postmenopausal women.', *Obesity research*, 6(4), pp. 257–61. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9688101 (Accessed: 10 June 2018).
Nall, R. (Livestrong. com. (2017) *Consequences of Too Little Calories - LIVESTRONG.COM*. Available at: https://www.livestrong.com/article/431427-consequences-of-too-little-calories/ (Accessed: 22 October 2018).
Nam, G. E. *et al.* (2018) 'Impact of body mass index and body weight variabilities on mortality: a nationwide cohort study', *International Journal of Obesity*. doi: 10.1038/s41366-018-0079-0.
Nam, G. E. *et al.* (2019) 'Impact of body mass index and body weight variabilities on mortality: a nationwide cohort study', *International Journal of Obesity*, 43(2), pp. 412–423. doi: 10.1038/s41366-018-0079-0.
Nam, G. E. *et al.* (2020) 'Body Weight Variability and the Risk of Cardiovascular Outcomes and Mortality in Patients With Type 2 Diabetes: A Nationwide Cohort Study', *Diabetes Care*, p. dc192552. doi: 10.2337/dc19-2552.
Neamat-Allah, J. *et al.* (2015) 'Weight cycling and the risk of type 2 diabetes in the EPIC-Germany cohort', *Diabetologia*, 58(12), pp. 2718–2725. doi: 10.1007/s00125-015-3755-9.
Nguyen, N. D. *et al.* (2007) 'Bone Loss, Weight Loss, and Weight Fluctuation Predict Mortality Risk in Elderly Men and Women', *Journal of Bone and Mineral Research*, 22(8), pp. 1147–1154. doi: 10.1359/jbmr.070412.

Nicklas, B. J. *et al.* (2001) 'Genetic variation in the peroxisome proliferator-activated receptor-gamma2 gene (Pro12Ala) affects metabolic responses to weight loss and subsequent weight regain.', *Diabetes*, 50(9), pp. 2172–6. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11522688 (Accessed: 12 September 2018).
Nicklas, B. J. *et al.* (no date) 'Brief Genetics Report Genetic Variation in the Peroxisome Proliferator–Activated Receptor-?2 Gene (Pro12Ala) Affects Metabolic Responses to Weight Loss and Subsequent Weight Regain'. Available at: http://diabetes.diabetesjournals.org/content/diabetes/50/9/2172.full.pdf (Accessed: 22 December 2017).
Nielsen, S. *et al.* (2000) 'Body composition and resting energy expenditure in humans: Role of fat, fat-free mass and extracellular fluid', *International Journal of Obesity*, 24(9), pp. 1153–1157. doi: 10.1038/sj.ijo.0801317.
Norgan, N. G. and Durnin, J. V. G. A. (1980) 'The effect of 6 weeks of overfeeding on the body weight, body composition, and energy metabolism of young men', *American Journal of Clinical Nutrition*, 33(5), pp. 978–988. doi: 10.1093/ajcn/33.5.978.
Nudelman, G. and Shiloh, S. (2016) 'Understanding behavioural clusters: Identifying differences between clusters of health behaviours on key constructs', *Psychology and Health*, 31(12), pp. 1375–1390. doi: 10.1080/08870446.2016.1208822.
Nymo, S. *et al.* (2017) 'Timeline of changes in appetite during weight loss with a ketogenic diet', *International Journal of Obesity*, 41(8), pp. 1224–1231. doi: 10.1038/ijo.2017.96.
Nymo, S. *et al.* (2018) 'Investigation of the long-term sustainability of changes in appetite after weight loss', *International Journal of Obesity*, 42(8), pp. 1489–1499. doi: 10.1038/s41366-018-0119-9.
O'Driscoll, R. *et al.* (2018) 'How well do activity monitors estimate energy expenditure? A systematic review and meta-analysis of the validity of current technologies', *British Journal of Sports Medicine*, p. bjsports-2018-099643. doi: 10.1136/bjsports-2018-099643.
O'Driscoll, R. *et al.* (2019) 'The validity of two widely used commercial and research-grade activity monitors, during resting, household and activity behaviours', *Health and Technology*, pp. 1–12. doi: 10.1007/s12553-019-00392-7.
O'Driscoll, R. *et al.* (2020) 'A novel scaling methodology to reduce the biases associated with missing data from commercial activity monitors', *PLOS ONE*. Edited by B. Najafi, 15(6), p. e0235144. doi: 10.1371/journal.pone.0235144.
O'Driscoll, Ruairi *et al.* (2020) 'Improving energy expenditure estimates from wearable devices: A machine learning approach', *Journal of Sports Sciences*, 38(13), pp. 1496–1505. doi: 10.1080/02640414.2020.1746088.
Ochner, C. N. *et al.* (2013) 'Biological mechanisms that promote weight regain following weight loss in obese humans', *Physiology and Behavior*, 120, pp. 106–113. doi: 10.1016/j.physbeh.2013.07.009.
Oh, T. J. *et al.* (2019) 'Body-Weight Fluctuation and Incident Diabetes Mellitus, Cardiovascular Disease, and Mortality: A 16-Year Prospective Cohort Study', *The Journal of Clinical Endocrinology & Metabolism*, 104(3), pp. 639–646. doi: 10.1210/jc.2018-01239.
Olson, M. B. *et al.* (2000) 'Weight cycling and high-density lipoprotein cholesterol in women: evidence of an adverse effect: a report from the NHLBI-sponsored WISE study. Women's Ischemia Syndrome Evaluation Study Group.', *Journal of the American College of Cardiology*, 36(5), pp. 1565–71. doi: 10.1016/s0735-1097(00)00901-3.
Orsama, A.-L. *et al.* (2014) 'Weight rhythms: weight increases during weekends and decreases during weekdays.', *Obesity facts*, 7(1), pp. 36–47. doi: 10.1159/000356147.
Osborn, R. L. *et al.* (2011) 'Yo-yo dieting in African American women: weight cycling and health.', *Ethnicity & disease*, 21(3), pp. 274–80. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21942158 (Accessed: 22 June 2018).
Ostendorf, D. M. *et al.* (2019) 'Physical Activity Energy Expenditure and Total Daily Energy Expenditure in Successful Weight Loss Maintainers', *Obesity*, 27(3), pp. 496–504. doi:

10.1002/oby.22373.
Oustric, P. *et al.* (2018) 'Changes in food reward during weight management interventions - a systematic review', *Obesity Reviews*, 19(12), pp. 1642–1658. doi: 10.1111/obr.12754.
Pacanowski, C. R. *et al.* (2018) 'Psychological status and weight variability over eight years: Results from Look AHEAD.', *Health Psychology*, 37(3), pp. 238–246. doi: 10.1037/hea0000547.
Painter, S. L. *et al.* (2017) 'What Matters in Weight Loss? An In-Depth Analysis of Self-Monitoring.', *Journal of medical Internet research*, 19(5), p. e160. doi: 10.2196/jmir.7457.
Paisey, R. B. *et al.* (2002) 'Five year results of a prospective very low calorie diet or conventional weight loss programme in type 2 diabetes.', *Journal of human nutrition and dietetics : the official journal of the British Dietetic Association*, 15(2), pp. 121–7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11972741 (Accessed: 13 November 2018).
Palm, I. *et al.* (2017) 'Body Weight Cycling with Identical Diet Composition Does Not Affect Energy Balance and Has No Adverse Effect on Metabolic Health Parameters', *Nutrients*, 9(10), p. 1149. doi: 10.3390/nu9101149.
Pan, A. *et al.* (2012) 'Bidirectional association between depression and obesity in middle-aged and older women', *International Journal of Obesity*, 36(4), pp. 595–602. doi: 10.1038/ijo.2011.111.
Park, K.-Y. *et al.* (2019) 'Body Weight Fluctuation as a Risk Factor for Type 2 Diabetes: Results from a Nationwide Cohort Study', *Journal of Clinical Medicine*, 8(7), p. 950. doi: 10.3390/jcm8070950.
Pasman, W. J., Westerterp-Plantenga, M. S. and Saris, W. H. (1997) 'The effectiveness of long-term supplementation of carbohydrate, chromium, fibre and caffeine on weight maintenance.', *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity*, 21(12), pp. 1143–51. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9426382 (Accessed: 12 September 2018).
Pasquet, P. and Apfelbaum, M. (1994) 'Recovery of initial body weight and composition after long-term massive overfeeding in men', *American Journal of Clinical Nutrition*, 60(6), pp. 861–863. doi: 10.1093/ajcn/60.6.861.
Payne, P. R. and Dugdale, A. E. (1977) 'MECHANISMS FOR THE CONTROL OF BODY-WEIGHT', *The Lancet*, 309(8011), pp. 583–586. doi: 10.1016/S0140-6736(77)92010-4.
De Pergola, G. and Silvestris, F. (2013) 'Obesity as a major risk factor for cancer.', *Journal of obesity*, 2013, p. 291546. doi: 10.1155/2013/291546.
Peters, E. T. *et al.* (1995) 'Changes in body weight in relation to mortality in 6441 European middle-aged men: the Seven Countries Study.', *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity*, 19(12), pp. 862–8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8963353 (Accessed: 10 June 2018).
Petroni, M. L., Villanova, N., Avagnina, S., Fusco, M. A., Fatati, G., Compare, A. and Marchesini, G. (2007) 'Psychological distress in morbid obesity in relation to weight history', *Obesity Surgery*, 17(3), pp. 391–399. doi: 10.1007/s11695-007-9069-3.
Petroni, M. L., Villanova, N., Avagnina, S., Fusco, M. A., Fatati, G., Compare, A., Marchesini, G., *et al.* (2007) 'Psychological Distress in Morbid Obesity in Relation to Weight History', *Obesity Surgery*, 17(3), pp. 391–399. doi: 10.1007/s11695-007-9069-3.
Phelan, S. *et al.* (2008) 'Holiday weight management by successful weight losers and normal weight individuals.', *Journal of consulting and clinical psychology*, 76(3), pp. 442–8. doi: 10.1037/0022-006X.76.3.442.
Pi-Sunyer, X. (2009) 'The medical risks of obesity', *Postgraduate Medicine*, 121(6), pp. 21–33. doi: 10.3810/pgm.2009.11.2074.
Piernas, C., Aveyard, P. and Jebb, S. A. (2016) 'Recent trends in weight loss attempts: Repeated cross-sectional analyses from the health survey for England', *International Journal of Obesity*, 40(11), pp. 1754–1759. doi: 10.1038/ijo.2016.141.
Pietiläinen, K. H. *et al.* (2012) 'Does dieting make you fat? A twin study', *International Journal of Obesity*, 36(3), pp. 456–464. doi: 10.1038/ijo.2011.160.
Pilgrim, A. L. *et al.* (2015) 'An overview of appetite decline in older people.', *Nursing older people*,

27(5), pp. 29–35. doi: 10.7748/nop.27.5.29.e697.
Polidori, D. *et al.* (2016) 'How Strongly Does Appetite Counter Weight Loss? Quantification of the Feedback Control of Human Energy Intake.', *Obesity (Silver Spring, Md.)*, 24(11), pp. 2289–2295. doi: 10.1002/oby.21653.
Pownall, H. J. *et al.* (2015) 'Changes in body composition over 8 years in a randomized trial of a lifestyle intervention: The look AHEAD study', *Obesity*, 23(3), pp. 565–572. doi: 10.1002/oby.21005.
Preuss, H. G. *et al.* (2004) 'Obesity and cancer', in *Phytopharmaceuticals in Cancer Chemoprevention*. CRC Press, pp. 197–204. doi: 10.1634/theoncologist.2009-0285.
Pruessner, J. C. *et al.* (2003) 'Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change.', *Psychoneuroendocrinology*, 28(7), pp. 916–31. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12892658 (Accessed: 3 September 2019).
Purcell, K. *et al.* (2014) 'The effect of rate of weight loss on long-term weight management: a randomised controlled trial', *The Lancet Diabetes & Endocrinology*, 2(12), pp. 954–962. doi: 10.1016/S2213-8587(14)70200-1.
R Core Team (2019) *R: The R Stats Package*. Available at: https://stat.ethz.ch/R-manual/R-devel/library/stats/html/00Index.html (Accessed: 8 July 2019).
Racette, S. B. *et al.* (2008) 'Influence of weekend lifestyle patterns on body weight.', *Obesity (Silver Spring, Md.)*, 16(8), pp. 1826–30. doi: 10.1038/oby.2008.320.
Rantou, K.-E., Karagrigoriou, A. and Vonta, I. (2017) 'On imputation methods in univariate time series', *Journal | MESA*, 8(2), pp. 239–251. Available at: http://nonlinearstudies.com/index.php/mesa/article/view/1522 (Accessed: 20 June 2019).
Reed, G. W. and Hill, J. O. (1993) 'Weight Cycling: A Review of the Animal Literature', *Obesity Research*, 1(5), pp. 392–402. doi: 10.1002/j.1550-8528.1993.tb00019.x.
Reid, R. and Hackett, A. F. (1999) 'Changes in nutritional status in adults over Christmas 1998', *Journal of Human Nutrition and Dietetics*, 12(6), pp. 513–516. doi: 10.1046/j.1365-277x.1999.00205.x.
Rhee, E.-J. (2017) 'Weight Cycling and Its Cardiometabolic Impact', *Journal of Obesity & Metabolic Syndrome*, 26(4), pp. 237–242. doi: 10.7570/jomes.2017.26.4.237.
Rhee, E.-J. *et al.* (2018) 'Increased risk of diabetes development in individuals with weight cycling over 4 years: The Kangbuk Samsung Health study', *Diabetes Research and Clinical Practice*, 139, pp. 230–238. doi: 10.1016/j.diabres.2018.03.018.
Ripley, B. (2020) *MASS PACKAGE - R*. Available at: https://cran.r-project.org/web/packages/MASS/MASS.pdf (Accessed: 3 August 2020).
Roberts, S. B. *et al.* (1996) 'Effects of Age on Energy Expenditure and Substrate Oxidation During Experimental Underfeeding in Healthy Men', *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, 51A(2), pp. B158–B166. doi: 10.1093/gerona/51a.2.b158.
Roberts, S. B. (2009) 'Holiday Weight Gain: Fact or Fiction?', *Nutrition Reviews*, 58(12), pp. 378–379. doi: 10.1111/j.1753-4887.2000.tb01839.x.
Rodin, J. *et al.* (1994) 'Weight cycling and fat distribution', *Int J Obes.*, 14(4), pp. 303–10.
Roehrig, M. *et al.* (2009) 'Dieting Frequency in Obese Patients With Binge Eating Disorder: Behavioral and Metabolic Correlates', *Obesity*, 17(4), pp. 689–697. doi: 10.1038/oby.2008.600.
Room, R. *et al.* (2012) 'Times to drink: cross-cultural variations in drinking in the rhythm of the week', *International Journal of Public Health*, 57(1), pp. 107–117. doi: 10.1007/s00038-011-0259-3.
Rosenbaum, D. L. *et al.* (2016) 'Energy intake highs and lows: how much does consistency matter in weight control?', *Clinical Obesity*, 6(3), pp. 193–201. doi: 10.1111/cob.12142.
Rosenbaum, M. *et al.* (1997) 'Effects of Weight Change on Plasma Leptin Concentrations and Energy Expenditure [1]', *The Journal of Clinical Endocrinology & Metabolism*, 82(11), pp. 3647–3654. doi: 10.1210/jcem.82.11.4390.
Rosenbaum, M. *et al.* (2005) 'Low-dose leptin reverses skeletal muscle, autonomic, and neuroendocrine adaptations to maintenance of reduced weight', *Journal of Clinical Investigation*,

115(12), pp. 3579–3586. doi: 10.1172/JCI25977.
Rosenbaum, Michael *et al.* (2005) 'Low-dose leptin reverses skeletal muscle, autonomic, and neuroendocrine adaptations to maintenance of reduced weight', *Journal of Clinical Investigation*, 115(12), pp. 3579–3586. doi: 10.1172/JCI25977.
Rosenbaum, M. and Leibel, R. L. (2010) 'Adaptive thermogenesis in humans', *International Journal of Obesity*, 34(0 1), pp. S47–S55. doi: 10.1038/ijo.2010.184.
Rosenbaum, M. and Leibel, R. L. (2014) 'Role of leptin in energy homeostasis in humans', *Journal of Endocrinology*, 223(1), pp. T83–T96. doi: 10.1530/JOE-14-0358.
Rosenman, R., Tennekoon, V. and Hill, L. G. (2011) 'Measuring bias in self-reported data', *International Journal of Behavioural and Healthcare Research*, 2(4), p. 320. doi: 10.1504/ijbhr.2011.043414.
Rubin, M. (2017) 'Do P Values Lose Their Meaning in Exploratory Analyses? It Depends How You Define the Familywise Error Rate', *Review of General Psychology*, 21(3), pp. 269–275. doi: 10.1037/gpr0000123.
Ryan, A. S., Serra, M. C. and Goldberg, A. P. (2018) 'Metabolic Benefits of Prior Weight Loss with and without Exercise on Subsequent 6-Month Weight Regain', *Obesity*, 26(1), pp. 37–44. doi: 10.1002/oby.22032.
Ryan, K., Dockray, S. and Linehan, C. (2019) 'A systematic review of tailored eHealth interventions for weight loss', *Digital Health*. SAGE Publications Inc. doi: 10.1177/2055207619826685.
Rzehak, P. *et al.* (2007) 'Weight change, weight cycling and mortality in the ERFORT Male Cohort Study', *European Journal of Epidemiology*, 22(10), pp. 665–673. doi: 10.1007/s10654-007-9167-5.
Sabaka, P. *et al.* (2017) 'The effects of body weight loss and gain on arterial hypertension control: an observational prospective study', *Eur J Med Res*, 22, p. 43. doi: 10.1186/s40001-017-0286-5.
Sainsbury, K. *et al.* (2019) 'Attribution of weight regain to emotional reasons amongst European adults with overweight and obesity who regained weight following a weight loss attempt'. doi: 10.1007/s40519-018-0487-0.
Saito, Y. *et al.* (2017) 'Associations between body fat variability and later onset of cardiovascular disease risk factors', *PLOS ONE*. Edited by D. Meyre, 12(4), p. e0175057. doi: 10.1371/journal.pone.0175057.
Sandoz, E. K. *et al.* (2013) 'Assessment of body image flexibility: The Body Image-Acceptance and Action Questionnaire', *Journal of Contextual Behavioral Science*, 2(1–2), pp. 39–48. doi: 10.1016/j.jcbs.2013.03.002.
Sanghvi, A. *et al.* (2015) 'Validation of an inexpensive and accurate mathematical method to measure long-term changes in free-living energy intake', *American Journal of Clinical Nutrition*, 102(2), pp. 353–358. doi: 10.3945/ajcn.115.111070.
Santos, I. *et al.* (2017) 'Prevalence of personal weight control attempts in adults: a systematic review and meta-analysis.', *Obesity reviews : an official journal of the International Association for the Study of Obesity*, 18(1), pp. 32–50. doi: 10.1111/obr.12466.
Saris, W. H. M. (2001) 'Very-Low-Calorie Diets and Sustained Weight Loss', *Obesity Research*, 9(S11), pp. 295S-301S. doi: 10.1038/oby.2001.134.
Sawamoto, R. *et al.* (2017) 'Predictors of successful long-term weight loss maintenance: A two-year follow-up', *BioPsychoSocial Medicine*, 11(1), p. 14. doi: 10.1186/s13030-017-0099-3.
Sayer, R. D. *et al.* (2018) 'Hunger, Food Cravings, and Diet Satisfaction are Related to Changes in Body Weight During a 6-Month Behavioral Weight Loss Intervention: The Beef WISE Study.', *Nutrients*, 10(6). doi: 10.3390/nu10060700.
Sbrocco, T. *et al.* (1999) 'Behavioral choice treatment promotes continuing weight loss: preliminary results of a cognitive-behavioral decision-based treatment for obesity.', *Journal of consulting and clinical psychology*, 67(2), pp. 260–6. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10224737 (Accessed: 22 October 2018).
Schofield, S. E. *et al.* (2017) 'Metabolic dysfunction following weight cycling in male mice.', *International journal of obesity (2005)*, 41(3), pp. 402–411. doi: 10.1038/ijo.2016.193.

Schulz, M. *et al.* (2005) 'Associations of short-term weight changes and weight cycling with incidence of essential hypertension in the EPIC-Potsdam study', *Journal of Human Hypertension*, 19(1), pp. 61–67. doi: 10.1038/sj.jhh.1001776.
Scott, S. E. *et al.* (2019) 'The NoHoW protocol: a multicentre 2×2 factorial randomised controlled trial investigating an evidence-based digital toolkit for weight loss maintenance in European adults.', *BMJ open*, 9(9), p. e029425. doi: 10.1136/bmjopen-2019-029425.
Sebire, S. J., Standage, M. and Vansteenkiste, M. (2008) 'Development and validation of the goal content for exercise questionnaire', *Journal of Sport and Exercise Psychology*, 30(4), pp. 353–377. doi: 10.1123/jsep.30.4.353.
Sellahewa, L. *et al.* (2016) 'A Systematic Review of Evidence on the Use of Very Low Calorie Diets in People with Diabetes', *Current Diabetes Reviews*, 13(1), pp. 35–46. doi: 10.2174/1573399812666151005123431.
Senechal, M. *et al.* (2011) 'Weight gain since menopause and its associations with weight loss maintenance in obese postmenopausal women', *Clinical Interventions in Aging*, 6, p. 221. doi: 10.2147/CIA.S23574.
Shaffer, J. A. *et al.* (2014) 'An inexpensive device for monitoring patients' weights via automated hovering', *Int J Cardiol*, 172(2), pp. 263–264. doi: 10.1016/j.ijcard.2013.12.123.
Sheth, A., Jaimini, U. and Yip, H. Y. (2018) 'How Will the Internet of Things Enable Augmented Personalized Health?', *IEEE intelligent systems*, 33(1), pp. 89–97. doi: 10.1109/MIS.2018.012001556.
Shieh, C. *et al.* (2016) 'Self-weighing in weight management interventions: A systematic review of literature', *Obesity Research and Clinical Practice*. Elsevier Ltd, pp. 493–519. doi: 10.1016/j.orcp.2016.01.004.
Shimizu, H. *et al.* (1997) 'Serum leptin concentration is associated with total body fat mass, but not abdominal fat distribution.', *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity*, 21(7), pp. 536–41. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9226482 (Accessed: 22 October 2018).
Shriver, L. *et al.* (2019) 'Longitudinal Associations between Emotion Regulation and Adiposity in Late Adolescence: Indirect Effects through Eating Behaviors', *Nutrients*, 11(3), p. 517. doi: 10.3390/nu11030517.
Siangphoe, U. and Wheeler, D. C. (2015) 'Evaluation of the performance of smoothing functions in generalized additive models for spatial variation in disease.', *Cancer informatics*, 14(Suppl 2), pp. 107–16. doi: 10.4137/CIN.S17300.
Sigmundová, D. *et al.* (2016) 'Weekday-weekend patterns of physical activity and screen time in parents and their pre-schoolers', *BMC Public Health*, 16(1), p. 898. doi: 10.1186/s12889-016-3586-8.
Silva, A. M. *et al.* (2018) 'What is the effect of diet and/or exercise interventions on behavioural compensation in non-exercise physical activity and related energy expenditure of free-living adults? A systematic review', *British Journal of Nutrition*, 119(12), pp. 1327–1345. doi: 10.1017/S000711451800096X.
Silva, D. F. O. *et al.* (2018) 'Motivations for weight loss in adolescents with overweight and obesity: a systematic review', *BMC Pediatrics*, 18(1), p. 364. doi: 10.1186/s12887-018-1333-2.
Simonds, S. E., Pryor, J. T. and Cowley, M. A. (2018a) 'Repeated weight cycling in obese mice causes increased appetite and glucose intolerance', *Physiology & Behavior*, 194, pp. 184–190. doi: 10.1016/j.physbeh.2018.05.026.
Simonds, S. E., Pryor, J. T. and Cowley, M. A. (2018b) 'Repeated weight cycling in obese mice causes increased appetite and glucose intolerance', *Physiology & Behavior*, 194, pp. 184–190. doi: 10.1016/j.physbeh.2018.05.026.
Smith, D. L. *et al.* (2018) 'Weight Cycling Increases Longevity Compared with Sustained Obesity in Mice', *Obesity*, 26(11), pp. 1733–1739. doi: 10.1002/oby.22290.
Sniehotta, F. F., Scholz, U. and Schwarzer, R. (2005) 'Bridging the intention-behaviour gap: Planning, self-efficacy, and action control in the adoption and maintenance of physical exercise', *Psychology and Health*, 20(2), pp. 143–160. doi: 10.1080/08870440512331317670.

Soeliman, F. A. and Azadbakht, L. (2014) 'Weight loss maintenance: A review on dietary related strategies.', *Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences*, 19(3), pp. 268–75. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24949037 (Accessed: 19 April 2019).
Soenen, S. *et al.* (2012) 'Relatively high-protein or "low-carb" energy-restricted diets for body weight loss and body weight maintenance?', *Physiology & Behavior*, 107(3), pp. 374–380. doi: 10.1016/j.physbeh.2012.08.004.
Soleymani, T., Daniel, S. and Garvey, W. T. (2016) 'Weight maintenance: Challenges, tools and strategies for primary care physicians', *Obesity Reviews*, 17(1), pp. 81–93. doi: 10.1111/obr.12322.
Sparti, A. *et al.* (1997) 'Relationship between resting metabolic rate and the composition of the fat-free mass.', *Metabolism: clinical and experimental*, 46(10), pp. 1225–30. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9322812 (Accessed: 22 July 2018).
Speakman, J. R. *et al.* (2011) 'Set points, settling points and some alternative models: Theoretical options to understand how genes and environments combine to regulate body adiposity', *DMM Disease Models and Mechanisms*. Company of Biologists, pp. 733–745. doi: 10.1242/dmm.008698.
Speakman, J. R., Stubbs, R. J. and Mercer, J. G. (2002) 'Does body mass play a role in the regulation of food intake?', *Proceedings of the Nutrition Society*, 61(4), pp. 473–487. doi: 10.1079/pns2002194.
Sponholtz, T. R. *et al.* (2019) 'Association of variability in body mass index and metabolic health with cardiometabolic disease risk', *Journal of the American Heart Association*, 8(7). doi: 10.1161/JAHA.118.010793.
Steinberg, D. M. *et al.* (2013) 'The efficacy of a daily self-weighing weight loss intervention using smart scales and e-mail', *Obesity*, 21(9), p. n/a-n/a. doi: 10.1002/oby.20396.
Stekhoven, D. J. and Buhlmann, P. (2012) 'MissForest--non-parametric missing value imputation for mixed-type data', *Bioinformatics*, 28(1), pp. 112–118. doi: 10.1093/bioinformatics/btr597.
Stevens, J. and Lissner, L. (1990) 'Body weight variability and mortality in the Charleston Heart Study.', *International journal of obesity*, 14(4), pp. 385–6. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2361815 (Accessed: 21 June 2018).
Stevens, S. L. *et al.* (2016) 'Blood pressure variability and cardiovascular disease: systematic review and meta-analysis.', *BMJ (Clinical research ed.)*, 354, p. i4098. doi: 10.1136/BMJ.I4098.
Stevenson, J. L. *et al.* (2013) 'Effects of exercise during the holiday season on changes in body weight, body composition and blood pressure', *European Journal of Clinical Nutrition*, 67(9), pp. 944–949. doi: 10.1038/ejcn.2013.98.
Stewart-Brown, S. *et al.* (2009) 'Internal construct validity of the Warwick-Edinburgh Mental Well-Being Scale (WEMWBS): A Rasch analysis using data from the Scottish Health Education Population Survey', *Health and Quality of Life Outcomes*, 7. doi: 10.1186/1477-7525-7-15.
Stice, E. *et al.* (2011) 'Weight suppression and risk of future increases in body mass: effects of suppressed resting metabolic rate and energy expenditure 1-3', *Original Research Communications Am J Clin Nutr*, 94, pp. 7–11. doi: 10.3945/ajcn.110.010025.
Stice, E. *et al.* (2020) 'Weight suppression increases odds for future onset of anorexia nervosa, bulimia nervosa, and purging disorder, but not binge eating disorder', *The American Journal of Clinical Nutrition*. doi: 10.1093/ajcn/nqaa146.
Strychar, I. *et al.* (2009) 'Anthropometric, Metabolic, Psychosocial, and Dietary Characteristics of Overweight/Obese Postmenopausal Women with a History of Weight Cycling: A MONET (Montreal Ottawa New Emerging Team) Study', *Journal of the American Dietetic Association*, 109(4), pp. 718–724. doi: 10.1016/j.jada.2008.12.026.
Stubbs, J. *et al.* (2011) 'Problems in identifying predictors and correlates of weight loss and maintenance: implications for weight control therapies based on behaviour change', *Obesity Reviews*, 12(9), p. no-no. doi: 10.1111/j.1467-789X.2011.00883.x.
Stubbs, R. J. *et al.* (2018) 'Potential effects of fat mass and fat-free mass on energy intake in different states of energy balance', *European Journal of Clinical Nutrition*, 72(5), pp. 698–709. doi: 10.1038/s41430-018-0146-6.

Stunkard, A. J., Van Itallie, T. B. and Reis, B. B. (1955) 'The Mechanism of Satiety:Effect of Glucagon on Gastric Hunger Contractions in Man. (21776)', *Proceedings of the Society for Experimental Biology and Medicine*, 89(2), pp. 258–261. doi: 10.3181/00379727-89-21776.
Stunkard, A. J. and Messick, S. (1985) 'The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger.', *Journal of psychosomatic research*, 29(1), pp. 71–83. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3981480 (Accessed: 10 April 2018).
Sumithran, P. *et al.* (2011) 'Long-Term Persistence of Hormonal Adaptations to Weight Loss', *N Engl J Med*, 17365(27), pp. 1597–604. Available at: https://www.nejm.org/doi/pdf/10.1056/NEJMoa1105816 (Accessed: 17 July 2018).
Sumithran, P. and Proietto, J. (2013) 'The defence of body weight: a physiological basis for weight regain after weight loss', *Clinical Science*, 124(4), pp. 231–241. doi: 10.1042/CS20120223.
Swift, D. L. *et al.* (2014) 'The role of exercise and physical activity in weight loss and maintenance.', *Progress in cardiovascular diseases*, 56(4), pp. 441–7. doi: 10.1016/j.pcad.2013.09.012.
Taing, K. Y., Ardern, C. I. and Kuk, J. L. (2012) 'Effect of the Timing of Weight Cycling During Adulthood on Mortality Risk in Overweight and Obese Postmenopausal Women', *Obesity*, 20(2), pp. 407–413. doi: 10.1038/oby.2011.207.
Tang, F. and Ishwaran, H. (2017) 'Random forest missing data algorithms', *Statistical Analysis and Data Mining*, 10(6), pp. 363–377. doi: 10.1002/sam.11348.
Tate, D. F. *et al.* (2007) 'Long-term weight losses associated with prescription of higher physical activity goals. Are higher levels of physical activity protective against weight regain?', *American Journal of Clinical Nutrition*, 85(4), pp. 954–959. doi: 10.1093/ajcn/85.4.954.
Teixeira, Pedro J., Carraça, E. V., *et al.* (2012) 'Exercise, physical activity, and self-determination theory: A systematic review', *International Journal of Behavioral Nutrition and Physical Activity*. BioMed Central, p. 78. doi: 10.1186/1479-5868-9-78.
Teixeira, Pedro J., Silva, M. N., *et al.* (2012) 'Motivation, self-determination, and long-term weight control', *International Journal of Behavioral Nutrition and Physical Activity*. BioMed Central, p. 22. doi: 10.1186/1479-5868-9-22.
Teixeira, Pedro J *et al.* (2012) 'Motivation, self-determination, and long-term weight control', *International Journal of Behavioral Nutrition and Physical Activity*, 9(1), p. 22. doi: 10.1186/1479-5868-9-22.
Teixeira, P. J. *et al.* (2015a) 'Successful behavior change in obesity interventions in adults: a systematic review of self-regulation mediators.', *BMC medicine*, 13, p. 84. doi: 10.1186/s12916-015-0323-6.
Teixeira, P. J. *et al.* (2015b) 'Successful behavior change in obesity interventions in adults: a systematic review of self-regulation mediators', *BMC Medicine*, 13(1), p. 84. doi: 10.1186/s12916-015-0323-6.
Tennant, R. *et al.* (2007) 'The Warwick-Dinburgh mental well-being scale (WEMWBS): Development and UK validation', *Health and Quality of Life Outcomes*, 5(1), p. 63. doi: 10.1186/1477-7525-5-63.
Terrence Jorgensen (2018) *Package 'simsem' Type Package Title SIMulated Structural Equation Modeling*. Available at: http://www.simsem.org (Accessed: 18 October 2019).
Thomas, D. M. *et al.* (2012) 'Why do individuals not lose more weight from an exercise intervention at a defined dose? an energy balance analysis', *Obesity Reviews*, 13(10), pp. 835–847. doi: 10.1111/j.1467-789X.2012.01012.x.
Thomas, D. M. *et al.* (2014) 'Effect of dietary adherence on the body weight plateau: A mathematical model incorporating intermittent compliance with energy intake prescription', *American Journal of Clinical Nutrition*, 100(3), pp. 787–795. doi: 10.3945/ajcn.113.079822.
Von Thun, N. L. *et al.* (2014) 'Does bone loss begin after weight loss ends? Results 2 years after weight loss or regain in postmenopausal women', *Menopause*, 21(5), pp. 501–508. doi: 10.1097/GME.0b013e3182a76fd5.
van der Toorn, J. E. *et al.* (2020) 'Seasonal variation of diet quality in a large middle-aged and elderly Dutch population-based cohort', *European Journal of Nutrition*, 59(2), pp. 493–504. doi:

10.1007/s00394-019-01918-5.
Toray, T. and Cooley, E. (1997) 'Weight Fluctuation, Bulimic Symptoms, and Self-Efficacy for Control of Eating', *The Journal of Psychology*, 131(4), pp. 383–392. doi: 10.1080/00223989709603524.
Torgo, L. (2013) 'Package "DMwR"', *Comprehensive R Archive Network*.
Toubro, S. and Astrup, A. (1997) 'Randomised comparison of diets for maintaining obese subjects' weight after major weight loss: ad lib, low fat, high carbohydrate diet v fixed energy intake.', *BMJ (Clinical research ed.)*, 314(7073), pp. 29–34. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9001476 (Accessed: 22 October 2018).
Tremblay, A. and Chaput, J. P. (2009) 'Adaptive reduction in thermogenesis and resistance to lose fat in obese men', *British Journal of Nutrition*, 102(4), pp. 488–492. doi: 10.1017/S0007114508207245.
Tremmel, M. *et al.* (2017) 'Economic Burden of Obesity: A Systematic Literature Review.', *International journal of environmental research and public health*, 14(4). doi: 10.3390/ijerph14040435.
Trompetter, H. R. *et al.* (2013) 'Measuring values and committed action with the engaged living scale (ELS): Psychometric evaluation in a nonclinical sample and a chronic pain sample', *Psychological Assessment*, 25(4), pp. 1235–1246. doi: 10.1037/a0033813.
Tudor-Locke, C. *et al.* (2011) 'How many steps/day are enough? for adults', *International Journal of Behavioral Nutrition and Physical Activity*, 8. doi: 10.1186/1479-5868-8-79.
Turicchi, J. *et al.* (2019) 'Associations between the rate, amount, and composition of weight loss as predictors of spontaneous weight regain in adults achieving clinically significant weight loss: A systematic review and meta-regression.', *Obesity Reviews*, p. obr.12849. doi: 10.1111/obr.12849.
Turicchi, Jake, O'Driscoll, R., Finlayson, G., Duarte, C., Hopkins, M., *et al.* (2020) 'Associations between the proportion of fat-free mass loss during weight loss, changes in appetite, and subsequent weight change: Results from a randomized 2-stage dietary intervention trial', *American Journal of Clinical Nutrition*, 111(3), pp. 536–544. doi: 10.1093/ajcn/nqz331.
Turicchi, Jake, O'Driscoll, Ruairi, Horgan, G., Duarte, C., Santos, Inês, Encantado, J., *et al.* (2020) 'Body weight variability is not associated with changes in risk factors for cardiometabolic disease', *International Journal of Cardiology: Hypertension*, 6, p. 100045. doi: 10.1016/j.ijchy.2020.100045.
Turicchi, Jake, O'Driscoll, R., Finlayson, G., Duarte, C., Palmeira, Antonio L, *et al.* (2020) 'Data imputation and body weight variability calculation using linear and non-linear methods in data collected from digital smart scales: a simulation and validation study', *JMIR Preprints*. doi: 10.2196/17977.
Turicchi, Jake, O'Driscoll, R., Finlayson, G., Duarte, C., Palmeira, A L, *et al.* (2020) 'Data Imputation and Body Weight Variability Calculation Using Linear and Nonlinear Methods in Data Collected From Digital Smart Scales: Simulation and Validation Study.', *JMIR mHealth and uHealth*, 8(9), p. e17977. doi: 10.2196/17977.
Turicchi, J. (2020a) *GitHub - Study Code JMIR*. Available at: https://github.com/jaketuricchi/BodyWeight_Imputation_Validation_Variability (Accessed: 13 June 2020).
Turicchi, J. (2020b) *jaketuricchi/Publication_scripts: Scripts associations with published studies*, *GitHub*. Available at: https://github.com/jaketuricchi/Publication_scripts (Accessed: 24 August 2020).
Turicchi, J. *et al.* (2020) 'The impact of early body-weight variability on long-term weight maintenance: exploratory results from the NoHoW weight-loss maintenance intervention', *International Journal of Obesity*. doi: 10.1038/s41366-020-00706-0.
Turicchi, Jake, O'Driscoll, Ruairi, Horgan, G., Duarte, C., Palmeira, Antonio L., Larsen, S. C., *et al.* (2020) 'Weekly, seasonal and holiday body weight fluctuation patterns among individuals engaged in a European multi-centre behavioural weight loss maintenance intervention', *PLOS ONE*. Edited by R. Ferrer, 15(4), p. e0232152. doi: 10.1371/journal.pone.0232152.
Turpie, A. G. G. *et al.* (2002) 'Overweight and obesity as determinants of cardiovascular risk: The Framingham experience', *Archives of Internal Medicine*, 162(16), pp. 1867–1872. doi:

10.1001/archinte.162.16.1867.
Tylka, T. L. and Kroon Van Diest, A. M. (2013) 'The Intuitive Eating Scale–2: Item refinement and psychometric evaluation with college women and men.', *Journal of Counseling Psychology*, 60(1), pp. 137–153. doi: 10.1037/a0030893.
Unick, J. L. *et al.* (2015) 'Weight change in the first 2 months of a lifestyle intervention predicts weight changes 8 years later', *Obesity*, 23(7), pp. 1353–1356. doi: 10.1002/oby.21112.
Uusi-Rasi, K. *et al.* (2010) 'Three-month weight reduction does not compromise bone strength in obese premenopausal women', *Bone*, 46(5), pp. 1286–1293. doi: 10.1016/j.bone.2009.10.013.
Vadiveloo, M. *et al.* (2016) 'Greater Healthful Dietary Variety Is Associated with Greater 2-Year Changes in Weight and Adiposity in the Preventing Overweight Using Novel Dietary Strategies (POUNDS Lost) Trial.', *The Journal of nutrition*, 146(8), pp. 1552–9. doi: 10.3945/jn.115.224683.
Vainik, U. *et al.* (2015) 'Eating traits questionnaires as a continuum of a single concept. Uncontrolled eating', *Appetite*, 90, pp. 229–239. doi: 10.1016/j.appet.2015.03.004.
Vainik, U. *et al.* (2016) 'Diet misreporting can be corrected: confirmation of the association between energy intake and fat-free mass in adolescents', *British Journal of Nutrition*, 116(08), pp. 1425–1436. doi: 10.1017/S0007114516003317.
Valle, C. G., Deal, A. M. and Tate, D. F. (2017) 'Preventing weight gain in African American breast cancer survivors using smart scales and activity trackers: a randomized controlled pilot study', *Journal of Cancer Survivorship*, 11(1), pp. 133–148. doi: 10.1007/s11764-016-0571-2.
Vanwormer, J. J. *et al.* (2008) 'The impact of regular self-weighing on weight management: a systematic literature review.', *The international journal of behavioral nutrition and physical activity*, 5, p. 54. doi: 10.1186/1479-5868-5-54.
Varkevisser, R. D. M. *et al.* (2019) 'Determinants of weight loss maintenance: a systematic review', *Obesity Reviews*, 20(2), pp. 171–211. doi: 10.1111/obr.12772.
Venditti, E. M. *et al.* (1996) 'Weight cycling, psychological health, and binge eating in obese women.', *Journal of Consulting and Clinical Psychology*, 64(2), pp. 400–405. doi: 10.1037/0022-006X.64.2.400.
Verdich, C. *et al.* (2011) 'Changes in body composition during weight loss in obese subjects in the NUGENOB study: Comparison of bioelectrical impedance vs. dual-energy X-ray absorptiometry', *Diabetes & Metabolism*, 37(3), pp. 222–229. doi: 10.1016/j.diabet.2010.10.007.
Vergnaud, A.-C. *et al.* (2008) 'Weight fluctuations and risk for metabolic syndrome in an adult cohort', *International Journal of Obesity*, 32(2), pp. 315–321. doi: 10.1038/sj.ijo.0803739.
Verhoef, S. P. *et al.* (2013) 'Concomitant changes in sleep duration and body weight and body composition during weight loss and 3-mo weight maintenance', *The American Journal of Clinical Nutrition*, 98(1), pp. 25–31. doi: 10.3945/ajcn.112.054650.
Vickers, A. J. and Altman, D. G. (2001) 'Analysing controlled trials with baseline and follow up measurements', *British Medical Journal*, pp. 1123–1124. doi: 10.1136/bmj.323.7321.1123.
Vink, R. G. *et al.* (2016) 'The effect of rate of weight loss on long-term weight regain in adults with overweight and obesity', *Obesity*, 24(2), pp. 321–327. doi: 10.1002/oby.21346.
Vogels, N. and Westerterp-Plantenga, M. S. (2007) 'Successful Long-term Weight Maintenance: A 2-year Follow-up*', *Obesity*, 15(5), pp. 1258–1266. doi: 10.1038/oby.2007.147.
Wadden, T. A. *et al.* (1996) 'Effects of weight cycling on the resting energy expenditure and body composition of obese women', *International Journal of Eating Disorders*, 19(1), pp. 5–12. doi: 10.1002/(SICI)1098-108X(199601)19:1<5::AID-EAT2>3.0.CO;2-T.
Wadden, T. A. *et al.* (2011) 'Four-Year Weight Losses in the Look AHEAD Study: Factors Associated With Long-Term Success', *Obesity*, 19(10), pp. 1987–1998. doi: 10.1038/oby.2011.230.
Wadden, T. A., Anderson, D. A. and Foster, G. D. (1999) 'Two-year changes in lipids and lipoproteins associated with the maintenance of a 5 % to 10% reduction in initial weight: some findings and some questions', *Obesity Research*, 7(2), pp. 170–178. doi: 10.1002/j.1550-8528.1999.tb00699.x.
Wadden, T. A., Foster, G. D. and Letizia, K. A. (1994) 'One-year behavioral treatment of obesity: comparison of moderate and severe caloric restriction and the effects of weight maintenance therapy.', *Journal of consulting and clinical psychology*, 62(1), pp. 165–71. Available at:

http://www.ncbi.nlm.nih.gov/pubmed/8034818 (Accessed: 22 October 2018).
Wagner, D. R., Larson, J. N. and Wengreen, H. (2012) 'Weight and body composition change over a six-week holiday period', *Eating and Weight Disorders - Studies on Anorexia, Bulimia and Obesity*, 17(1), pp. e54–e56. doi: 10.1007/BF03325328.
WANG, X. *et al.* (2008) 'Weight Regain Is Related to Decreases in Physical Activity during Weight Loss', *Medicine & Science in Sports & Exercise*, 40(10), pp. 1781–1788. doi: 10.1249/MSS.0b013e31817d8176.
Wang, Z. M. *et al.* (2010) 'Specific metabolic rates of major organs and tissues across adulthood: Evaluation by mechanistic model of resting energy expenditure', *American Journal of Clinical Nutrition*, 92(6), pp. 1369–1377. doi: 10.3945/ajcn.2010.29885.
Wannamethee, S. G., Shaper, A. G. and Walker, M. (2002) 'Weight Change, Weight Fluctuation, and Mortality', *Archives of Internal Medicine*, 162(22), p. 2575. doi: 10.1001/archinte.162.22.2575.
Wardle, J. and Griffith, J. (2001) 'Socioeconomic status and weight control practices in British adults', *Journal of Epidemiology and Community Health*, 55(3), pp. 185–190. doi: 10.1136/jech.55.3.185.
Waring, M. E. *et al.* (2010) 'Incident diabetes in relation to weight patterns during middle age.', *American journal of epidemiology*, 171(5), pp. 550–6. doi: 10.1093/aje/kwp433.
Waters, D. L. *et al.* (2013) 'Long-term maintenance of weight loss after lifestyle intervention in frail, obese older adults.', *The journal of nutrition, health & aging*, 17(1), pp. 3–7. doi: 10.1007/s12603-012-0421-5.
Weinsier, R. L. *et al.* (2000) 'Energy expenditure and free-living physical activity in black and white women: Comparison before and after weight loss', *American Journal of Clinical Nutrition*, 71(5), pp. 1138–1146. doi: 10.1093/ajcn/71.5.1138.
Weise, C. M. *et al.* (2013) 'Fat-free body mass but not fat mass is associated with reduced gray matter volume of cortical brain regions implicated in autonomic and homeostatic regulation.', *NeuroImage*, 64, pp. 712–21. doi: 10.1016/j.neuroimage.2012.09.005.
Westenhoefer, J. (1991) 'Dietary restraint and disinhibition: is restraint a homogeneous construct?', *Appetite*, 16(1), pp. 45–55. doi: 10.1016/0195-6663(91)90110-e.
Westerterp-Plantenga, M. S., Kempen, K. P. and Saris, W. H. (1998) 'Determinants of weight maintenance in women after diet-induced weight reduction.', *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity*, 22(1), pp. 1–6. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9481593 (Accessed: 20 November 2018).
Westerterp, K. R. *et al.* (1995) 'Energy intake, physical activity and body weight: a simulation model', *British Journal of Nutrition*, 73(3), pp. 337–347. doi: 10.1079/bjn19950037.
White, F. M. M., Pereira, L. H. and Garner, J. B. (1986) 'Associations of body mass index and waist:hip ratio with hypertension', *Canadian Medical Association Journal*, 135(4), pp. 313–320. Available at: /pmc/articles/PMC1491450/?report=abstract (Accessed: 26 August 2020).
Williams, E. D. *et al.* (2011) 'Assessment of physical activity levels in South Asians in the UK: Findings from the Health Survey for England', *Journal of Epidemiology and Community Health*, 65(6), pp. 517–521. doi: 10.1136/jech.2009.102509.
Williamson, D. A., Bray, G. A. and Ryan, D. H. (2015) 'Is 5% weight loss a satisfactory criterion to define clinically significant weight loss?', *Obesity*, 23(12), pp. 2319–2320. doi: 10.1002/oby.21358.
Williamson, P. J., Atkinson, G. and Batterham, A. M. (2018) 'Inter-individual differences in weight change following exercise interventions: a systematic review and meta-analysis of randomized controlled trials', *Obesity Reviews*. Blackwell Publishing Ltd, pp. 960–975. doi: 10.1111/obr.12682.
Wing, R. R. (1992) 'Weight Cycling in Humans: A Review of the Literature', *Annals of Behavioral Medicine*, 14(2), pp. 113–119. doi: 10.1093/abm/14.2.113.
Wing, R. R. *et al.* (2006) 'A Self-Regulation Program for Maintenance of Weight Loss', *New England Journal of Medicine*, 355(15), pp. 1563–1571. doi: 10.1056/NEJMoa061883.
Wing, Rena R *et al.* (2011a) 'Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes.', *Diabetes care*, 34(7), pp. 1481–6. doi:

10.2337/dc10-2415.
Wing, Rena R *et al.* (2011b) 'Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes.', *Diabetes care*, 34(7), pp. 1481–6. doi: 10.2337/dc10-2415.
Wing, Rena R. *et al.* (2011) 'Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes', *Diabetes Care*, 34(7), pp. 1481–1486. doi: 10.2337/dc10-2415.
Wing, R. R., Jeffery, R. W. and Hellerstedt, W. L. (1995) 'A Prospective Study of Effects of Weight Cycling on Cardiovascular Risk Factors', *Archives of Internal Medicine*, 155(13), pp. 1416–1422. doi: 10.1001/archinte.1995.00430130102011.
Wing, R. R. and Phelan, S. (2005) 'Long-term weight loss maintenance.', *The American journal of clinical nutrition*. Oxford Academic, pp. 222–227. doi: 10.1093/ajcn/82.1.222s.
Wingo, B. C. *et al.* (2013) 'Self-efficacy as a predictor of weight change and behavior change in the PREMIER trial', *Journal of Nutrition Education and Behavior*, 45(4), pp. 314–321. doi: 10.1016/j.jneb.2012.12.004.
Winter, S. R. *et al.* (2017) 'Elevated reward response to receipt of palatable food predicts future weight variability in healthy-weight adolescents', *American Journal of Clinical Nutrition*, 105(4), pp. 781–789. doi: 10.3945/ajcn.116.141143.
Womble, L. G. *et al.* (2001) 'Psychosocial variables associated with binge eating in obese males and females.', *The International journal of eating disorders*, 30(2), pp. 217–21. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11449457 (Accessed: 21 June 2018).
World Health Organisation (2016) *WHO | By category | Prevalence of overweight among adults, BMI ≥ 25, crude - Estimates by country*, *WHO*. World Health Organization.
Wu, F., Wu, T. and Yuce, M. (2018) 'An Internet-of-Things (IoT) Network System for Connected Safety and Health Monitoring Applications', *Sensors*, 19(1), p. 21. doi: 10.3390/s19010021.
Xiao, Q. *et al.* (2017) 'Neighborhood Socioeconomic Deprivation and Weight Change in a Large U.S. Cohort', *American Journal of Preventive Medicine*, 52(6), pp. e173–e181. doi: 10.1016/J.AMEPRE.2017.01.036.
Yanovski, J. A. *et al.* (2000) 'A Prospective Study of Holiday Weight Gain', *New England Journal of Medicine*, 342(12), pp. 861–867. doi: 10.1056/NEJM200003233421206.
Yau, Y. H. C. and Potenza, M. N. (2013) 'Stress and eating behaviors.', *Minerva endocrinologica*, 38(3), pp. 255–67. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24126546 (Accessed: 13 January 2018).
Yeboah, P. *et al.* (2019) 'Body Mass Index, Change in Weight, Body Weight Variability and Outcomes in Type 2 Diabetes Mellitus (from the ACCORD Trial)', *The American Journal of Cardiology*, 123(4), pp. 576–581. doi: 10.1016/j.amjcard.2018.11.016.
Yokomichi, H. *et al.* (2017) 'Weight cycling and the subsequent onset of type 2 diabetes mellitus: 10-year cohort studies in urban and rural Japan.', *BMJ open*, 7(5), p. e014684. doi: 10.1136/bmjopen-2016-014684.
Young, D. R. *et al.* (2009) 'Patterns of physical activity among overweight and obese adults.', *Preventing chronic disease*, 6(3), p. A90. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19527591 (Accessed: 16 July 2019).
Yu, Y., Deng, C. and Huang, X.-F. (2009) 'Obese reversal by a chronic energy restricted diet leaves an increased Arc NPY/AgRP, but no alteration in POMC/CART, mRNA expression in diet-induced obese mice', *Behavioural Brain Research*, 205(1), pp. 50–56. doi: 10.1016/j.bbr.2009.07.003.
Zamarron, B. F. (2017) 'Metabolic Abnormalities and Adipose Tissue Leukocyte Dynamics in a Murine Model of Obesity, Weight Loss, and Weight Regain'. Available at: https://deepblue.lib.umich.edu/bitstream/handle/2027.42/137037/zamarrbf_1.pdf?sequence=1&isAllowed=y (Accessed: 10 June 2018).
Zapka, J. *et al.* (2009) 'Factors related to weight loss behavior in a multiracial/ethnic workforce.', *Ethnicity & disease*, 19(2), pp. 154–60. Available at:

http://www.ncbi.nlm.nih.gov/pubmed/19537226 (Accessed: 6 December 2019).
Zeigler, Z. S. *et al.* (2018) 'Fatness and Fluctuating Body Weight: Effect on Central Vasculature', *Biores Open Access*, 7(1), pp. 90–100. doi: 10.1089/biores.2017.0044.
Zhan, C. *et al.* (2013) 'Acute and long-term suppression of feeding behavior by POMC neurons in the brainstem and hypothalamus, respectively', *Journal of Neuroscience*, 33(8), pp. 3624–3632. doi: 10.1523/JNEUROSCI.2742-12.2013.
Zhang, H. *et al.* (2005) 'Long-Term Body Weight Fluctuation is Associated With Metabolic Syndrome Independent of Current Body Mass Index Among Japanese Men', *Circulation Journal*, 69(1), pp. 13–18. doi: 10.1253/circj.69.13.
Zhang, J. and Yen, S. T. (2015) 'Physical Activity, Gender Difference, and Depressive Symptoms.', *Health services research*, 50(5), pp. 1550–73. doi: 10.1111/1475-6773.12285.
Zhang, Y. *et al.* (1994) 'Positional cloning of the mouse obese gene and its human homologue', *Nature*, 372(6505), pp. 425–432. doi: 10.1038/372425a0.
Zhang, Y. *et al.* (2017) 'Long-term weight-change slope, weight fluctuation and risk of type 2 diabetes mellitus in middle-aged Japanese men and women: Findings of Aichi Workers' Cohort Study', *Nutrition and Diabetes*, 7(3). doi: 10.1038/nutd.2017.5.
Zhang, Y. *et al.* (2019) 'The association between weight fluctuation and all-cause mortality', *Medicine*, 98(42), p. e17513. doi: 10.1097/MD.0000000000017513.
Zhang, Z. (2016) 'Variable selection with stepwise and best subset approaches', *Annals of Translational Medicine*, 4(7). doi: 10.21037/atm.2016.03.35.
Zheng, Y. *et al.* (2015a) 'Self-weighing in weight management: A systematic literature review', *Obesity*, 23(2), pp. 256–265. doi: 10.1002/oby.20946.
Zheng, Y. *et al.* (2015b) 'Self-weighing in weight management: A systematic literature review', *Obesity*. Blackwell Publishing Inc., pp. 256–265. doi: 10.1002/oby.20946.
Zoppini, G. *et al.* (2008) 'Variability of body weight, pulse pressure and glycaemia strongly predict total mortality in elderly type 2 diabetic patients. The Verona Diabetes Study', *Diabetes/Metabolism Research and Reviews*, 24(8), pp. 624–628. doi: 10.1002/dmrr.897.
Zou, H. *et al.* (2019a) 'Body-Weight Fluctuation Was Associated With Increased Risk for Cardiovascular Disease, All-Cause and Cardiovascular Mortality: A Systematic Review and Meta-Analysis', *Frontiers in Endocrinology*, 10, p. 728. doi: 10.3389/fendo.2019.00728.
Zou, H. *et al.* (2019b) 'Body-Weight Fluctuation Was Associated With Increased Risk for Cardiovascular Disease, All-Cause and Cardiovascular Mortality: A Systematic Review and Meta-Analysis', *Frontiers in Endocrinology*, 10, p. 728. doi: 10.3389/fendo.2019.00728.
de Zwaan, M. *et al.* (1994) 'Eating related and general psychopathology in obese females with binge eating disorder.', *The International journal of eating disorders*, 15(1), pp. 43–52. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8124326 (Accessed: 21 June 2018).
de Zwaan, M. (2001) 'Binge eating disorder and obesity', *International Journal of Obesity*, 25(1), pp. S51–S55. doi: 10.1038/sj.ijo.0801699.
de Zwaan, M., Engeli, S. and Müller, A. (2015a) 'Temperamental factors in severe weight cycling. A cross-sectional study', *Appetite*, 91, pp. 336–342. doi: 10.1016/J.APPET.2015.04.064.
de Zwaan, M., Engeli, S. and Müller, A. (2015b) 'Temperamental factors in severe weight cycling. A cross-sectional study', *Appetite*, 91, pp. 336–342. doi: 10.1016/j.appet.2015.04.064.

List of Abbreviations

ADP - Air Displacement Plethysmography

ANOVA – Analysis of Variance

ASSRKS - ARIMA state-space representation with Kalman Smoother

BIA – Bioeletrical Impedance Analysis

BMI – Body Mass Index

BPM – Beats Per Minute

BWV – Body Weight Variability

CCK – Cholecystokinin

CID – Clinical Investigation Day

CV – Coefficient of Variation

CVD – Cardiovascular Disease

DBP – Diastolic Blood Pressure

DiOGenes - Diet, Obesity, and Genes (trial)

DXA – Dual-Energy X-Ray Absorptiometry

EB – Energy Balance

EE – Energy Expenditure

EI – Energy Intake

EWMA – Exponentially Weighted Moving Average

FFM – Fat Free Mass

FFML – Fat Free Mass Loss

FM - Fat Mass

FML – Fat Mass Loss

GLP-1 – Glucagon-Like Peptide 1

HbA1c – Haemoglobin A1c

HDL – High Density Lipoprotein

KNN – K-Nearest Neighbours

LCD – Low Calorie Diet

LDL – Low Density Lipoprotein

LOESS – Locally Weighted Smoother

MAR – Missing At Random

MASWV – Mean Absolute Successive Weight Variability

MCAR – Missing Completely At Random

MJ – Megajoule

NEAT – Non-Exercise Activity Thermogenesis

NLMD – Non-Linear Mean Deviation

NMAR – Not Missing At Random

PA – Physical Activity

PAEE – Physical Activity Energy Expenditure

PMM – Predictive Means Matching

PYY – Peptide YY

RCT – Randomised Control Trial

RF – Random Forest

RHR – Resting Heart Rate

RMR – Resting Metabolic Rate

RMSE – Root Mean Square Error

RPM – Real Patterns of Missingness

SBP – Systolic Blood Pressure

SMKS – Structural Modelling with Kalman Smoother

T2D – Type 2 Diabetes

TEF – Thermic Effect of Food

V2V – Visit To Visit

VAS – Visual Analouge Scale

VLCD – Very Low Calorie Diet

WHO – World Health Organisation

WLM – Weight Loss Maintenance

Appendices

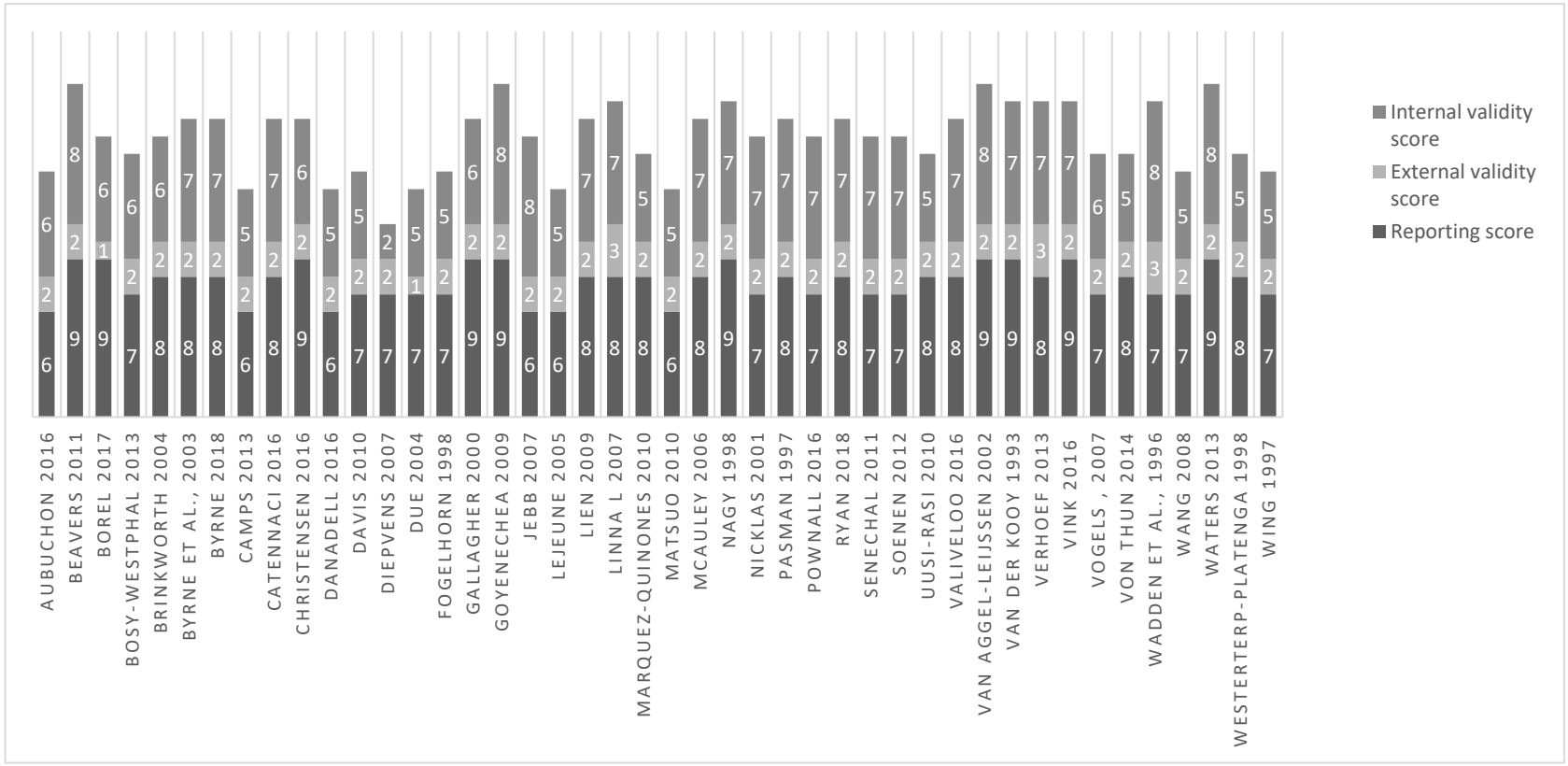
Appendix 2.1. Search Strategy

Appendix 2.1. Search Strategy

	Terms
1.	Weight adj (cycl* or regain or maintenance or loss maintenance)
2. AND	Body composition or body composition/ or fat-free mass/ or fat-free mass or fat mass or fat mass/ or ffm or lean body mass or lbm or body fat
3. NOT	Bariatric OR surgery OR sleeve OR laparoscopic
4.	Human studies in English language

Appendix 2.1. Search strategy used to perform a systematic search of the literature on MEDLINE, EMBASE and PubMed databases. A combination of the three searches was used as a final search. "/" indicates use of MeSH term.

Appendix 2.2: Bias Testing for Systematic Review and Meta-Analysis



Appendix 2.2. Risk of bias using a modified Downs and Black tool (Deeks et al., 2003). High, medium and low risk of bias were assessed as follows: high (>7 reporting; >1 external validity; >5 internal validity); medium (>3 reporting; >1 external validity; >3 internal validity) and low (<3 reporting; <1 external validity; <3 internal validity).

Appendix 2.3 Test of Collinearity for Model 3 Variables

Variables	Tolerance	VIF
All		
1 Weight loss	0.631	1.59
2 factor(diet.group)2	0.620	1.61
3 factor(diet.group)3	0.566	1.77
4 factor(diet.group)4	0.588	1.70
5 factor(diet.group)5	0.582	1.72
6 factor(centre)1	0.462	2.16
7 factor(centre)2	0.547	1.83
8 factor(centre)3	0.879	1.14
9 Baseline weight	0.580	1.73
10 Baseline body fat	0.817	1.22
11 %FFML	0.700	1.43
Males		
Variables	Tolerance	VIF
1 weight loss	0.759	1.32
2 factor(diet.group)2	0.576	1.74
3 factor(diet.group)3	0.436	2.29
4 factor(diet.group)4	0.528	1.90
5 factor(diet.group)5	0.511	1.96
6 factor(centre)1	0.329	3.04
7 factor(centre)2	0.437	2.29
8 factor(centre)3	0.854	1.17
9 Baseline weight	0.495	2.02
10 Baseline body fat	0.528	1.89
11 %FFML	0.681	1.47
Females		
Variables	Tolerance	VIF
1 Weight loss	0.600	1.67
2 factor(diet.group)2	0.599	1.67
3 factor(diet.group)3	0.578	1.73
4 factor(diet.group)4	0.595	1.68
5 factor(diet.group)5	0.575	1.74
6 factor(centre)1	0.444	2.25
7 factor(centre)2	0.566	1.77
8 factor(centre)3	0.818	1.22
9 Baseline weight	0.482	2.08
10 Baseline body fat	0.492	2.03
11 %FFML	0.738	1.35

Supplementary table. Showing variance inflation factors (VIF) and tolerance as a test of multi-collinearity for variables included in model 3 for all, male and female groups.

Appendix 2.4: Supplementary Analysis 1 - Associations between appetite perception responses and subsequent weight regain.

In order to fully explore a model in which percentage fat free mass loss (%FFML) is predictive of weight regain by producing increased appetite, we examined the effect of changes in appetite of weight regain at 26 weeks, though mediation analysis was not possible due to the low sample size.

Methods

A sample of 40 individuals (males = 17, females = 23) used previously in the second analysis of the main study was used. In short, these individuals attended both clinical investigation day (CID) 1 in which appetite was measured by visual analogue scale in response to a fixed pasta-based test meal providing 1.6MJ of energy. Next, they were provided with an 8-week low calorie diet (LCD) and those who achieved at least 8% body weight loss attended CID2 where appetite measurements were taken again. Therefore, these individuals had data on both (1) change in appetite and (2) weight change at 26 weeks. We tested the association between these two variables using Pearson correlation. We were limited to basic correlation analyses and were unable to produce multivariate models due to the low sample sizes.

Results and discussion

The results can be found below in supplementary table 4. Weak correlation values were observed for all but one association which was significant (prospective consumption in men). All associations were generally in a direction representative of increased appetite (i.e. generally those with greater overall increases in appetite during the low-calorie diet

regained more weight at 26 weeks) though due to a low sample size most of these did not reach significance. The present relationships examined require further study in trials designed to test associations between functional changes in body composition, appetite and weight outcomes.

Supplementary table . Correlations between changes in appetite markers during LCD and weight regain at 26 weeks

Change in appetite measure	Weight regain					
	All (n=40)		Males (n=17)		Females (n=23)	
	R	p-value	R	p-value	R	p-value
Fullness	-0.22	0.171	-0.32	0.211	-0.17	0.453
Hunger	0.18	0.253	0.32	0.204	0.18	0.412
Desire to eat	0.18	0.267	0.36	0.153	0.19	0.389
Prospective consumption	0.19	0.241	0.52	0.031	0.07	0.744

Supplementary table. Correlation and associated p-values for Pearson correlation between change in appetite perceptions (collected by visual analogue scale in response to a test meal before and after an 8-week low calorie diet) and weight change at 26-week follow-up period in 40 individuals

Appendix 2.5: Supplementary Analysis 2 - Associations of reduction in fat-free mass (FFM) and fat mass (FM) from baseline on weight change and appetite.

Introduction

Weight loss produces proportionate changes in fat mass FM and FFM compartments which change dependent on one another and are therefore an integrated response. For this reason, we examined the effect of proportionate change in both compartments using:

$$\%FFML = (\Delta FFM/\Delta weight)*100$$

In which case we can assume that:

$$\%FML = 100 - \%FFML$$

Or:

$$\%FML = (\Delta FM/\Delta weight)*100$$

However, it may be the case that a signal influencing appetite and/or weight regain arises independently from a change in one single compartment, rather than a proportional change. To examine this further, we define changes in FFM and FM from baseline during the 8-week LCD and their effects on subsequent weight at follow-up and appetite changes.

Methods

We termed the reduction in FFM and FM from baseline as “independent %FFML” (denoted by dFFM) and “independent %FML” (denoted by dFM) (though we are aware these are not physiologically independent). These were calculated as follows:

$$dFFML = (\Delta FFM / \text{baseline FFM}) * 100$$

$$dFML = (\Delta FM / \text{baseline FM}) * 100$$

Both dFFM and dFM were entered into our final adjusted models (from the primary analysis of the current paper) predicting weight change at 26 weeks in place of the original in place of our main predictor variable (integrated %FFML). The results are presented in supplementary table 5.

Next, we examined the effect of dFFM and dFM on changes in appetite markers before and after the low-calorie diet (LCD). We plotted these in figures 1 and 2 respectively, and these plots show independent %FFML adjusted for independent %FML and vice versa.

Results & discussion

We observed no clear associations between either % change in FFM nor FM from baseline. We did observe a tendency for independent reduction in FFM to increase weight regain at 26 weeks in men (β = 1.01 (-0.05, 2.06), p=0.065) though this was not seen in the whole group or in females. Similar to the primary results, baseline factors (e.g. initial weight and

body fat) were generally predictive of weight regain, and to a lesser extent weight loss (again, in males and less so females).

With regards to change in appetite perceptions, the associations between independent change in FFM and FM (adjusted for one another) can be seen in figures 1A-C for FFM and 2A-C for FM for all individuals (A), males (B) and females (C). For independent reduction in FFM, the results generally suggested that increase loss of FFM from baseline was associated with an increase in appetite perceptions. Again, this result was more prominent in males than females. In contrast, there was no associations between reductions in FM in comparison to baseline and appetitive changes.

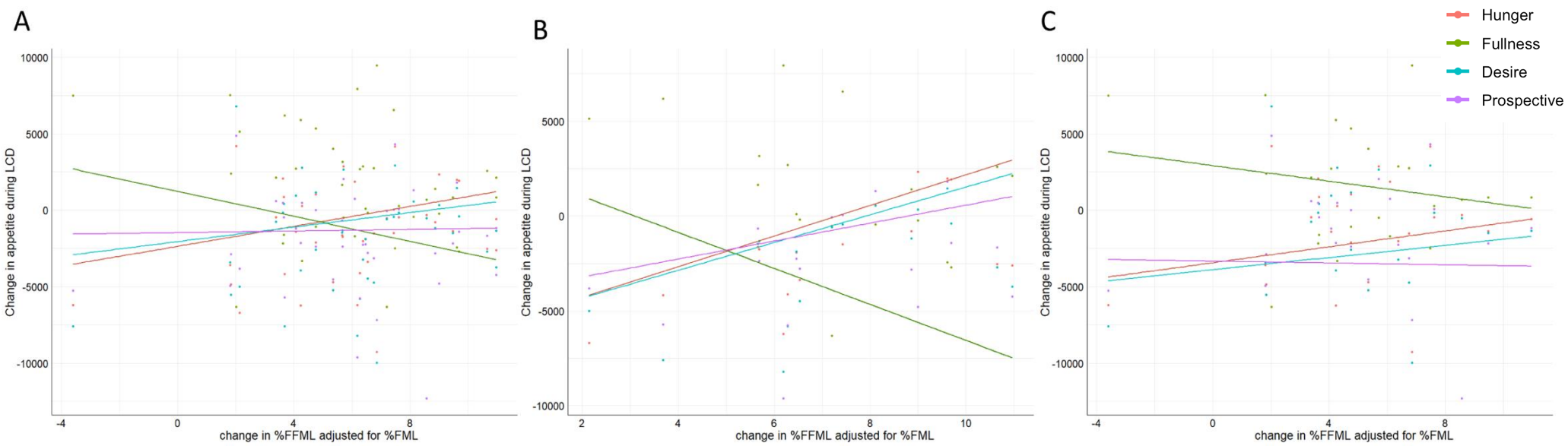
Similar to the main analyses, the present results are both inconsistent (i.e. presence of gender differences) and weak. However, they are consistent with the main results that there is potentially a signal generated by reduction in FFM compartments which influence appetite in a manner which promotes weight regain. Further study is required to investigate these effects using high resolution body composition models.

Supplementary table. Multivariate linear regression models predicting weight regain at 26 weeks

	All (n=209)			Males (n=77)			Females (n=132)		
Predictor	β Coefficient (95% CI)	P-value	Adjusted R^2	β Coefficient (95% CI)	P-value	Adjusted R^2	β Coefficient (95% CI)	P-value	Adjusted R^2
Multivariate model*		<0.001	21.3%		<0.001	32.4%		0.010	10.8%
Baseline weight (kg)	0.09 (0.01, 0.18)	0.032		0.23 (0.08, 0.38)	0.004		0.10 (-0.06, 0.25)	0.219	
Baseline body fat (%)	-0.22 (-0.35, -0.08)	0.002		-0.28 (-0.63, 0.06)	0.111		0.02 (-0.27, 0.31)	0.873	
Weight loss (kg)	0.65 (-0.08, 1.38)	0.083		1.54 (0.24, 2.85)	0.024		1.12 (-0.33, 2.56)	0.132	
dFFM (%)	0.17 (-0.31, 0.64)	0.496		1.01 (-0.05, 2.06)	0.065		0.30 (-0.48, 1.08)	0.448	
dFM (%)	-0.003 (-0.29, 0.28)	0.986		0.23 (-0.24, 0.71)	0.337		0.23 (-0.35, 0.81)	0.436	

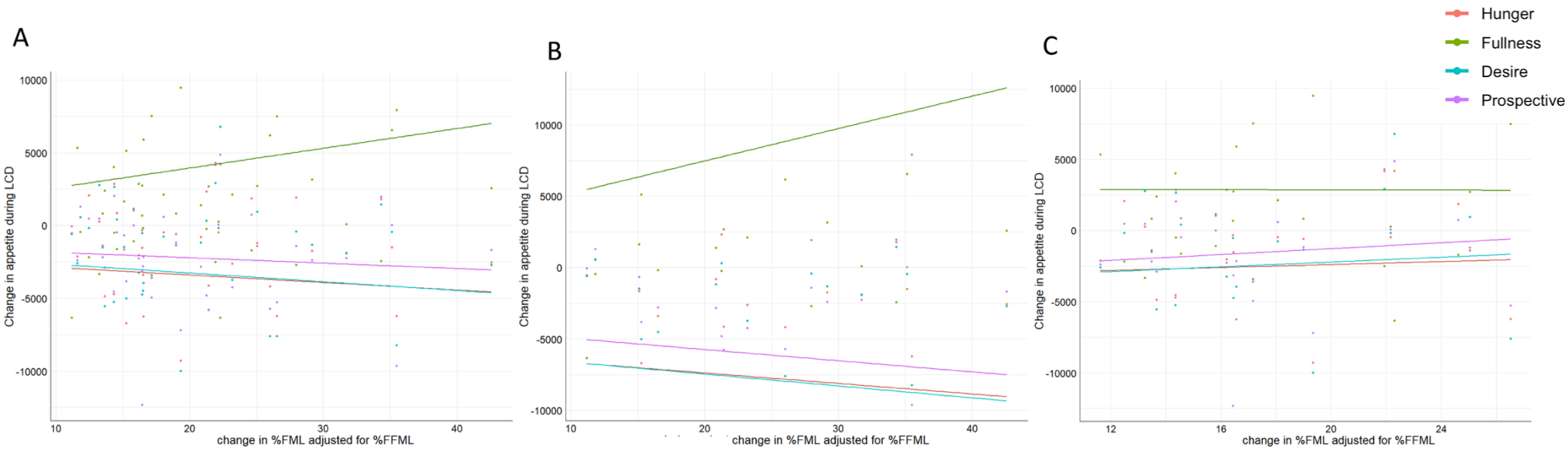
Supplementary table. Multivariate linear regression model predicting weight change at 26 weeks. *Model adjusted for dietary arm and trial centre. Abbreviations; Independent change in fat free mass (dFFM); Independent change in fat mass (dFM). Each unstandardised beta-coefficient represents 1kg weight change at 26 weeks per unit of the predictor variable. For example, a beta value of 0.65 (-0.08, 1.38) kg for weight loss means that for every 1kg of weight regained, an average of 0. 65 kg (ranging from -0.08 – 1.38kg of weight was lost).

Supplementary figure: Associations between reductions in FFM from baseline and change in appetite perceptions



Supplementary figure: Scatterplots and linear trendlines showing associations between loss of fat-free mass relative to baseline (adjusted for reductions in fat mass from baseline) during an 8-week LCD and changes in appetite during the 8 weeks. Results are reported for hunger (red), fullness (green), desire to eat (blue) and prospective consumption (purple). Scores were calculated as the total difference in area under of curve from 8 repeated measures around a fixed test meal, and change scores were calculated as the difference between clinical investigation day 1 and 2. Abbreviations; visual analogue scale (VAS), area under curve (AUC), percentage fat-free mass loss (%FFML) percentage fat mass loss (%FML).

Supplementary figure: Associations between reductions in FM from baseline and change in appetite perceptions



Supplementary figure: Scatterplots and linear trendlines showing associations between loss of fat mass relative to baseline (adjusted for reductions in fat-free mass from baseline) during an 8-week LCD and changes in appetite during the 8 weeks in all individuals (A, n=40); males (B; n=17) and C. Results are reported for hunger (red), fullness (green), desire to eat (blue) and prospective consumption (purple). Scores were calculated as the total difference in area under of curve from 8 repeated measures around a fixed test meal, and change scores were calculated as the difference between clinical investigation day 1 and 2. Abbreviations; visual analogue scale (VAS), area under curve (AUC), percentage fat mass loss (%FML), percentage fat free mass loss (%FFML).

Appendix 6.1 Tukey Post Hoc Results for Day of Week Comparisons

Day of Week	Comparison	Coefficient	Error	T-Value	P-value
		Gender			
Mon	Female - Male	-0.074	0.011	-6.666	<0.001
Tues	Female - Male	0.003	0.011	0.253	0.801
Wed	Female - Male	0.037	0.011	3.559	<0.001
Thurs	Female - Male	0.024	0.011	2.212	0.027
Fri	Female - Male	0.016	0.011	1.493	0.135
Sat	Female - Male	0.009	0.012	0.711	0.477
Sun	Female - Male	-0.027	0.013	-2.048	0.041
		Centre			
Mon	Portugal - Denmark	0.086	0.012	6.936	<0.001
Mon	UK - Denmark	0.011	0.012	0.841	0.678
Mon	UK - Portugal	-0.076	0.012	-5.940	<0.001
Tues	Portugal - Denmark	0.015	0.012	1.238	0.431
Tues	UK - Denmark	0.007	0.012	0.575	0.833
Tues	UK - Portugal	-0.008	0.012	-0.646	0.795
Wed	Portugal - Denmark	-0.005	0.012	-0.421	0.907
Wed	UK - Denmark	-0.004	0.012	-0.334	0.94
Wed	UK - Portugal	0.001	0.012	0.079	0.997
Thurs	Portugal - Denmark	0.016	0.012	1.366	0.359
Thurs	UK - Denmark	0.014	0.012	1.130	0.496
Thurs	UK - Portugal	-0.003	0.012	-0.210	0.976
Fri	Portugal - Denmark	-0.015	0.012	-1.214	0.445
Fri	UK - Denmark	-0.002	0.012	-0.180	0.982
Fri	UK - Portugal	0.012	0.012	1.000	0.577
Sat	Portugal - Denmark	-0.074	0.014	-5.439	<0.001
Sat	UK - Denmark	-0.042	0.014	-3.139	0.005
Sat	UK - Portugal	0.032	0.014	2.297	0.056
Sun	Portugal - Denmark	-0.038	0.014	-2.634	0.023
Sun	UK - Denmark	-0.011	0.014	-0.732	0.745
Sun	UK - Portugal	0.027	0.014	1.844	0.155
		BMI Status			
Mon	Obese C1 - Healthy weight	-0.048	0.016	-2.997	0.014
Mon	Obese C2-3 - Healthy weight	-0.093	0.016	-5.048	<0.0010
Mon	Overweight - Healthy weight	-0.010	0.016	-0.692	0.898
Mon	Obese C2-3 - Obese C1	-0.045	0.016	-2.590	0.046
Mon	Overweight - Obese C1	0.038	0.016	2.922	0.018
Mon	Overweight - Obese C2-3	0.083	0.016	5.226	<0.001
Tues	Obese C1 - Healthy weight	-0.019	0.015	-1.259	0.584
Tues	Obese C2-3 - Healthy weight	-0.011	0.015	-0.612	0.927
Tues	Overweight - Healthy weight	0.011	0.015	0.773	0.864
Tues	Obese C2-3 - Obese C1	0.008	0.015	0.504	0.957

Tues	Overweight - Obese C1	0.030	0.015	2.385	0.078
Tues	Overweight - Obese C2-3	0.021	0.015	1.398	0.496
Wed	Obese C1 - Healthy weight	0.011	0.015	0.725	0.885
Wed	Obese C2-3 - Healthy weight	0.038	0.015	2.176	0.127
Wed	Overweight - Healthy weight	0.003	0.015	0.222	0.996
Wed	Obese C2-3 - Obese C1	0.027	0.015	1.610	0.368
Wed	Overweight - Obese C1	-0.008	0.015	-0.639	0.918
Wed	Overweight - Obese C2-3	-0.035	0.015	-2.296	0.097
Thurs	Obese C1 - Healthy weight	0.009	0.015	0.621	0.924
Thurs	Obese C2-3 - Healthy weight	0.011	0.015	0.603	0.93
Thurs	Overweight - Healthy weight	0.007	0.015	0.541	0.948
Thurs	Obese C2-3 - Obese C1	0.001	0.015	0.075	1
Thurs	Overweight - Obese C1	-0.002	0.015	-0.167	0.998
Thurs	Overweight - Obese C2-3	-0.003	0.015	-0.217	0.996
Fri	Obese C1 - Healthy weight	0.031	0.015	1.999	0.184
Fri	Obese C2-3 - Healthy weight	0.050	0.015	2.796	0.026
Fri	Overweight - Healthy weight	-0.007	0.015	-0.548	0.946
Fri	Obese C2-3 - Obese C1	0.019	0.015	1.116	0.675
Fri	Overweight - Obese C1	-0.038	0.015	-3.025	0.013
Fri	Overweight - Obese C2-3	-0.057	0.015	-3.697	0.001
Sat	Obese C1 - Healthy weight	0.044	0.017	2.525	0.055
Sat	Obese C2-3 - Healthy weight	0.018	0.017	0.894	0.805
Sat	Overweight - Healthy weight	0.016	0.017	1.024	0.731
Sat	Obese C2-3 - Obese C1	-0.026	0.017	-1.367	0.515
Sat	Overweight - Obese C1	-0.028	0.017	-1.963	0.198
Sat	Overweight - Obese C2-3	-0.002	0.017	-0.114	0.999
Sun	Obese C1 - Healthy weight	-0.021	0.019	-1.114	0.677
Sun	Obese C2-3 - Healthy weight	-0.023	0.019	-1.104	0.683
Sun	Overweight - Healthy weight	-0.026	0.019	-1.568	0.392
Sun	Obese C2-3 - Obese C1	-0.003	0.019	-0.132	0.999
Sun	Overweight - Obese C1	-0.005	0.019	-0.327	0.988
Sun	Overweight - Obese C2-3	-0.002	0.019	-0.127	0.999
	Age Group				
Mon	30 to 45 - under 30	0.083	0.019	4.273	<0.001
Mon	46 to 60 - under 30	0.019	0.019	0.990	0.746
Mon	over 60 - under 30	-0.027	0.019	-1.157	0.643
Mon	46 to 60 - 30 to 45	-0.063	0.019	-5.536	<0.001
Mon	over 60 - 30 to 45	-0.110	0.019	-6.374	<0.001
Mon	over 60 - 46 to 60	-0.046	0.019	-2.661	0.037
Tues	30 to 45 - under 30	-0.022	0.019	-1.168	0.635
Tues	46 to 60 - under 30	-0.033	0.019	-1.748	0.286
Tues	over 60 - under 30	-0.075	0.019	-3.323	0.004
Tues	46 to 60 - 30 to 45	-0.011	0.019	-1.026	0.724
Tues	over 60 - 30 to 45	-0.053	0.019	-3.236	0.006
Tues	over 60 - 46 to 60	-0.042	0.019	-2.533	0.051
Wed	30 to 45 - under 30	-0.036	0.018	-1.931	0.205

Wed	46 to 60 - under 30	-0.025	0.018	-1.323	0.535
Wed	over 60 - under 30	-0.074	0.018	-3.333	0.004
Wed	46 to 60 - 30 to 45	0.011	0.018	1.020	0.728
Wed	over 60 - 30 to 45	-0.039	0.018	-2.362	0.08
Wed	over 60 - 46 to 60	-0.050	0.018	-3.001	0.013
Thurs	30 to 45 - under 30	-0.009	0.019	-0.486	0.96
Thurs	46 to 60 - under 30	0.023	0.019	1.191	0.62
Thurs	over 60 - under 30	0.012	0.019	0.550	0.944
Thurs	46 to 60 - 30 to 45	0.032	0.019	2.889	0.019
Thurs	over 60 - 30 to 45	0.022	0.019	1.304	0.547
Thurs	over 60 - 46 to 60	-0.010	0.019	-0.604	0.927
Fri	30 to 45 - under 30	-0.024	0.019	-1.253	0.58
Fri	46 to 60 - under 30	0.037	0.019	1.949	0.198
Fri	over 60 - under 30	0.085	0.019	3.712	0.001
Fri	46 to 60 - 30 to 45	0.061	0.019	5.518	<0.001
Fri	over 60 - 30 to 45	0.108	0.019	6.496	<0.001
Fri	over 60 - 46 to 60	0.048	0.019	2.815	0.023
Sat	30 to 45 - under 30	0.020	0.022	0.942	0.773
Sat	46 to 60 - under 30	0.040	0.022	1.823	0.251
Sat	over 60 - under 30	0.102	0.022	3.953	<0.001
Sat	46 to 60 - 30 to 45	0.019	0.022	1.547	0.396
Sat	over 60 - 30 to 45	0.081	0.022	4.392	<0.001
Sat	over 60 - 46 to 60	0.062	0.022	3.349	0.004
Sun	30 to 45 - under 30	0.009	0.023	0.406	0.976
Sun	46 to 60 - under 30	-0.037	0.023	-1.627	0.351
Sun	over 60 - under 30	0.023	0.023	0.848	0.824
Sun	46 to 60 - 30 to 45	-0.047	0.023	-3.505	0.002
Sun	over 60 - 30 to 45	0.014	0.023	0.700	0.892
Sun	over 60 - 46 to 60	0.060	0.023	3.081	0.01

Appendix 6.2 Tukey Post Hoc Results for Christmas Comparisons

Group	Comparison	Coefficients	Error	T-stat	P-Value
Gender	Female - Male	0.066	0.120	0.552	0.581
Centre	Portugal - Denmark	-0.164	0.128	-1.283	0.405
	UK - Denmark	0.228	0.122	1.864	0.150
	UK - Portugal	0.392	0.129	3.036	0.007
BMI group	Healthy weight - Obese C2-3	-0.118	0.192	-0.614	0.926
	Overweight - Obese C2-3	-0.004	0.166	-0.024	1.000
	Obese C1 - Obese C2-3	0.074	0.182	0.404	0.977
	Overweight - Healthy weight	0.114	0.152	0.750	0.875
	Obese C1 - Healthy weight	0.191	0.169	1.130	0.667
	Obese C1 - Overweight	0.078	0.139	0.557	0.944
Age group	46 to 60 - 30 to 45	-0.080	0.118	-0.675	0.902
	over 60 - 30 to 45	0.006	0.177	0.036	1.000
	under 30 - 30 to 45	-0.312	0.190	-1.641	0.344
	over 60 - 46 to 60	0.086	0.178	0.484	0.961
	under 30 - 46 to 60	-0.232	0.191	-1.215	0.606
	under 30 - over 60	-0.318	0.232	-1.372	0.505

Appendix 6.3 Tukey Post Hoc Results for Between Season Comparisons

Season	Comparison	Coefficients	Error	T-Value	P-Value
	Gender				
Winter to Spring	Female - Male	-0.096	0.042	-2.306	0.021
Spring to Summer	Female - Male	0.054	0.041	1.306	0.192
Summer to Autumn	Female - Male	0.039	0.050	0.791	0.429
Autumn to Winter	Female - Male	0.004	0.031	0.123	0.902
	Centre				
Winter to Spring	Portugal - Denmark	0.106	0.048	2.206	0.07
Winter to Spring	UK - Denmark	-0.071	0.046	-1.547	0.269
Winter to Spring	UK - Portugal	-0.177	0.047	-3.775	0
Spring to Summer	Portugal - Denmark	-0.106	0.048	-2.220	0.068
Spring to Summer	UK - Denmark	-0.180	0.046	-3.958	0
Spring to Summer	UK - Portugal	-0.074	0.046	-1.609	0.242
Summer to Autumn	Portugal - Denmark	-0.038	0.057	-0.672	0.78
Summer to Autumn	UK - Denmark	0.155	0.054	2.872	0.011
Summer to Autumn	UK - Portugal	0.194	0.056	3.454	0.002
Autumn to Winter	Portugal - Denmark	0.009	0.035	0.246	0.967
Autumn to Winter	UK - Denmark	0.045	0.034	1.321	0.383
Autumn to Winter	UK - Portugal	0.036	0.034	1.043	0.549
	BMI Status				
Winter to Spring	Obese C1 - Healthy weight	-0.175	0.060	-2.946	0.017
Winter to Spring	Obese C2-3 - Healthy weight	-0.131	0.069	-1.896	0.226
Winter to Spring	Overweight - Healthy weight	-0.034	0.054	-0.626	0.922
Winter to Spring	Obese C2-3 - Obese C1	0.044	0.065	0.673	0.905
Winter to Spring	Overweight - Obese C1	0.142	0.048	2.934	0.017
Winter to Spring	Overweight - Obese C2-3	0.098	0.060	1.632	0.356
Spring to Summer	Obese C1 - Healthy weight	0.007	0.059	0.115	0.999
Spring to Summer	Obese C2-3 - Healthy weight	-0.068	0.068	-1.005	0.742
Spring to Summer	Overweight - Healthy weight	-0.037	0.053	-0.702	0.894
Spring to Summer	Obese C2-3 - Obese C1	-0.075	0.064	-1.169	0.642
Spring to Summer	Overweight - Obese C1	-0.044	0.048	-0.915	0.793
Spring to Summer	Overweight - Obese C2-3	0.031	0.059	0.532	0.95
Summer to Autumn	Obese C1 - Healthy weight	0.034	0.071	0.473	0.964
Summer to Autumn	Obese C2-3 - Healthy weight	0.182	0.081	2.233	0.112
Summer to Autumn	Overweight - Healthy weight	0.008	0.064	0.123	0.999
Summer to Autumn	Obese C2-3 - Obese C1	0.148	0.076	1.938	0.209
Summer to Autumn	Overweight - Obese C1	-0.026	0.057	-0.448	0.969
Summer to Autumn	Overweight - Obese C2-3	-0.174	0.070	-2.486	0.061
Autumn to Winter	Obese C1 - Healthy weight	0.107	0.044	2.446	0.067
Autumn to Winter	Obese C2-3 - Healthy weight	0.033	0.050	0.662	0.91
Autumn to Winter	Overweight - Healthy weight	0.061	0.039	1.556	0.399
Autumn to Winter	Obese C2-3 - Obese C1	-0.074	0.047	-1.563	0.395
Autumn to Winter	Overweight - Obese C1	-0.046	0.035	-1.293	0.563

Autumn to Winter	Overweight - Obese C2-3	0.028	0.043	0.647	0.915
	Age Group				
Winter to Spring	46 to 60 - 30 to 45	-0.045	0.043	-1.032	0.722
Winter to Spring	over 60 - 30 to 45	-0.165	0.066	-2.494	0.058
Winter to Spring	under 30 - 30 to 45	0.114	0.067	1.687	0.32
Winter to Spring	over 60 - 46 to 60	-0.120	0.067	-1.791	0.268
Winter to Spring	under 30 - 46 to 60	0.158	0.069	2.310	0.091
Winter to Spring	under 30 - over 60	0.279	0.085	3.283	0.005
Spring to Summer	46 to 60 - 30 to 45	-0.027	0.043	-0.630	0.919
Spring to Summer	over 60 - 30 to 45	-0.045	0.065	-0.688	0.898
Spring to Summer	under 30 - 30 to 45	-0.071	0.067	-1.057	0.706
Spring to Summer	over 60 - 46 to 60	-0.018	0.066	-0.271	0.993
Spring to Summer	under 30 - 46 to 60	-0.044	0.068	-0.647	0.913
Spring to Summer	under 30 - over 60	-0.026	0.084	-0.311	0.989
Summer to Autumn	46 to 60 - 30 to 45	0.101	0.051	1.973	0.19
Summer to Autumn	over 60 - 30 to 45	0.202	0.078	2.606	0.043
Summer to Autumn	under 30 - 30 to 45	0.000	0.078	0.004	1
Summer to Autumn	over 60 - 46 to 60	0.101	0.079	1.278	0.566
Summer to Autumn	under 30 - 46 to 60	-0.101	0.079	-1.275	0.568
Summer to Autumn	under 30 - over 60	-0.202	0.098	-2.053	0.162
Autumn to Winter	46 to 60 - 30 to 45	-0.002	0.032	-0.068	1
Autumn to Winter	over 60 - 30 to 45	0.017	0.048	0.347	0.985
Autumn to Winter	under 30 - 30 to 45	-0.019	0.049	-0.386	0.98
Autumn to Winter	over 60 - 46 to 60	0.019	0.049	0.385	0.98
Autumn to Winter	under 30 - 46 to 60	-0.017	0.049	-0.336	0.986
Autumn to Winter	under 30 - over 60	-0.035	0.061	-0.579	0.936

Appendix 7.1 – DXA Sub-analysis

Supplementary Analysis. Analysis of body composition outcomes in sub-sample

In addition to bioelectrical impedance analysis (BIA), we measured body composition by dual-energy X-ray absorptiometry (DXA) at two centres: Portugal (Hologic Explorer-W, Waltham, USA) and Denmark (Norland XR-800, Swissray, USA). This generated a sub-sample of participants eligible for this analysis (n=439). The relevant characteristics for this sample are given in supplementary table 3. These individuals gained 0.9 (6.2) kg, accompanied by a 0.06 (4.7) % increase in body fat.

Supplementary table 1. Characteristics of sub-samples with available DXA measurements

	All (n=439)	Male (n=122)	Female (n=317)	P value
Country (%)				
Denmark	329 (74.9)	59 (48.4)	270 (85.2)	<0.001
Portugal	110 (25.1)	63 (51.6)	47 (14.8)	
Age (years)	46.2 (11.5)	45.8 (12.0)	46.4 (11.3)	0.595
BMI (kg/m2)	29.7 (5.0)	29.4 (4.6)	29.9 (5.2)	0.35
Initial steps	10693.8 (3481.5)	11273.6 (3915.4)	10470.6 (3278.8)	0.03
Weight (kg)	85.7 (16.7)	93.0 (17.3)	82.9 (15.6)	<0.001
Initial body fat (%)	28.4 (8.4)	21.5 (7.7)	31.1 (7.0)	<0.001

We modelled response in bodyfat using three multivariate linear regression models similar to the full sample, using a pre-post approach in which the post value was the dependent variable and the pre-value was included as a covariate. Model 1 included weight change, weight variability (with separate models for each of the 4 measures used) and baseline value; model 2 included model 1 and additionally adjusted for baseline BMI, age and gender; model 3 included model 2 and additionally adjusted for initial and change in physical activity over 12 months.

The results from each of the models are given in supplementary table 4. Weight change was directly associated with change in body fat ($p<0.001$ for all analyses) which explained between 9-11% of the variance. Significant, negative associations between BWV

(by CV and RMSE) were observed in all models ($p<0.05$ for all), though these explained <0.5% of the change in body fat. No associations were observed for other measures of BWV.

Supplementary table 2. Multivariate linear regression results predicting change in body fat (%) measured by DXA

		Bodyfat (DXA)		
Model	Predictor	β (SE)	P-value	ΔR2
1	NLMD	-1.58 (0.77)	0.055	0.002
	Weight change	0.47 (0.03)	<0.001	0.111
	CV	-0.5 (0.14)	<0.001	0.005
	Weight change	0.45 (0.03)	<0.001	0.1
	RMSE	-0.77 (0.27)	0.007	0.003
	Weight change	0.45 (0.03)	<0.001	0.097
	MASWV	-0.57 (0.69)	0.537	0
	Weight change	0.47 (0.03)	<0.001	0.11
2	NLMD	-1.6 (0.81)	0.112	0.001
	Weight change	0.47 (0.03)	<0.001	0.111
	CV	-0.48 (0.14)	0.001	0.004
	Weight change	0.46 (0.03)	<0.001	0.1
	RMSE	-0.76 (0.28)	0.016	0.003
	Weight change	0.45 (0.03)	<0.001	0.096
	MASWV	-0.6 (0.69)	0.543	0
	Weight change	0.48 (0.03)	<0.001	0.111
3	NLMD	-1.58 (0.81)	0.127	0.001
	Weight change	0.47 (0.03)	<0.001	0.105
	CV	-0.47 (0.14)	0.003	0.004
	Weight change	0.45 (0.03)	<0.001	0.096
	RMSE	-0.73 (0.28)	0.027	0.003
	Weight change	0.45 (0.03)	<0.001	0.092
	MASWV	-0.6 (0.69)	0.501	0
	Weight change	0.47 (0.03)	<0.001	0.105

Supplementary table 2. Multivariate linear regression results from three models predicting body fat measured by DXA after 12-months of weight maintenance intervention. Beta (β)

coefficients are standardised with associated standard errors. ΔR2 describes the changes in outcome variance explained when the predictor is added to the full model. Model 1 is adjusted for baseline values; model 2 is adjusted for model 1 and baseline BMI, age and gender; model 3 is adjusted for model 3 and initial and change in physical activity. Abbreviations; NLMD, non-linear mean deviation; CV, co-efficient of variation; RMSE, root-mean square-error; MASWV, mean average successive weight variability.

Appendix 7.2 – Longitudinal Sensitivity Analyses

Rationale for sensitivity analysis

In the primary analysis we are limited by the lack of temporal separation between the primary exposure of interest (body weight variability (BWV)) and the outcome. Resultantly, the analysis is subject to similar limitations of a cross-sectional design, in that we cannot infer causality in the associations examined. In order to address this limitation, we opted to design a sensitivity analysis with a true longitudinal structure, in which weight change and BWV in the first six months of the trial is used to predict change in outcomes from months 6 to 12.

Methods

Participants

A sample of the total NoHoW group who had available data for outcome and covariate measures at 0, 6 and 12-months were analysed (n=1028). Sufficient data must have been available for outcome measures, scales data and physical activity data. By excluding some cardiometabolic outcomes due to availability of data at 6-months (details below), the sample size increased from the primary analysis.

Measures

Since blood lipids, (cholesterols and triglycerides), HbA1c and body composition measured by dual x-ray absorptiometry were only available at visits 0 and 12, we were not able to include these in this current sensitivity analysis. Therefore, the outcome measures in this analysis were: systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), percentage body fat (by bioelectrical impedance analysis (BIA)) and waist to hip ratio (WHR). Systolic and diastolic BP and resting heart rate (RHR) were recorded every 6 months by a Microlife BP A2 blood pressure monitor after resting in a sitting position for 10 minutes. Three readings were taken, and the average values were used. Body composition was estimated at baseline, 6 and 12 months by bio-impedance analysis (BIA) using the ImpediMed SFB7 multifrequency bio-impedance analyser in all three centres following the manufacturer's instructions and by dual-energy X-ray absorptiometry (DXA) at two centres: Portugal (Hologic Explorer-W, Waltham, USA) and Denmark (Norland XR-800, Swissray, USA). Estimates of body composition byio-electrical impedance were transformed using Moissl equations (Moissl *et al.*, 2006). Percent body fat was calculated by dividing fat (kg) by

body weight (kg) and multiplying by 100. A tape measure was used to record the hip and waist circumference to the nearest centimetre. The waist–hip ratio (WHR) was calculated by dividing hip and waist circumference.

Weight variability

Body weight variability (BWV) was measured using the same four methods as in the primary analysis (methods detailed in supplementary material 2). However, BWV was measured over the first 6-months, and participants were required to have ≥ 15 weight measurements during this period.

Physical activity

Physical activity (PA) was measured using the same method as in the primary analysis (method detailed in supplementary material 1). However, PA metrics were produced for months 6-12 in order to adjust for the confounding effect of PA on health and body composition during the outcome period. We required a minimum of 16 weeks of data over the last 26 weeks of the measurement period.

Statistical analysis

Implausible physiological data were treated as outliers and removed. Body weight data from scales was screened for outliers based on limits of physiologically plausibility of weight change. All key variables were assessed for normality via visual inspection of QQ plots and histograms. Characteristics of the population at baseline were described by mean and standard deviation in the whole group and by gender due to known differences in physiological variables (particularly body composition) between genders. Differences between genders were tested using student t-tests (for continuous variables) and chi-squared tests (for categorical variables).

Similar to the primary analysis, three statistical models were generated to test the effect of body weight predictor variables on outcomes. First, a crude model including weight variability and relative weight change over 0-6 months (using different models for each method), and outcome value at 6 months was used to predict outcome at 12 months. Next, model 2 adjusted for model 1 and baseline factors (age, gender, BMI) and lastly model 3, adjusted for model 2 and initial and change in physical activity (steps) (due to the known confounding effect on physical activity on the relationship between weight, health and body composition). We have not reported the influence of weight change from 0-6 months on change in health markers, as our hypotheses are related to BWV. All p-values within models

were adjusted for multiple comparisons using the Bonferroni-Holt method. Model results are given in table 2 which summarise the effects of BWV on outcome variables using standardized β-coefficients, standard errors p-values. In order to compare the effect size of BWV estimates and weight change on outcomes, we calculated the change in the R^2 value of the model when the variable of interest (BWV estimate or weight change) was added to the model (which was complete except this variable); these values are summarized in figures 1-2. Significant effects were observed at $p<0.05$.

Results

The characteristics of the sample are presented in table 1. A total of 1028 (719 females) met the criteria for inclusion. On average, participants were aged 45.5 (±11.7) years, overweight (BMI=29.4 (±5.0) kg/m^2) and achieving above recommended steps per day (Tudor-Locke *et al.*, 2011) (mean steps = 10616 (±5425)) at baseline. Average values for all health measures were within normal range (not hypertensive, hyperglycaemic or hyperlipidaemic). Between 6 and 12 months of the trial, participants on average gained an average of 1 (4.2) % (ranging from -18.2% to +25.8%); SBP and DBP decreased by 1.4 (10.0) and 0.6 (6.3) mmHg respectively and heart rate increased by 0.6 (8.2) bpm. Body fat measured by BIA increased by 0.15 (4.7) %. Hip and waist circumferences increased by 0.73 (4.2) and 0.22 (4.6) cm respectively, resulting in a -0.004 (0.04) change in WHR. During 6-12 months of the trial, participants weighed on average 89 (45) times.

Associations between BWV and health markers varied by the method used (figure 1). Generally, results were inconsistent and non-significant. Greater BWV as measured by RMSE and NLMD was positively associated with increased FM in all models, though these effect sizes did not exceed $R^2 = 0.2\%$. Further, greater RMSE predicted increased percentage body fat in all models, but this was not significant for any other method of WV. Greater MASWV predicted reduced DBP in model 1, but then effect was attenuated following adjustment in models 2 and 3. No significant effects were observed in any models for SBP, heart rate, FFM or WHR ($p>0.05$ for all).

Discussion

In the present sensitivity analysis, we confirmed the results of our primary analysis which provided that, regardless of the method used for calculation or the statistical adjustments made, BWV measured over a 6-month period appears not to be associated with changes in blood pressure or body composition at 6-month follow up, in a large group

of recent weight losers. Again, as, expected, weight loss was consistently associated with improvements in blood pressure and body composition in all models.

For the present sensitivity analysis, we opted to analyse the data using a true longitudinal structure by allowing a temporal separation between BWV and changes in health markers. This approach is often used in studies examining the associations between BWV and hard outcomes such as cardiovascular disease (Lorna S Aucott *et al.*, 2016; Bangalore *et al.*, 2017; Kim *et al.*, 2018), type 2 diabetes incidence (Saito *et al.*, 2017; Yokomichi *et al.*, 2017; Rhee *et al.*, 2018) and mortality (Kim *et al.*, 2018; Nam *et al.*, 2018). In these studies, body weight is measured infrequently (e.g. every year) over an exposure period of several years, and the BWV calculated during this period is used to predict the risk of a given outcome over the proceeding follow-up period. Typically, there will additionally be adjustment for weight change (similar to the statistical structure of our present models).

This statistical approach has also been used when the outcome variables are health markers and not necessarily disease incidence. For example, Saito and colleagues (2017) examined body fat (%) variability over three periods (2005, 2007 and 2009) and used the RMSE of body fat (%) to predict hypertension during the follow-up period (between 2009 and 2014) (Saito *et al.*, 2017). Such an analysis holds similarities to the present one in that BWV and change in markers are separated in time. However, limitations associated with (a) significant temporal distance between body measures; (b) a limited number of body measures and (c) an assumption of linearity in body measures are common in such studies and not in the present, though we are limited by a short duration.

It is important to consider the physiological plausibility of the relationship between weight change (be that weight loss/gain or weight variability) and changes in health markers or body composition when implementing an analysis structure. Indeed, when the relationship between (specifically) weight loss and outcomes are examined, they are done so over the same time, and causation is naturally inferred. However, studies examining the effect of BWV on changes in health or risk of disease have always separated these into exposure and follow-up period. Physiologically, it is likely that changes in health occur in time with changes in weight, and therefore it is more plausible to expect these associations to be present over the same time. Therefore, for our primary analysis, we considered BWV and change in health markers over the same period, while accepting the limitation that reverse causality cannot be excluded.

Supplementary Table 1. Participant Characteristics

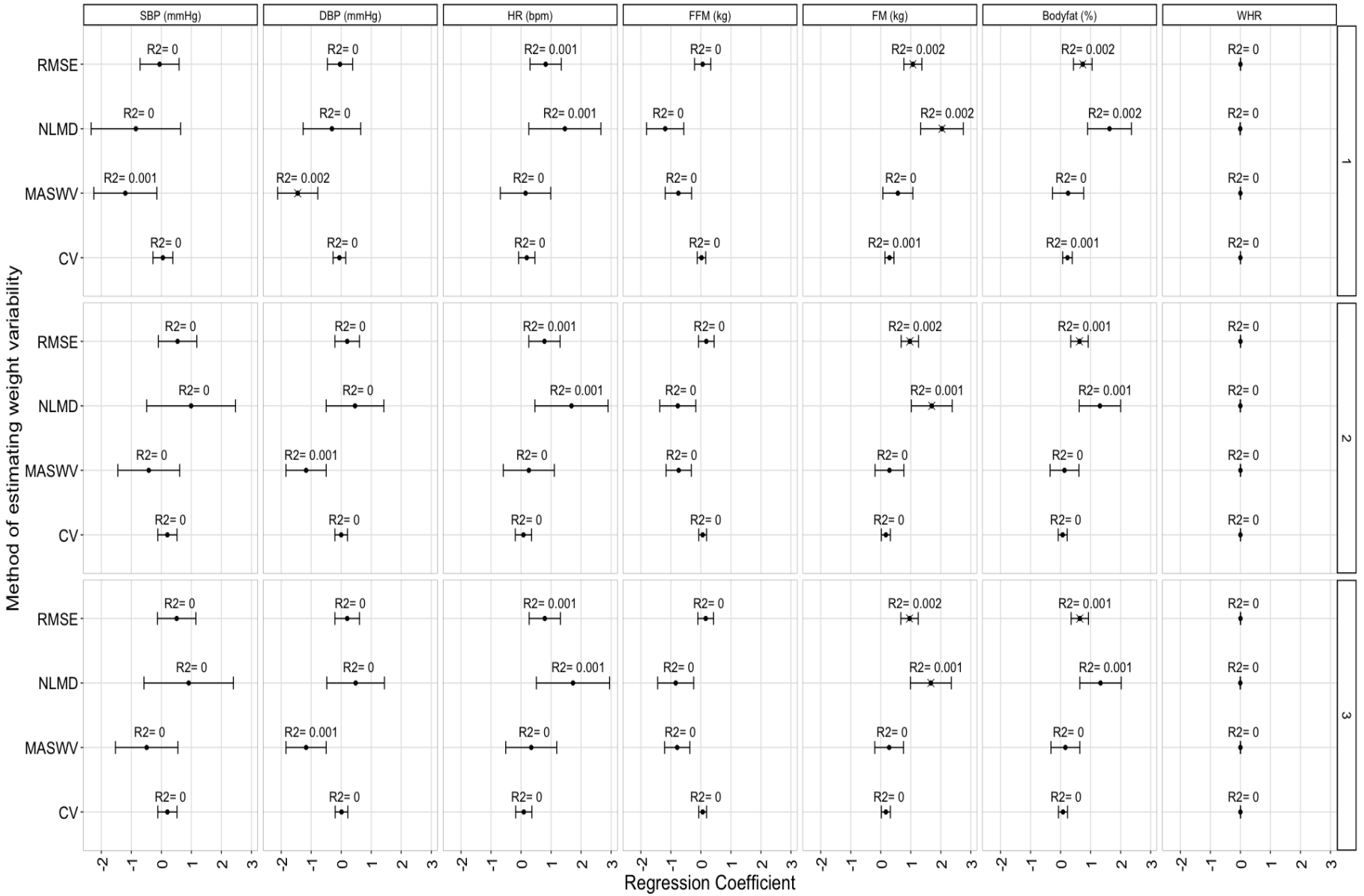
	Overall (n=1028)	Male (n=309)	Female (n=719)	P-value
Centre (%)				<0.001
CPH	372 (36.2)	65 (21.0)	307 (42.7)	
LIS	323 (31.4)	177 (57.3)	146 (20.3)	
UL	333 (32.4)	67 (21.7)	266 (37.0)	
Age (years)	45.5 (11.7)	43.7 (10.7)	46.2 (12.0)	0.002
BMI (kg/m2)	29.4 (5.0)	29.3 (4.4)	29.5 (5.3)	0.521
Weight (kg)	83.9 (16.4)	91.9 (15.7)	80.5 (15.5)	<0.001
Initial steps*	10616.1 (5425.2)	11041.1 (5931.6)	10433.4 (5186.1)	0.1
Body weight Measurements*	89 (45)	93 (46)	87 (44)	<0.001
Weight change (%)*	1.0 (4.2)	0.6 (4.0)	1.3 (4.3)	0.014
SBP (mmHg)	122.2 (14.8)	128.0 (13.6)	119.6 (14.6)	<0.001
DBP (mmHg)	76.5 (8.9)	80.4 (8.6)	74.9 (8.5)	<0.001
HR (BPM)	65.6 (10.5)	62.5 (10.5)	66.9 (10.3)	<0.001
Fat free mass (kg)	56.6 (10.9)	66.8 (9.9)	52.2 (8.0)	<0.001
Fat mass (kg)	27.2 (9.9)	24.9 (9.1)	28.3 (10.0)	<0.001
Body fat (%)	32.0 (7.6)	26.5 (6.7)	34.4 (6.7)	<0.001
Hip (cm)	109.1 (10.7)	106.3 (8.3)	110.3 (11.4)	<0.001
Waist (cm)	93.9 (13.7)	99.7 (13.0)	91.4 (13.3)	<0.001
WHR	0.86 (0.09)	0.94 (0.08)	0.83 (0.07)	<0.001

Supplementary Table 1. Baseline characteristics reported as mean and standard deviation unless stated otherwise. P-values denote results of student t-tests for continuous variables and chi-squared tests for categorical variables between genders. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol. * denotes data from 6 to 12 months.

Supplementary Table 2. Association between weight variability measures, weight change and changes in blood pressure and body composition

		Outcomes													
Model	Weight variability	SBP (mmHg)		DBP (mmHg)		Heart rate (bpm)		Fat mass (kg)		Fat-free mass (kg)		Body fat (%)		Waist-hip ratio	
		β (SE)	P	β (SE)	P	β (SE)	P	β (SE)	P	β (SE)	P	β (SE)	P	β (SE)	P
1	NLMD	-0.85 (1.49)	0.7 56	-0.31 (0.96)	0.7 46	1.46 (1.2)	0.2 54	-1.19 (0.62)	0.0 73	2.04 (0.71)	0.0 06	1.63 (0.73)	0.0 5	-0.007 (0.006)	0.2 52
1	CV	0.05 (0.33)	0.8 84	-0.06 (0.21)	0.7 9	0.19 (0.27)	0.6 39	0.02 (0.14)	0.9 79	0.29 (0.15)	0.0 76	0.23 (0.16)	0.1 88	-0.001 (0.001)	0.5 08
1	RMSE	-0.06 (0.65)	0.9 29	-0.04 (0.42)	0.9 22	0.82 (0.52)	0.1 57	0.06 (0.27)	0.8 7	1.07 (0.3)	0.0 01	0.74 (0.31)	0.0 35	0.001 (0.003)	0.8 2
1	MASWV	-1.2 (1.05)	0.3 39	-1.45 (0.67)	0.0 41	0.15 (0.84)	0.9 49	-0.75 (0.44)	0.0 88	0.57 (0.5)	0.2 62	0.25 (0.52)	0.7 86	-0.001 (0.004)	0.8 12
2	NLMD	0.99 (1.48)	0.5 03	0.46 (0.96)	0.6 3	1.68 (1.22)	0.1 76	-0.77 (0.6)	0.2 3	1.7 (0.68)	0.0 15	1.31 (0.69)	0.0 57	-0.003 (0.006)	0.6 26
2	CV	0.2 (0.32)	0.5 3	0 (0.21)	0.9 89	0.08 (0.27)	0.8 55	0.06 (0.13)	0.6 46	0.17 (0.15)	0.2 95	0.07 (0.15)	0.6 2	0 (0.001)	0.9 24
2	RMSE	0.54 (0.64)	0.4	0.2 (0.41)	0.6 31	0.78 (0.52)	0.1 57	0.18 (0.26)	0.4 88	0.97 (0.29)	0.0 01	0.63 (0.29)	0.0 33	0.002 (0.003)	0.3 72
2	MASWV	-0.42 (1.03)	0.8 02	-1.17 (0.67)	0.0 88	0.26 (0.85)	0.7 84	-0.74 (0.42)	0.0 92	0.29 (0.48)	0.5 64	0.13 (0.48)	0.7 8	0.001 (0.004)	0.8 53
3	NLMD	0.91 (1.49)	0.6 9	0.48 (0.96)	0.6 2	1.73 (1.22)	0.1 87	-0.84 (0.6)	0.2 45	1.67 (0.68)	0.0 16	1.33 (0.69)	0.0 52	-0.004 (0.006)	0.5 73
3	CV	0.2 (0.32)	0.6 73	0.01 (0.21)	0.9 7	0.09 (0.27)	0.8 35	0.06 (0.13)	0.7 48	0.17 (0.15)	0.2 69	0.08 (0.15)	0.5 97	0 (0.001)	0.9 45
3	RMSE	0.51 (0.64)	0.5 52	0.2 (0.41)	0.6 32	0.79 (0.52)	0.1 72	0.16 (0.26)	0.6 18	0.96 (0.29)	0.0 01	0.64 (0.29)	0.0 3	0.002 (0.003)	0.4 59
3	MASWV	-0.49 (1.04)	0.8 22	-1.17 (0.67)	0.0 98	0.34 (0.85)	0.7 69	-0.79 (0.42)	0.0 91	0.28 (0.48)	0.6 27	0.16 (0.48)	0.7 38	0 (0.004)	0.9 22

Supplementary Table 2. Summary results from 3 multiple linear regression models. Results are given as standardised β values and associated standard errors and significance values for the two predictors of interest. Model 1 was adjusted for baseline values of the outcome, weight change and weight variability (separate models for each method of estimating weight variability). Model 2 was adjusted for model one plus baseline BMI, age and gender. Model 3 was adjusted for model 2 plus initial and change in physical activity estimated from Fitbit devices. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; NLMD, non-linear mean deviation; CV, co-efficient of variation; RMSE, root-mean square-error; MASWV, mean average successive weight variability.


SBP (mmHg)
DBP (mmHg)
HR (bpm)
FFM (kg)
FM (kg)
Bodyfat (%)
WHR
Method of estimating weight variability
RMSE
NLMD
MASWV
CV
1
2
3
R2= 0
R2= 0.001
R2= 0.002
Regression Coefficient
-2
-1
0
1
2
3

Supplementary Figure 1. Multivariate regression results showing the association between 0-6 month weight variability (by numerous methods) and concurrent change in cardiometabolic health outcomes. The right panels refer to the model number. Model 1 included only the baseline outcome value, weight change (%) and weight variability as covariates; Model 2 included the same variables as model 1 and in addition age, gender, BMI and model 3 included the same variables as model 2 plus initial and change in PA (steps). Results are provided as standardised beta coefficients (and standard errors) and, in addition, the change in R^2 upon addition of weight change to the model. Abbreviations; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; bpm, beats per minute; FM, fat mass; FFM, fat-free mass; CV, co-efficient of variation; MASWV, mean average successive weight variability; NLMD, non-linear mean deviation; RMSE, root mean square error

Appendix 8.1. Supplementary Analysis - Associations between body weight variability and concurrent weight change

body weight variability (BWV) was estimated by root mean square error (RMSE) and non-linear mean deviation (NLMD) methods over the first 6, 9 and 12 weeks of the trial (for full details, see supplementary material 1). As an additional analysis, the correlation between BWV estimates were considered and weight change over each of these periods. The results are presented below:

Association between body weight variability and change during the initial period

Duration of period	RMSE	NLMD
6	-0.003	0.068
9	0.009	0.065
12	-0.029	0.058

Overall, there was no evidence of association between BWV and weight change over the same, initial and short duration, suggesting weight loss during the BWV period does not confound the association between BWV and longer-term weight change, as observed in the primary analysis.

Appendix 8.2. Model 2 Regression Results

Weight change Period (months)	WV duration	Covariate	β (SE)	P-value	Model R^2
6	6	BodyweightEndofWV	-0.023 (0.01)	0.1	0.054
6	6	Gender(Female)	-0.044 (0.353)	0.901	0.054
6	6	Age	-0.013 (0.014)	0.629	0.054
6	6	NumberScaleWeights	0.006 (0.017)	0.871	0.054
6	6	StudyArm	-0.042 (0.139)	0.871	0.054
6	6	PriorWeightChange	0.292 (0.052)	<0.001	0.054
6	6	WeightSuppression	-0.025 (0.029)	0.629	0.054
6	6	DurationFrom.cid6	0.123 (0.073)	0.28	0.054
6	6	BodyweightEndofWV	-0.018 (0.01)	0.235	0.060
6	6	Gender(Female)	0.04 (0.355)	0.91	0.060
6	6	Age	-0.011 (0.014)	0.637	0.060
6	6	NumberScaleWeights	0.007 (0.017)	0.859	0.060
6	6	StudyArm	-0.03 (0.139)	0.91	0.060
6	6	PriorWeightChange	0.283 (0.052)	<0.001	0.060
6	6	WeightSuppression	-0.03 (0.029)	0.558	0.060
6	6	NLMD_scaled	0.569 (0.263)	0.138	0.060
6	6	DurationFrom.cid6	0.119 (0.073)	0.235	0.060
6	6	BodyweightEndofWV	-0.022 (0.01)	0.169	0.055
6	6	Gender(Female)	-0.034 (0.354)	0.923	0.055
6	6	Age	-0.012 (0.014)	0.605	0.055
6	6	NumberScaleWeights	0.007 (0.017)	0.86	0.055
6	6	StudyArm	-0.039 (0.139)	0.877	0.055
6	6	PriorWeightChange	0.292 (0.052)	<0.001	0.055
6	6	WeightSuppression	-0.028 (0.029)	0.605	0.055
6	6	RMSE_scaled	0.13 (0.155)	0.605	0.055
6	6	DurationFrom.cid6	0.123 (0.073)	0.284	0.055
6	12	BodyweightEndofWV	-0.019 (0.008)	0.052	0.076
6	12	Gender(Female)	-0.069 (0.27)	0.798	0.076
6	12	Age	-0.009 (0.01)	0.594	0.076
6	12	NumberScaleWeights	-0.007 (0.007)	0.585	0.076
6	12	StudyArm	-0.078 (0.106)	0.618	0.076

6	12	PriorWeightChange	0.21 (0.031)	<0.001	0.076
6	12	WeightSuppression	-0.012 (0.022)	0.689	0.076
6	12	DurationFrom.cid6	0.104 (0.056)	0.193	0.076
6	12	BodyweightEndofWV	-0.016 (0.008)	0.125	0.084
6	12	Gender(Female)	-0.038 (0.269)	0.888	0.084
6	12	Age	-0.007 (0.01)	0.586	0.084
6	12	NumberScaleWeights	-0.006 (0.007)	0.586	0.084
6	12	StudyArm	-0.073 (0.106)	0.586	0.084
6	12	PriorWeightChange	0.204 (0.031)	<0.001	0.084
6	12	WeightSuppression	-0.022 (0.023)	0.586	0.084
6	12	NLMD_scaled	0.482 (0.204)	0.082	0.084
6	12	DurationFrom.cid6	0.103 (0.056)	0.15	0.084
6	12	BodyweightEndofWV	-0.018 (0.008)	0.096	0.082
6	12	Gender(Female)	-0.042 (0.269)	0.875	0.082
6	12	Age	-0.007 (0.01)	0.576	0.082
6	12	NumberScaleWeights	-0.006 (0.007)	0.576	0.082
6	12	StudyArm	-0.079 (0.106)	0.576	0.082
6	12	PriorWeightChange	0.211 (0.031)	<0.001	0.082
6	12	WeightSuppression	-0.02 (0.023)	0.576	0.082
6	12	RMSE_scaled	0.256 (0.119)	0.096	0.082
6	12	DurationFrom.cid6	0.109 (0.056)	0.115	0.082
6	9	BodyweightEndofWV	-0.018 (0.009)	0.181	0.068
6	9	Gender(Female)	-0.085 (0.307)	0.987	0.068
6	9	Age	-0.004 (0.012)	0.987	0.068
6	9	NumberScaleWeights	0.001 (0.01)	0.987	0.068
6	9	StudyArm	-0.002 (0.121)	0.987	0.068
6	9	PriorWeightChange	0.267 (0.039)	<0.001	0.068
6	9	WeightSuppression	-0.003 (0.025)	0.987	0.068
6	9	DurationFrom.cid6	0.078 (0.064)	0.593	0.068
6	9	BodyweightEndofWV	-0.013 (0.009)	0.423	0.077
6	9	Gender(Female)	-0.032 (0.306)	0.921	0.077
6	9	Age	-0.002 (0.012)	0.921	0.077
6	9	NumberScaleWeights	0.004 (0.01)	0.921	0.077
6	9	StudyArm	0.012 (0.12)	0.921	0.077

6	9	PriorWeightChange	0.258 (0.039)	<0.001	0.077
6	9	WeightSuppression	-0.012 (0.025)	0.921	0.077
6	9	NLMD_scaled	0.594 (0.233)	0.05	0.077
6	9	DurationFrom.cid6	0.078 (0.064)	0.491	0.077
6	9	BodyweightEndofWV	-0.016 (0.009)	0.3	0.070
6	9	Gender(Female)	-0.077 (0.307)	0.909	0.070
6	9	Age	-0.003 (0.012)	0.909	0.070
6	9	NumberScaleWeights	0.003 (0.01)	0.909	0.070
6	9	StudyArm	0 (0.121)	0.998	0.070
6	9	PriorWeightChange	0.266 (0.039)	<0.001	0.070
6	9	WeightSuppression	-0.008 (0.026)	0.909	0.070
6	9	RMSE_scaled	0.148 (0.139)	0.642	0.070
6	9	DurationFrom.cid6	0.082 (0.064)	0.596	0.070
12	6	BodyweightEndofWV	-0.035 (0.015)	0.055	0.033
12	6	Gender(Female)	0.233 (0.517)	0.857	0.033
12	6	Age	-0.006 (0.02)	0.857	0.033
12	6	NumberScaleWeights	-0.005 (0.025)	0.857	0.033
12	6	StudyArm	-0.041 (0.203)	0.857	0.033
12	6	PriorWeightChange	0.253 (0.076)	0.008	0.033
12	6	WeightSuppression	0.099 (0.043)	0.055	0.033
12	6	DurationFrom.cid12	0.075 (0.087)	0.698	0.033
12	6	BodyweightEndofWV	-0.027 (0.015)	0.161	0.040
12	6	Gender(Female)	0.358 (0.519)	0.735	0.040
12	6	Age	-0.003 (0.02)	0.945	0.040
12	6	NumberScaleWeights	-0.002 (0.025)	0.945	0.040
12	6	StudyArm	-0.022 (0.203)	0.945	0.040
12	6	PriorWeightChange	0.239 (0.076)	0.017	0.040
12	6	WeightSuppression	0.092 (0.043)	0.092	0.040
12	6	NLMD_scaled	0.857 (0.384)	0.092	0.040
12	6	DurationFrom.cid12	0.071 (0.086)	0.735	0.040
12	6	BodyweightEndofWV	-0.032 (0.015)	0.11	0.035
12	6	Gender(Female)	0.254 (0.517)	0.935	0.035
12	6	Age	-0.004 (0.02)	0.978	0.035
12	6	NumberScaleWeights	-0.001 (0.026)	0.984	0.035

12	6	StudyArm	-0.033 (0.203)	0.978	0.035
12	6	PriorWeightChange	0.252 (0.076)	0.009	0.035
12	6	WeightSuppression	0.093 (0.043)	0.11	0.035
12	6	RMSE_scaled	0.278 (0.227)	0.501	0.035
12	6	DurationFrom.cid12	0.072 (0.087)	0.733	0.035
12	12	BodyweightEndofWV	-0.031 (0.013)	0.054	0.044
12	12	Gender(Female)	0.204 (0.463)	0.797	0.044
12	12	Age	-0.002 (0.018)	0.894	0.044
12	12	NumberScaleWeights	-0.018 (0.012)	0.236	0.044
12	12	StudyArm	-0.071 (0.182)	0.797	0.044
12	12	PriorWeightChange	0.187 (0.053)	0.004	0.044
12	12	WeightSuppression	0.113 (0.038)	0.013	0.044
12	12	DurationFrom.cid12	0.102 (0.078)	0.342	0.044
12	12	BodyweightEndofWV	-0.023 (0.013)	0.185	0.058
12	12	Gender(Female)	0.276 (0.461)	0.707	0.058
12	12	Age	0.004 (0.018)	0.837	0.058
12	12	NumberScaleWeights	-0.015 (0.012)	0.315	0.058
12	12	StudyArm	-0.061 (0.181)	0.829	0.058
12	12	PriorWeightChange	0.172 (0.053)	0.006	0.058
12	12	WeightSuppression	0.09 (0.039)	0.06	0.058
12	12	NLMD_scaled	1.116 (0.348)	0.006	0.058
12	12	DurationFrom.cid12	0.097 (0.077)	0.315	0.058
12	12	BodyweightEndofWV	-0.025 (0.013)	0.132	0.065
12	12	Gender(Female)	0.295 (0.459)	0.669	0.065
12	12	Age	0.006 (0.018)	0.754	0.065
12	12	NumberScaleWeights	-0.014 (0.012)	0.357	0.065
12	12	StudyArm	-0.071 (0.18)	0.754	0.065
12	12	PriorWeightChange	0.19 (0.053)	0.001	0.065
12	12	WeightSuppression	0.085 (0.038)	0.079	0.065
12	12	RMSE_scaled	0.803 (0.203)	0.001	0.065
12	12	DurationFrom.cid12	0.107 (0.077)	0.297	0.065
12	9	BodyweightEndofWV	-0.03 (0.014)	0.09	0.039
12	9	Gender(Female)	0.17 (0.488)	0.97	0.039
12	9	Age	0.002 (0.019)	0.99	0.039

12	9	NumberScaleWeights	-0.008 (0.016)	0.97	0.039
12	9	StudyArm	-0.002 (0.192)	0.99	0.039
12	9	PriorWeightChange	0.229 (0.062)	0.002	0.039
12	9	WeightSuppression	0.12 (0.04)	0.011	0.039
12	9	DurationFrom.cid12	0.069 (0.082)	0.716	0.039
12	9	BodyweightEndofWV	-0.022 (0.014)	0.294	0.051
12	9	Gender(Female)	0.268 (0.487)	0.873	0.051
12	9	Age	0.006 (0.019)	0.903	0.051
12	9	NumberScaleWeights	-0.003 (0.016)	0.903	0.051
12	9	StudyArm	0.023 (0.191)	0.903	0.051
12	9	PriorWeightChange	0.213 (0.062)	0.006	0.051
12	9	WeightSuppression	0.105 (0.04)	0.029	0.051
12	9	NLMD_scaled	1.101 (0.371)	0.014	0.051
12	9	DurationFrom.cid12	0.063 (0.081)	0.788	0.051
12	9	BodyweightEndofWV	-0.026 (0.014)	0.153	0.044
12	9	Gender(Female)	0.197 (0.488)	0.952	0.044
12	9	Age	0.006 (0.019)	0.952	0.044
12	9	NumberScaleWeights	-0.003 (0.016)	0.952	0.044
12	9	StudyArm	0.005 (0.192)	0.977	0.044
12	9	PriorWeightChange	0.227 (0.062)	0.003	0.044
12	9	WeightSuppression	0.108 (0.041)	0.035	0.044
12	9	RMSE_scaled	0.432 (0.22)	0.151	0.044
12	9	DurationFrom.cid12	0.068 (0.082)	0.727	0.044
18	6	BodyweightEndofWV	-0.029 (0.018)	0.455	0.028
18	6	Gender(Female)	0.405 (0.627)	0.992	0.028
18	6	Age	-0.011 (0.024)	0.992	0.028
18	6	NumberScaleWeights	0 (0.031)	0.992	0.028
18	6	StudyArm	0.052 (0.247)	0.992	0.028
18	6	PriorWeightChange	0.093 (0.093)	0.835	0.028
18	6	WeightSuppression	0.184 (0.052)	0.003	0.028
18	6	DurationFrom.cid18	0.012 (0.08)	0.878	0.028
18	6	BodyweightEndofWV	-0.02 (0.018)	0.745	0.035
18	6	Gender(Female)	0.564 (0.629)	0.745	0.035
18	6	Age	-0.008 (0.024)	0.924	0.035

18	6	NumberScaleWeights	0.004 (0.031)	0.924	0.035
18	6	StudyArm	0.076 (0.246)	0.924	0.035
18	6	PriorWeightChange	0.076 (0.093)	0.745	0.035
18	6	WeightSuppression	0.175 (0.052)	0.007	0.035
18	6	NLMD_scaled	1.081 (0.466)	0.093	0.035
18	6	DurationFrom.cid18	0.008 (0.08)	0.924	0.035
18	6	BodyweightEndofWV	-0.023 (0.018)	0.608	0.032
18	6	Gender(Female)	0.443 (0.626)	0.863	0.032
18	6	Age	-0.007 (0.024)	0.908	0.032
18	6	NumberScaleWeights	0.008 (0.031)	0.908	0.032
18	6	StudyArm	0.066 (0.246)	0.908	0.032
18	6	PriorWeightChange	0.093 (0.092)	0.71	0.032
18	6	WeightSuppression	0.173 (0.052)	0.008	0.032
18	6	RMSE_scaled	0.494 (0.276)	0.331	0.032
18	6	DurationFrom.cid18	0.007 (0.08)	0.934	0.032
18	12	BodyweightEndofWV	-0.024 (0.017)	0.413	0.037
18	12	Gender(Female)	0.419 (0.577)	0.749	0.037
18	12	Age	-0.007 (0.022)	0.883	0.037
18	12	NumberScaleWeights	-0.011 (0.014)	0.749	0.037
18	12	StudyArm	0.019 (0.227)	0.934	0.037
18	12	PriorWeightChange	0.106 (0.066)	0.413	0.037
18	12	WeightSuppression	0.201 (0.048)	<0.001	0.037
18	12	DurationFrom.cid18	0.024 (0.073)	0.884	0.037
18	12	BodyweightEndofWV	-0.012 (0.017)	0.86	0.059
18	12	Gender(Female)	0.532 (0.572)	0.794	0.059
18	12	Age	0.002 (0.022)	0.914	0.059
18	12	NumberScaleWeights	-0.006 (0.014)	0.914	0.059
18	12	StudyArm	0.035 (0.225)	0.914	0.059
18	12	PriorWeightChange	0.083 (0.066)	0.629	0.059
18	12	WeightSuppression	0.165 (0.048)	0.003	0.059
18	12	NLMD_scaled	1.739 (0.433)	0.001	0.059
18	12	DurationFrom.cid18	0.018 (0.073)	0.914	0.059
18	12	BodyweightEndofWV	-0.014 (0.016)	0.698	0.073
18	12	Gender(Female)	0.565 (0.567)	0.698	0.073

18	12	Age	0.006 (0.022)	0.934	0.073
18	12	NumberScaleWeights	-0.004 (0.014)	0.934	0.073
18	12	StudyArm	0.018 (0.223)	0.934	0.073
18	12	PriorWeightChange	0.11 (0.065)	0.273	0.073
18	12	WeightSuppression	0.156 (0.047)	0.005	0.073
18	12	RMSE_scaled	1.306 (0.251)	<0.001	0.073
18	12	DurationFrom.cid18	0.013 (0.072)	0.934	0.073
18	9	BodyweightEndofWV	-0.023 (0.017)	0.48	0.034
18	9	Gender(Female)	0.378 (0.601)	0.937	0.034
18	9	Age	-0.003 (0.023)	0.937	0.034
18	9	NumberScaleWeights	-0.002 (0.02)	0.937	0.034
18	9	StudyArm	0.084 (0.237)	0.937	0.034
18	9	PriorWeightChange	0.121 (0.077)	0.464	0.034
18	9	WeightSuppression	0.206 (0.05)	<0.001	0.034
18	9	DurationFrom.cid18	0.026 (0.077)	0.836	0.034
18	9	BodyweightEndofWV	-0.012 (0.018)	0.861	0.048
18	9	Gender(Female)	0.506 (0.598)	0.861	0.048
18	9	Age	0.003 (0.023)	0.911	0.048
18	9	NumberScaleWeights	0.004 (0.02)	0.911	0.048
18	9	StudyArm	0.118 (0.235)	0.911	0.048
18	9	PriorWeightChange	0.1 (0.077)	0.574	0.048
18	9	WeightSuppression	0.185 (0.05)	0.002	0.048
18	9	NLMD_scaled	1.429 (0.456)	0.008	0.048
18	9	DurationFrom.cid18	0.021 (0.076)	0.911	0.048
18	9	BodyweightEndofWV	-0.016 (0.017)	0.798	0.046
18	9	Gender(Female)	0.426 (0.598)	0.857	0.046
18	9	Age	0.004 (0.023)	0.866	0.046
18	9	NumberScaleWeights	0.007 (0.02)	0.866	0.046
18	9	StudyArm	0.099 (0.235)	0.866	0.046
18	9	PriorWeightChange	0.117 (0.076)	0.382	0.046
18	9	WeightSuppression	0.184 (0.05)	0.002	0.046
18	9	RMSE_scaled	0.779 (0.27)	0.018	0.046

Appendix 9.1 Correlations Between Psychometric Variables and Body Weight Variability

Variable	Correlation with BWV (RMSE_12_log)
BWV (RMSE_12_log)	1.00
Wellbeing	-0.17
Quality of Life	0.06
Regulation of Weight Maintenance Scale	
Controlled Motivation	0.01
Automated Motivation	0.02
External Motivation	-0.04
Introjected Motivation	0.07
Identified Motivation	0.03
Integrated Motivation	-0.01
Intrinsic Motivation	0.03
Self-Efficacy for Weight Loss Maintenance	-0.04
Regulation of Eating Behaviour Scale	
Relative Automaticity Index	0.03
Controlled Motivation	0.02
Autonomous Motivation	0.03
Amotivation	-0.04
External motivation	-0.04
Introjected Motivation	0.08
Identified Motivation	0.06
Integrated Motivation	-0.01
Intrinsic Motivation	0.04
Behavioural Regulation of Exercise Scale	
Relative Automaticity Index	-0.07
Controlled Motivation	0.03
Autonomous Motivation	-0.08
Intrinsic Regulation	-0.09
Integrated Regulation	-0.09
Identified Regulation	-0.02
Introjected Regulation	0.03
External Motivation	0.01
Amotivation	-0.05
Goal Content for Weight Loss Maintenance	
Challenge	-0.02
Social	0.09
Image	0.09
Health	-0.02
Basic Personality and Needs Scale	

Global	-0.09
Relatedness	-0.09
Social Support	-0.08
Competence	-0.09
Autonomy	-0.03
Action Control Scale	
Effort	0.09
Self-Monitoring	0.07
Awareness	0.10
Total Action Control	0.09
Coping Plannng	-0.04
Action Planning	-0.03
EQ Decentring	-0.09
Mindful Attention and Awareness	-0.07
Difficulties Regulated Emotions Scale	
Clarity	0.11
Strategies	0.12
Impulse	0.13
Goals	0.11
Non-Acceptance	0.10
Total	0.13
Enriched Living Scale	
Life Fulfilment	-0.13
Valued Living	-0.11
Total Enriched Living Score	-0.13
Body Image Acceptance & Action	-0.18
Compassionate Actions and Attributes Scale	
Compassion for Others Actions	-0.05
Compassion for Others Engagement	-0.05
Compassion for Others Total	-0.05
Self-Compassion Engagement	-0.12
Self-Compassion Actions	-0.05
Self-Compassion Total	-0.10
Weight Focused External Shame	0.12
Weight-Focused Forms of Self-Criticising/Attacking and Self-Reassuring Scale	
Reassured Self	-0.12
Hated Self	0.17
Inadequate Self	0.15
Depression, Anxiety and Stress Scale	
Stress	0.09
Anxiety	0.10
Depression	0.15

Perceived Stress	0.14
Binge Eating Scale	0.21
Intuitive Eating Scale	
Reliance on Internal Hunger and Satiety Cues	-0.10
Eating for Physical rather than Emotional Reasons	0.07
Unconditional Permission to Eat	-0.06
Eating in The Absence of Hunger Scale	
Beginning to Eat Total	0.09
Beginning to Eat Physical	0.09
Beginning to Eat Environmental	0.02
Beginning to Eat Emotional	0.10
Control of Eating Total	0.06
Control of Eating Physical	0.06
Control of Eating Environmental	0.02
Control of Eating Emotional	0.06
Controllability and Automaticity Scale	
Eating In Absence of Hunger – Loss of Control	0.07
Grazing - Loss of Control	0.01
Grazing - Severity	0.07
Binge Eating – Loss of Control	0.06
Binge Eating - Severity	0.12
Three-factor Eating Questionnaire	
Hunger	0.07
Disinhibition	0.14
Restraint	0.08

List of variables measured in the NoHoW trial at baseline and their Pearson correlation (r) with body weight variability measured as root mean square error (RMSE) – see section 4.2 for information on the calculation. Lines represent variables belonging to a new scale. Italtics are scale names