The University Of Sheffield.

Incorporating Psychological Mechanisms of Action in a Health Economic Model of Obesity

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A thesis submitted in partial fulfilment of the requirements for the degree of

Doctor of Philosophy

The University of Sheffield

Faculty of Medicine, Dentistry and Health

School of Health and Related Research

April 2021

ABSTRACT

Obesity is a major public health problem in the UK and worldwide and there is a need to develop cost-effective behavioural interventions. Estimating the cost-effectiveness of weight management interventions is challenging due to the number of factors that influence weight and the heterogeneity of intervention effectiveness. This thesis explores incorporating psychological mechanisms of action of a weight management intervention into a health economic model of obesity to inform the design and funding decisions of behavioural weight management interventions. This thesis consisted of a systematic review of health economic models of obesity, a mediation analysis of a randomised controlled trial of a weight management intervention, an adaptation of an existing health economic model of obesity to include psychological factors, a comparison of this adapted model to standard methods, and pre-trial modelling based on estimated changes in a mechanism of action. The review indicated that psychological factors were not considered in the simulation of weight change in health economic models. In the subsequent chapters, psychological mechanisms of action of a weight management intervention were identified and added into an existing health economic models of obesity to allow change in BMI to be conditional on change in these psychological factors. Estimated BMI and cost-effectiveness were similar to those generated when standard methods were used but the adapted model allowed a wider range of subgroup and sensitivity analyses. Although these additional analyses were unlikely to impact funding decisions for the intervention evaluated, it indicated the potential for this to be informative in other evaluations. Pre-trial modelling in which scenarios of changes in mechanisms of action were tested demonstrated how a model with these mechanisms of action included could be used as a tool in the design of interventions. Further research that examines associations between intervention content, mechanisms of action and weight change would enable development of the existing models to include more determinants of weight changes which has the potential to inform pre-trial modelling and economic evaluation of behavioural weight management interventions.

STATEMENT OF AUTHORSHIP

Chapters 2, 3, 4 and 5 feature papers that have been published, accepted for publication, submitted for publication or presented. Chapter 2 is published in *Medical Decision Making*, Chapter 3 is accepted for publication in *Annals of Behavioural Medicine*, Chapter 4 is a version of the paper presented at the Health Economists Study Group (HESG) and Chapter 5 is submitted for publication in *BMC Public Health*. The references for these papers are listed below:

Chapter 2: Bates, S., Bayley, T., Norman, P., Breeze, P. and Brennan, A., 2020. A Systematic Review of Methods to Predict Weight Trajectories in Health Economic Models of Behavioral Weight-Management Programs: The Potential Role of Psychosocial Factors. *Medical Decision Making*, *40*(1), pp.90-105.

Chapter 3: Bates, S., Norman, P., Breeze, P., Brennan, A., & Ahern, A. (2021). Mechanisms of action in a behavioural weight-management programme: latent growth curve analysis. Accepted for publication in *Annals of Behavioral Medicine.*

Chapter 4 was based on a working paper that was submitted to the Health Economists Study Group (HESG):

Chapter 4: Bates, S., Breeze, P., Norman, P., & Brennan, A. (2021). Validating the use of estimated intervention effects on psychological variables to predict BMI and the cost-effectiveness of a behavioural weight management intervention. Health Economists' Study Group Winter 2021:

Chapter 5: Bates, S., Thomas,C., Islam, N., Ahern, A., Breeze, P. , Griffin, S. & Brennan, A. Using Health economic modelling to inform the design and development of an intervention: estimating the justifiable cost of weight loss maintenance in the UK. *Submitted to BMC Public Health.*

ACKNOWLEDGEMENTS

I would like to extend my deepest gratitude to my supervisors Dr Penny Breeze, Professor Alan Brennan and Professor Paul Norman for all of their support and guidance throughout my PhD. You have provided me with invaluable advice, and I feel very extremely grateful to have had the opportunity to work with you all. I would like to thank the Wellcome Trust and University of Sheffield for providing the funding for this work. I've greatly valued being part of the first cohort of the Wellcome Trust Doctoral Training Centre and am very grateful to the directors and all members of the Training Centre who have contributed to an excellent programme that has supported both my PhD research and my wider professional development. In particular, I'm thankful to the other members of cohort 1; Tom Bayley, Genevieve David, Dr Simon McNamara and Robert Smith for their support from day 1 of this PhD journey.

I would like to thank the WRAP trial investigators for allowing me to use the WRAP trial data for analysis in Chapters 3, 4 and 6. In particular, I am very grateful to Amy Ahern for the advice and feedback and the opportunity to be involved on the *Scalable behavioural weight management programmes for the prevention and treatment of type 2* diabetes project while completing my PhD. I thank my co-authors, Dr Chloe Thomas, Dr Nazrul Islam and Professor Simon Griffin, for their valuable input and feedback on Chapter 5 and I'm grateful to the anonymous reviewers of Medical Decision Making and Annals of Behavioural Medicine for their comments on Chapters 2 and 3 respectively.

I am extremely grateful to my wonderful family, especially my parents, for unconditional support and encouragement throughout my life. I also thank my closest friends Lorraine, Jane, Louise and Tish for the outstanding support throughout my PhD and beyond. Finally, I'm eternally grateful to my partner Luke; we could never have imagined that we'd be writing up our PhD theses side by side at home during a global pandemic, but your perseverance has inspired me to keep going and I couldn't have done it without you. Thank you for everything.

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Abbreviations

AIC	Akaike Information Criterion
BCT	Behaviour Change Technique
BIC	Bayesian Information Criterion
BMI	Body Mass Index
CFI	Comparative Fit Index
CVD	Cardiovascular disease
EPIC	European prospective investigation of cancer
HSE	Health Survey for England
ICER	Incremental Cost-Effectiveness Ratio
LGCM	Latent Growth Curve Modelling
MI	Myocardial infarction
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
QALY	Quality Adjusted Life Year
RCT	Randomised Control Trial
RMSEA	Root Mean Square Error of Approximation
SBP	Systolic Blood Pressure
SPHR	School for Public Health Research
SRMR	Standardized Root Mean Square Residual
THIN	The Health Improvement Network
TIA	Trans-ischaemic attack
TFEQ	Three Factor Eating Questionnaire
VAS	Visual Analogue Scale
WHO	World Health Organisation
WLM	Weight Loss Maintenance
WRAP	Weight-loss programme referrals for adults in primary care

CHAPTER 1: INTRODUCTION

Obesity is high on the public health agenda both within the UK and globally (1). Individuals who are overweight or obese are at an increased risk of numerous health conditions (2) and all-cause mortality (3). Specifically, increased body mass index (BMI) is associated with an increased risk of type II diabetes, cardiovascular diseases (hypertension, coronary artery disease, congestive heart failure, pulmonary embolism, stroke), cancer (breast, colorectal endometrial, kidney, ovarian), asthma, osteoarthritis and chronic back pain (4). In 2016, 35.2% adults in England were overweight and 26.2% were obese and, by 2030, it is expected that obesity prevalence in the UK will rise to 41-48% in men and 35-43% in women. This is estimated to result in 544,000–668,000 new cases of diabetes, 331,000–461,000 cases of coronary heart disease and strokes and 87,000-130,000 new cases of cancer (5). As a result of the negative impact of obesity on health, the medical costs in the UK are predicted to approach £2 billion per year (5) and the indirect costs are expected to equal or exceed this figure (6).

Behavioural weight management programmes are recommended as a first-line treatment by the National Institute of Health and care Excellence (7). Systematic reviews (8-10) that have summarised the effectiveness of interventions have highlighted the heterogeneity of intervention content and impact on weight change across interventions. This has led to an increased focus on understanding how behavioural interventions work and the constructs that an intervention target to evoke behaviour change and weight loss (11, 12). Health economic models of obesity have been used to assess how short-term changes in weight or BMI are associated with long-term costs and benefits which can be used to inform funding decisions. However, the large number of influencing factors and consequences related to being overweight or obese, as well as the variation in intervention effect, presents a challenge when estimating the cost-effectiveness of a behavioural intervention (13). The work in this thesis aims to investigate the psychological constructs associated with the effectiveness of a weight management intervention and explore how these psychological constructs can be used to inform predictions of weight trajectories within a health economic model of obesity.

1.1 Understanding the effectiveness of behavioural weight management interventions

Many behavioural weight management interventions are associated with significant weight loss; however, the average weight loss varies across intervention (14, 15). For example, in a systematic review, the average weight loss across randomised controlled trials of weight loss interventions varied from -4.03kg to -21.3kg (16). Furthermore, the duration of the effect associated with these interventions is difficult to establish due to the limited amount of follow-up data available. The evidence of long-term weight maintenance is mixed; while reviews of weight loss and weight-loss-maintenance interventions indicate that any weight lost is regained by 5 years (8, 17), a large observational study indicated that those who have lost weight are able to maintain weight loss for up to ten years (18). The magnitude of weight loss and duration of weight loss maintenance impacts on the health benefits and therefore there is a need to understand this observed heterogeneity.

In order to understand the variation in weight loss across intervention and individuals, there has been a greater focus on understanding *how* an intervention is effective; specifically, the pathways through which the components of an intervention impact on weight or BMI (10). To facilitate this, there have been efforts to describe the content of an intervention. An intervention can be described in terms of behaviour change techniques (BCTs) or methods; a discernible component of an intervention designed to impact on determinants of behaviour (19). In order for a behaviour change techniques to be effective it must target and act on a determinant of a behaviour (20). Determinants are described as "generic modifiable psychological variables or regulatory process that are assumed, on the basis of empirical or theoretical evidence to be causal antecedents of behaviour" (20). The process through which a behaviour change technique impacts on a determinant of behaviour and therefore behaviour and health outcomes is described as the mechanism of action (MoA) (21). This is represented in Figure 1.1. Often the direct effect of the intervention on BMI or weight is the only effect of interest when evaluating an intervention (Figure 1.1, 1b) (10). Testing the indirect effect (Figure 1.1, 1a) of an intervention on weight change via determinants of behaviour change enables a better understanding of intervention effectiveness and can inform the design of effective interventions (12).

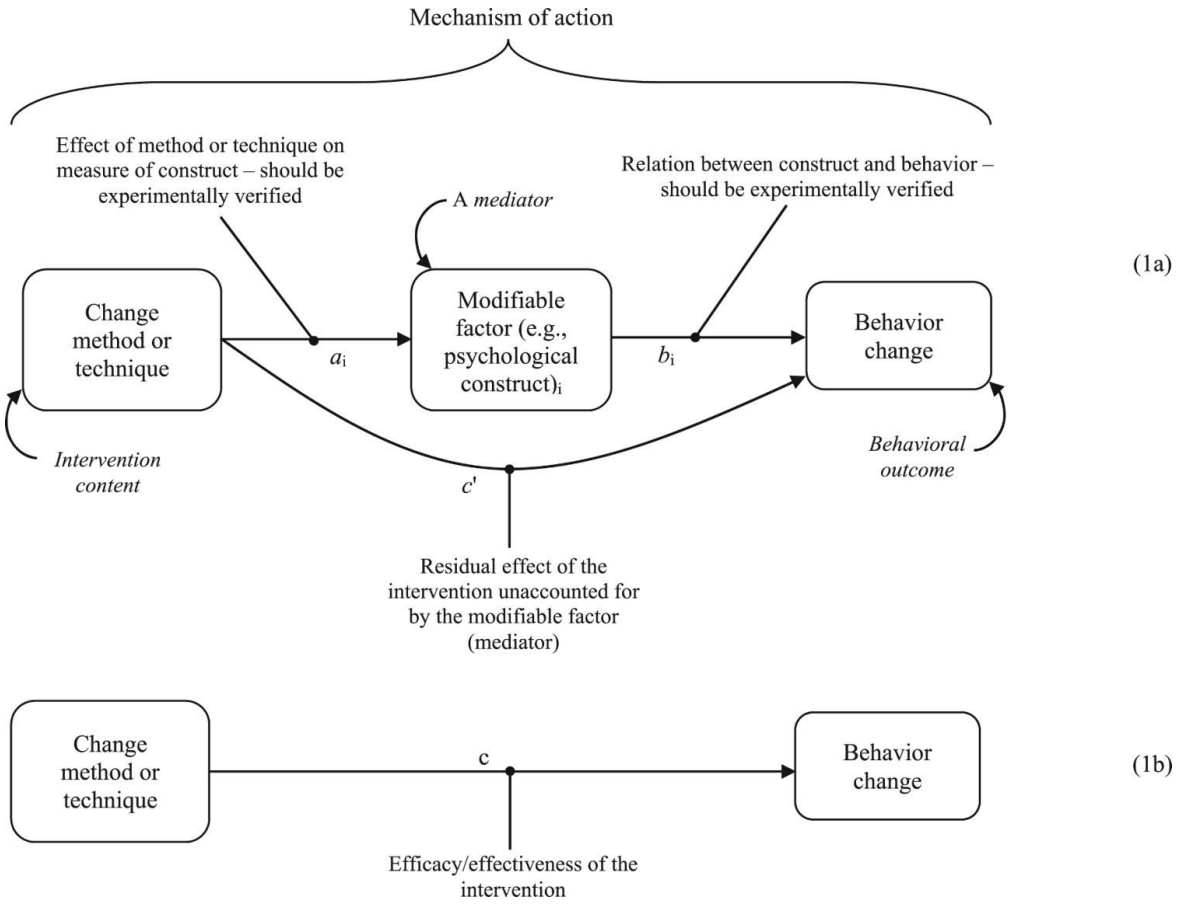

Figure 1.1. Indirect (mechanisms of action) and direct effect of a behaviour change techniques on behaviour change. Reprinted from Known knowns and known unknowns on behavior change interventions and mechanisms of action by M. S. Hagger, 2020, Health Psychology Review, 14(1), 199-212. Copyright 2021 by Taylor & Francis. Reprinted with permission.

Reviews of empirical and observational studies have summarised the evidence on determinants of weight change. These have found evidence that self-regulation skills, self-efficacy, autonomous motivation, flexible eating restraint, eating disinhibition, self-monitoring of weight, dietary restraint are modifiable determinants of weight loss (10, 22, 23). However, the reviews all highlighted a lack of formal mediation studies; that is testing of how the intervention content impacts on a determinant of behaviour change and how this then impacts on behaviour change (Figure 1.1 1a). This is reflected in a systematic meta-review of mechanisms of health behaviour change (not restricted to weight management interventions) which indicated that only 6% (4 out of 66) of the meta-analyses included in the meta-review directly examined the relationship between potential determinants of behaviour change and the outcomes to test the mechanisms of action of the intervention (24). Therefore, there is a need to investigate the mechanism of action to contribute to the

understanding of heterogeneity in effectiveness across intervention and inform the design of future interventions.

1.2 Estimating the cost-effectiveness of behavioural weight management interventions

Obesity is associated with a large financial burden in the UK (5) and the National Health Service (NHS) has a finite budget to spend on treatments. Thus, when proposing a new weight management intervention, a health economic evaluation that assesses costs and consequences associated with the intervention compared to those associated with an alternative or currently available treatment option should be conducted and used to inform decisions regarding funding (25).

The costs associated with an intervention include the cost of the intervention and disease related costs which, depending on the decision maker, may be healthcare-related only or include wider costs such as social care costs. The incremental cost is the difference between the costs associated with a proposed intervention and the costs associated with an alternative (often standard care) (25).

Within the UK, the preferred method of measuring consequences is quality adjusted life years (QALY's) which is calculated by multiplying the time spent in a certain health state by the preference weight of that state (26). This preference weight is a value usually anchored at 0 (dead) and 1 (full health) and, as such, QALYs take account of both length and quality of life. For example, 2 QALYs could represent 2 years at full health, 4 years at a health state of 0.5 or 8 years at a health state of 0.25. The incremental effect is the difference between the QALYs associated with a proposed intervention and the QALYs associated with an alternative (often standard care). An ICER is calculated by dividing the incremental cost by the incremental effect (25):

$$\text{ICER} = \frac{\text{Incremental costs}}{\text{Incremental QALYs}}$$

The ICER generated is then compared to a cost-effectiveness threshold which represents the maximum cost that is acceptable to pay per incremental QALY. In the UK, this threshold is estimated to be between £20000

and £30000 per QALY (27) but other factors are taken into consideration including how much uncertainty there is around the outcomes and whether the intervention is for end-of life care (28). If an intervention is more expensive and is less effective than a comparator, it is described as dominated whereas if an intervention is less expensive and more effective, it is described as dominant (25). Net Monetary Benefit (NMB) is another summary statistic that can be used to represent the value of an intervention in monetary terms rather than using a ratio like the ICER. This requires a known cost-effectiveness threshold.

NMB = (incremental benefit x threshold) – incremental cost

1.2.1 Health Economic modelling

The full costs and consequences of an effective weight management intervention are often not immediate. For example, when an individual reduces their BMI, their risk of developing certain conditions such as type 2 diabetes is reduced, however, an event (e.g. developing type 2 diabetes) may not have occurred, and therefore the related costs and benefits would not be captured, within the trial. In the absence of long-term data, health economic modelling can be utilised to predict the long-term effect of the intervention on costs and consequences based on the available short-term data (29). This allows an economic evaluation of the intervention over a time horizon that is expected to capture the relevant costs and consequences; this is particularly beneficial for weight management interventions when some impact of the intervention is likely to occur beyond the trial period.

A range of health economic modelling methods can be used to conduct cost-effectiveness analysis. Decision tree models involve comparing treatment options through a series of pathways which represent potential options or events that could impact an individual. In a Markov model, participants can be in one of a number of health states and, at each time cycle individuals can either remain in the same health state or change to another dependent on the transition probabilities (the probability of staying within the same health state or moving into another state). However, the complexity of conditions such as obesity can require more complex methods. For example, living with obesity is associated with an increased risk for many conditions and this would be challenging to represent in a decision tree model. The risk of conditions may also be related to past events such as a previous cardiac event or complication of diabetes and while Markov modelling methods have been developed to enable more complex scenarios, this can become increasingly difficult to implement.

Individual patient level simulation models enable simulated individuals to be monitored through different possible diagnoses and complications. Within this type of model, it is possible to represent an individual experiencing multiple events or conditions and the exact time to the event can be simulated. A range of individual characteristics such as age, gender and comorbidities, can inform the trajectory of health and risk of various conditions throughout the model (30). Although these models can require large amount of data and be computationally intensive, the potential to represent more complexity compared to decision tree and Markov models makes these model potentially more suitable for representing the many influential factors and consequences of obesity.

In health economic models, the input parameters values of the model, for example the association between BMI and blood pressure, can be derived from clinical trials, observational studies or expert opinion. Usually the point estimate (e.g. mean value) is used for all parameters in the main, or 'base case', analysis (25). In Probabilistic Sensitivity Analysis (PSA) the parameters are represented as distributions around the point estimate (31). The type of distribution is likely to differ depending on the parameter and are usually based on supporting evidence where this is available (25). In PSA, the model is run many times and each time a set of values is drawn by random sampling from the distribution of each parameter. Incremental costs, QALYs and an ICER is calculated for each model run. This is used to measure the uncertainty around the cost-effectiveness outcomes.

Health economic modelling is often used to estimate cost-effectiveness after a trial has been collected or based on available data. However, health economic modelling can also be used for pre-trial modelling. Prior economic evaluation was identified as a useful approach in medical research council guidelines for developing and evaluating complex interventions (32). This method can be used to estimate whether an intervention is likely to be cost-effective and inform decisions regarding whether to proceed with a full trial. This method has been used in development of interventions (33). For example, it was used to assess whether a fall-prevention intervention was likely to be cost-effective. Based on pilot trial data, the intervention was unlikely to be cost-effective and thus a full trial was not recommended (34). This type of analysis is based on an expected treatment effect, which may be based on a pilot study or on results from similar interventions. Pre-trial

modelling can reduce the chance that interventions unlikely to be cost-effective proceed to trial and can inform decisions about the design of the intervention; if pre-trial modelling indicates an intervention is likely to exceed the cost-effectiveness threshold, changes can be made, such as moving to an online format, to increase the likelihood of cost-effectiveness.

1.2.2 Challenges of Public Health Economic Modelling

With any economic evaluation there is uncertainty about the true costs and consequences associated with an intervention (35). When extrapolating results from one or more trials to a wider population, several factors could result in uncertainty including whether the data available, and assumptions made based on this, is generalisable to the wider population and the accuracy of the assumptions made in the model (25). Public health economic modelling has additional challenges because the target of these types of interventions is to change behaviour and there is likely to be a large number of factors that influence behaviour (36). In an economic evaluation of a weight management intervention, the area in which an individual lives and works, the behaviours of their family, their past experience, their reasons for the engaging in the unhealthy behaviours and their motivation for behaviour change might all have an impact on the outcomes of the intervention and so these should be considered (37). Furthermore, because of the wide range of possible determinants of weight change, the causal pattern through which the intervention is successful (if this is the case) is then difficult to establish which can make it challenging to estimate effectiveness for the population. Understanding what aspects of the intervention make it effective or not effective can be used to help decision-makers understand how different intervention options may be used for different subgroups or contexts (38).

One challenge specific to the health economic modelling of obesity is estimating the long-term weight trajectory of simulated individuals within the model. Because the follow-up after a trial is often short-term and rarely extends beyond 2 or 3 years (8) assumptions are made about weight trajectories between the end of the trial and the end of the time horizon. For example, it may be assumed within some health economic evaluations that all weight is regained after the final follow-up point in the trial whereas others might assume that all weight-loss is maintained until the end of the time horizon. Other studies may choose a rate or regain based on other data sources, such as another trials of a similar intervention (39). The weight trajectory chosen is likely to impact on costs and consequences through the potentially increased incidence of diseases such as diabetes

and heart disease (13). Differences in the weight trajectory simulated, therefore, has the potential to impact on the assessment of cost-effectiveness and ultimately funding decisions. For this reason, it is important to understand the factors that impact on weight trajectories and consider these when simulating weight trajectories in health economic modelling.

1.3 Inclusion of psychological factors in health economic models

To combat the challenges of understanding the causal relationships in public health economic modelling, it was recommended that insights from other disciplines are incorporated. Given the theoretical and empirical research indicating the role of psychological factors in weight loss and weight loss maintenance (10, 40, 41), there is justification to explore how adding relevant factors to health economic model of obesity could be beneficial. Adding psychological variables to health economic models could have two potential benefits. Firstly, including the predictors of weight loss and weight loss maintenance in the model may enable the model to better predict who maintains the weight loss during an intervention which, in turn, may lead to more accurate predictions of long-term health and will better inform decisions made regarding allocation of funding. Secondly, pre-trial modelling can be carried out to determine how much can be spent on an intervention that is expected to have a certain effect on psychological variable(s) in order for the interventions to be cost-effective. This will complement, and make use of, recent and ongoing research into describing the behaviour change techniques and how these impact on determinants of behaviour change to inform the design of future interventions.

Although psychological theories have been incorporated into mathematical models to estimate attendance at breast cancer (42) or diabetic retinopathy screening appointments (43), health economic models do not often incorporate psychological variables (44). These studies were limited by a lack of data linking the components of the theory to the screening behaviour. In one economic evaluation, predictors of treatment effectiveness was incorporated into a health economic model of type 1 diabetes (45) but there was not sufficient power in the prediction model to predict who would respond to treatment. As described in section 1.1, there is evidence linking psychological factors to weight management and therefore there is the potential for these to be incorporated into health economic models. Studies that examine the mechanisms of action of an intervention

would be most useful because they could inform both the understanding of the impact of the intervention on a determinant of behaviour and how this determinant is associated with weight change.

1.4 Aims and Research Questions

This thesis will build upon the previous research on psychological predictors of weight change and use this to inform the development of a health economic modelling of obesity. The overall aim of this thesis is to investigate the feasibility and benefits of including psychological factors in the prediction of BMI trajectories within health economic modelling of behavioural weight management interventions. This overarching aim can be subdivided into the following research questions

i. What are the current methods used within health economic models to predict weight trajectories and how have psychological factors been incorporated?
ii. What are the psychological constructs, or changes in constructs, that predict weight trajectories during and following a weight management intervention?
iii. What impact does incorporating these factors in an existing health economic model have on cost-effectiveness outcomes?
iv. How can inclusion of these factors in an existing health economic model facilitate pre-trial modelling for intervention design?

1.5 Outline of Thesis

Chapter 2 reports a systematic review of health economic models of obesity interventions. This had two aims. One aim of the review was to determine what methods are used within health economic modelling to predict weight trajectory of a population beyond the available data. The second aim was to determine to what extent psychology had been used within the health economic models to inform estimated weight trajectories. Chapter 3 reports an analysis of the data from the weight-loss programme referrals for adults in primary care (WRAP) randomised control trial (RCT) in which latent growth curve modelling (LGCM) was used to determine the association between psychological factors and weight loss maintenance up to 2-years post-randomisation. Chapter 4 describes an existing health economic model and how, using the output from the analysis in chapter 3, this model was adapted to include relevant psychological variables. It compared this adapted model with

the original model to determine what impact the adjustment has made. An intervention was examined using both the original and adapted model to determine the difference in terms of the costs, consequences, uncertainty and potential impact on decision making. Chapter 5 will show how a health economic model can be used in the design phase of a behavioural weight maintenance intervention using a justifiable costs analysis in which an estimated treatment effect on BMI is used to estimate long-term costs and consequences. This will show how pre-trial modelling can be conducted using the health economic without any psychological variables. Chapter 6 will use the adapted model in Chapter 4 model to conduct pre-trial modelling; the impact of hypothetical interventions, with associated changes in psychological factors, on cost-effectiveness will be examined. Figure 1.2 shows how the objectives of each chapter link to the research questions. Finally, Chapter 7 will summarise and discuss the findings of the thesis and will consider the novel contribution made by this work, the strengths and limitations and directions for further research.

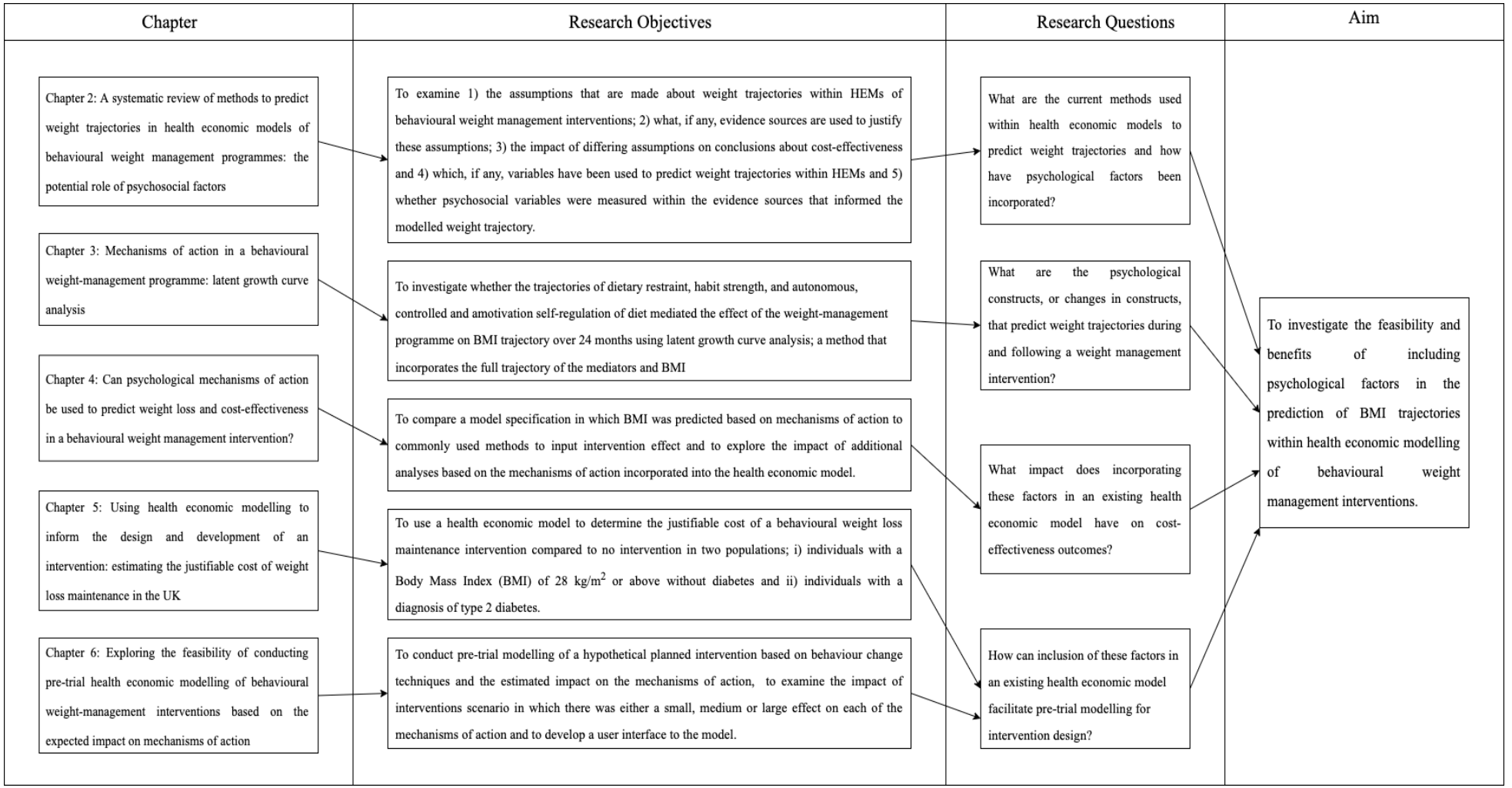

Figure 1.2. Summary of thesis structure

1.5.1 Formatting

The alternative thesis format (also known as the publication format thesis) was used for this thesis. Therefore, the following chapters (2-6) will be written in manuscript format. Each formed a separate paper either published (Chapters 2 and 3), submitted for publication (Chapter 5) or intended for publication (Chapter 4 and 6). In order to maximise readability, all will be included in the main text of the thesis and will follow contents pagination accordingly and figure and table numbers were updated in order to make navigation of the document easier. Manuscripts have also been rearranged to ensure that figures and tables are close to the reference in the text even where these are required to be at the end of the manuscript by journal guidelines. References to other parts of the thesis have also been added to aid understanding of the links between the work. Author contribution statements are in Appendix 1. References for each chapter will be included at the end of that chapter in line with the manuscript format. As required, all research was undertaken while supervised by University of Sheffield supervisors.

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CHAPTER 2: LITERATURE REVIEW OF HEALTH ECONOMIC MODELS OF OBESITY

This chapter reports a systematic review of health economic models of obesity with a specific focus on understanding the methods used to simulate weight trajectories. Specifically the aims were to examine the assumptions that are made about weight trajectories, the evidence sources used to justify these assumptions and the impact of differing assumptions on conclusions about cost-effectiveness. Furthermore, to understand if and how psychological factors have been used in health economic models of obesity, a further two aims were to examine which, if any, variables were used to predict weight trajectories within the health economic models of obesity and whether psychosocial variables were measured within the evidence sources that informed the modelled weight trajectory.

The review was first conducted in November 2017 and was then updated in July 2019 to identify additional papers. The paper was submitted and accepted for publication in *Medical Decision Making*:

Bates, S., Bayley, T., Norman, P., Breeze, P. and Brennan, A., 2020. A Systematic Review of Methods to Predict Weight Trajectories in Health Economic Models of Behavioral Weight-Management Programs: The Potential Role of Psychosocial Factors. *Medical Decision Making*, *40*(1), pp.90-105.

The content of the chapter is the same as the published version other than section 2.6 which has been added for this thesis version of the work. The article was published open access following the requirement of the Wellcome Trust who financially supported this work. The conditions of the open access publishing allow use of the final published PDF, original submission or accepted manuscript in this thesis (including in any electronic institutional repository or database). Full details of re-use guidelines are here: https://uk.sagepub.com/en-gb/eur/journal-author-archiving-policies-and-re-use.

The paper in the chapter was written with 4 co-authors; Thomas Bayley, Penny Breeze, Alan Brennan and Paul Norman. Sarah Bates conceived of the idea, designed and developed the search strategy, conducted the search and produced the original draft of the manuscript. Thomas Bayley reviewed 10% of the search results

and Penny Breeze, Alan Brennan and Paul Norman supervised and reviewed the work and provided feedback on the manuscript.

A SYSTEMATIC REVIEW OF METHODS TO PREDICT WEIGHT TRAJECTORIES IN HEALTH ECONOMIC MODELS OF BEHAVIOURAL WEIGHT MANAGEMENT PROGRAMMES: THE POTENTIAL ROLE OF PSYCHOSOCIAL FACTORS

2.1 Abstract

Objectives. There is limited evidence on the long-term effectiveness of behavioural weight-management interventions, and thus, when conducting health economic modelling, assumptions are made about weight trajectories. The aims of this review were to examine these assumptions made about weight trajectories, the evidence sources used to justify them, and the impact of assumptions on estimated cost-effectiveness. Given the evidence that some psychosocial variables are associated with weight-loss trajectories, we also aimed to examine the extent to which psychosocial variables have been used to estimate weight trajectories and whether psychosocial variables were measured within cited evidence sources.

Methods. A search of databases (Medline, PubMed, Cochrane, NHS Economic Evaluation, Embase, PSYCinfo, CINAHL, EconLit) was conducted using keywords related to overweight, weight-management, and economic evaluation. Economic evaluations of weight-management interventions that included modelling beyond trial data were included.

Results. Within the 38 eligible articles, 6 types of assumptions were reported (weight loss maintained, weight loss regained immediately, linear weight regain, subgroup-specific trajectories, exponential decay of effect, maintenance followed by regain). Fifteen articles cited at least 1 evidence source to support the assumption reported. The assumption used affected the assessment of cost-effectiveness in 9 of the 19 studies that tested this in sensitivity analyses. None of the articles reported using psychosocial factors to estimate weight trajectories. However, psychosocial factors were measured in evidence sources cited by 11 health economic models.

Conclusions. Given the range of weight trajectories reported and the potential impact on funding decisions, further research is warranted to investigate how psychosocial variables measured in trials can be used within health economic models to simulate heterogeneous weight trajectories and potentially improve the accuracy of cost-effectiveness estimates.

2.2 Introduction

Behavioural weight management programmes are the first line of treatment recommended by the National Institute for Health and Care Excellence (NICE) for individuals who have a body mass index (BMI) of over 25 in England (1). Systematic evidence reviews and large clinical trials show that many of these programmes are associated with significant weight loss (2, 3) but the long-term success, as measured by lasting weight loss maintenance, is harder to determine. Although there are weight management studies with a follow-up of up to 10 years or more (4, 5), the majority have a maximum of only 2-3 years (6). Moreover, the limited evidence available is mixed; while recent reviews have indicated that weight is regained by approximately 5 years (6, 7), in an observational study based in the USA, participants ($n > 4{,}000$) reported maintaining an average weight loss of 33kg, from an original weight of 105kg, for around 5.7 years (8, 9).

The lack of long-term data introduces additional uncertainty to decisions of whether to fund an intervention. One aspect considered in this decision making is cost-effectiveness analysis (CEA). Within CEA, health economic models (HEMs) can be used to extrapolate costs and effectiveness of weight management programmes beyond trial data to determine cost-effectiveness over a longer period of time (10). To conduct this analysis, an estimation of intervention effect is modelled (11) and, in the absence of long-term data, an assumption is made about weight trajectories beyond the trial period both with and without the intervention. For example, in the economic modelling conducted to inform NICE obesity guidelines, it was assumed that individuals regained 5% of the weight loss annually resulting in a return to the non-intervention weight trajectory after 20 years (12). The assumption used is partly determined by the HEM structure used (13) which can allow for estimating either a mean weight trajectory for all individuals, weight trajectories for certain subgroups or a weight trajectory for each individual. The assumption used determines the duration of benefits gained from an intervention which will impact on costs and consequences, the assessment of cost-effectiveness, and potentially the funding decision made.

Weight trajectories during and post-weight management interventions are likely to be affected by a variety of individual factors and consideration of these factors could potentially improve the accuracy of assumptions made with HEMs and of resulting cost-effectiveness estimates. Psychosocial variables are considered to be

important factors in obesity and are often the target for behavioural interventions (14, 15). There is growing evidence of associations between psychosocial factors, such as self-regulation, motivation, self-efficacy and habit, and weight loss maintenance (16-18). In a review of experimental studies, higher internal motivation compared to motivation driven by external pressure, self-efficacy (an individual's belief in their ability to change and maintain healthy behaviours) and self-regulation (monitoring of diet, exercise or weight) were predictive of weight loss (17). A positive body image, flexible dietary restraint (restriction of dietary intake) (16, 17), and habit (the extent to which healthy behaviours have become automatic) have also been associated with weight loss maintenance (16). Given there is strong evidence to indicate that psychosocial factors are important in weight trajectories, including these variables in HEMs has two potential benefits. First, in the absence of long-term data, these variables could be used to predict weight trajectories post-intervention and represent the heterogeneity in weight trajectories. This has the potential to increase the accuracy of estimates of long-term cost-effectiveness. Second, HEMs could be used to estimate the impact of planned behavioural interventions that are expected to change certain psychosocial factors (e.g. a habit-based intervention(19), and this can be used in the intervention design process.

There has been a broad review of HEMs used to estimate the cost-effectiveness of obesity prevention and treatment interventions (20) but none through September 2019 have specifically examined the assumptions made regarding weight trajectories. Given the potential impact of these assumptions on estimates of cost-effectiveness, the aims of this review are to examine 1) the assumptions that are made about weight trajectories within HEMs of behavioural weight management interventions for overweight and obesity; 2) what, if any, evidence sources are used to justify these assumptions; and 3) the impact of differing assumptions on conclusions about cost-effectiveness. Furthermore, given that there is evidence to indicate that inclusion of psychosocial factors may contribute to accurate predictions of weight trajectories, this review will also document 4) which, if any, variables have been used to predict weight trajectories within HEMs and 5) whether psychosocial variables were measured within the evidence sources that informed the modelled weight trajectory.

2.3 Methods

PRISMA guidelines were followed when conducting this systematic review (21).

2.3.1 Study searches

Searches were conducted in November 2017 in Medline, Pubmed, Cochrane, National Health Service (NHS) economic evaluation (EE) database, Embase, PSYCinfo, CINAHL, EconLit including terms related to overweight or obesity, weight loss management and recommended search terms for economic evaluations (22) with no restriction on year of publication. The reference lists of eligible articles were searched and retrieved, and citation searches were conducted. The search was updated in July 2019 using the same search strategy to identify any recent studies published. The full search strategy in Supplementary Material (Table 2.4).

2.3.2 Study selection

Titles and abstracts were reviewed and then the full text of remaining articles was screened to determine eligibility. A random selection (10%) of the full articles reviewed were screened by a second reviewer (T.B.) and any disagreements on eligibility were discussed. Studies were included if they reported an original economic evaluation (i.e. not a review of health economic evaluations or models) of at least one behavioural weight management intervention aimed at adults (aged 18-65) who were above a healthy weight (i.e., with a BMI > 25) with an aim of reducing weight. Studies also had to include modelling of weight trajectories beyond data available from the intervention trial. Studies were excluded if the intervention was aimed at a population with a health condition (this included diabetes, cancer, pregnancy, a history of recent surgery including bariatric surgery and in rehabilitation from a recent cardiovascular event) that could have impacted on weight trajectory or if more than half of the study sample had one of these conditions. The weight trajectories and the factors that impact these may differ for those with and without health conditions; for example, those with diabetes regain weight more quickly than those without (6). Studies were excluded if they did not include an evaluation of at least one behavioural weight management intervention or if the behavioural weight management intervention included a pharmacological or surgical component (e.g. weight management intervention paired with a weight loss medication). Studies were excluded if they did not report a full economic

evaluation; that is, if they did not include an assessment of both costs and outcomes and/or did not include a comparisons of 2 or more interventions (10). Publications in languages other than English were excluded

2.3.3 Study Characteristics

A data extraction form (Supplementary Material; Table 2.5) was used to extract details of the weight trajectory modelling methods. The assumptions made about weight trajectories, any cited evidence sources, and any sensitivity analysis conducted regarding the weight trajectory (and the related impact on outcomes) were extracted. Any psychosocial factors that had been used in the prediction of weight trajectories and the use of these factors within the articles, and in cited evidence sources, were also extracted.

2.3.4 Data Synthesis

As this is a review of methods rather than an estimation of treatment effects, we did not undertake a meta-analysis of studies or assess studies for quality. A detailed review of methods and a narrative synthesis were conducted; assumptions made about weight trajectories within HEMs were categorised and the evidence sources were examined and summarised. Any sensitivity analyses around the weight trajectory assumptions were reviewed and their impacts on the incremental cost-effectiveness ratio (ICER) described. The psychosocial variables used within the HEMs or measured within evidence sources cited, and any analysis conducted on these variables were summarised.

2.4 Results

Including the original and updated search, 4215 titles and abstracts were reviewed. Of these, the full text of 174 articles were reviewed and 136 were excluded; the most common reasons were that the articles were not a full health economic evaluation or that there was no modelling beyond the trial data. A total of 38 studies (listed in Supplementary Material; Table 2.6) met the eligibility criteria (Figure 2.1).

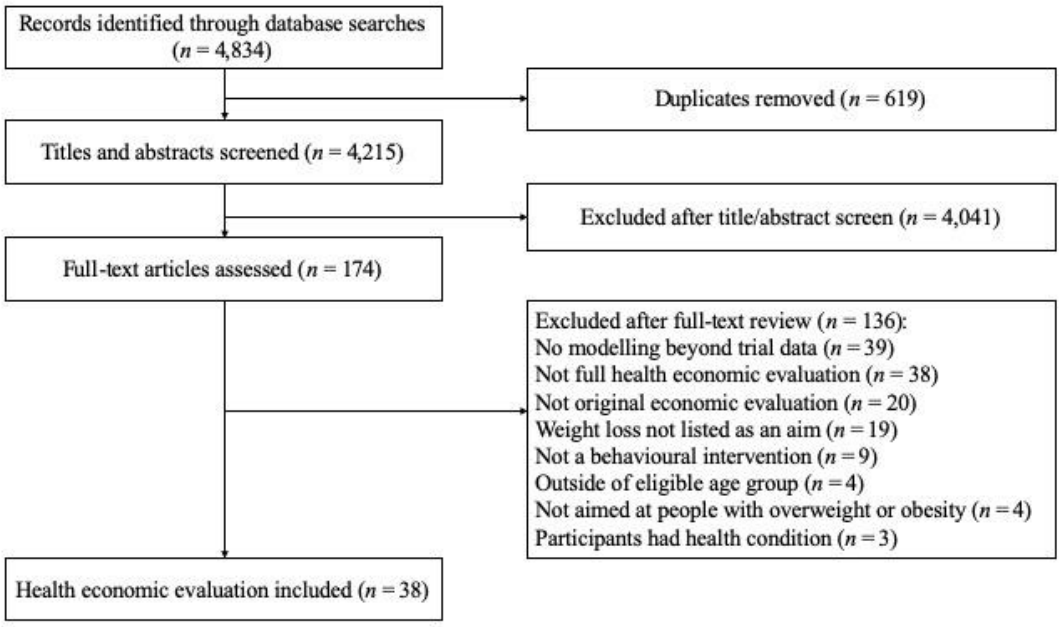

Figure 2.1. PRISMA flow diagram

2.4.1. Assumptions made about weight trajectories

Six different methods were used to predict weight trajectories in the HEMs; these are graphically represented in Figure 2.2.

a) Weight-loss maintained

Twelve HEMs (23-34) assumed that the weight loss experienced by the intervention group was maintained such that from the end of the trial, and for the remainder of the time horizon, the weight difference between the intervention and control group was maintained. The parallel weight trajectories were either stable (each group remained the post-intervention weight) for the remainder of the time horizon (23-28, 32, 33) or followed a natural history of weight in which individuals followed the expected trajectory of someone with their post-intervention weight (29-31, 34) (Figure 2.2a).

b) Weight-loss regained immediately

Eight HEMs (35-42) assumed that the intervention effect ceased after the trial follow-up and that those receiving the intervention immediately returned to the same weight as the control group. From this point onwards, there was no weight difference between the intervention and control groups; their weight either remained at that value for the remainder of the time horizon (35-39, 42) or followed a natural history trajectory (40, 41) (Figure 2.2b).

c) Linear weight regain

Eleven HEMs (43-53) assumed that the weight loss was regained by a set time after completion of the trial or intervention. The time at which all weight was regained varied from 5 months (52) to 5 years (43) post-intervention (Table 2.1). Following this, it was either assumed that both groups remained the same weight (43, 44, 47-49, 51, 52) or followed a natural history weight trajectory for the remainder of the time horizon (45, 46, 50, 53) (Figure 2.2c).

d) Subgroup-specific trajectories

Three HEMs (54-56) divided the population assigned to a weight management intervention into two groups with associated trajectories (e.g. Figure 2.2d). In one study (56) individuals were divided into short-term (6

months) and long-term (5 years) maintainers; the latter were then assumed to maintain this weight for the rest of the time horizon. The probabilities of long- and short-term weight maintenance were 20% and 67% respectively. Two HEMs (54, 55) divided individuals into responders and non-responders. Responders were defined as those who successfully lost weight (54) or successfully maintained the weight loss during the intervention (55). The percentage of responders ranged from 33% (54) to 40% (55) and responders were expected to maintain weight loss for 4 years before either regaining the weight immediately (54) or over a further 4 years to return to pre-intervention weight by 8 years post-intervention (55).

e) Exponential decay of effect

Two HEMs (57, 58) assumed an annual effect reduction per year (Figure 2.2e). Ginsberg and Rosenberg (2012) assumed an annual reduction of effect of 50%; in the first year 50% of the weight loss was regained, the following year 50% of the remaining weight loss was regained and this continued until the effect had effectively diminished. Cobiac and colleagues (57) did not report the rate at which the intervention effect declined, but they stated that the rate used resulted in almost complete weight regain by 5.5 years after baseline. In both models, it was assumed that the weight of the control group remained stable throughout the time horizon rather than follow a natural history weight trajectory.

f) Period of maintenance followed by regain

Two HEMs (59, 60) assumed that, for those participating in the weight management intervention, weight loss was maintained for 6 years and regained between 6 and 10 years (Figure 2.2f). In both of these models, it was assumed that the weight of the control group remained stable throughout the time horizon rather than follow a natural history weight trajectory.

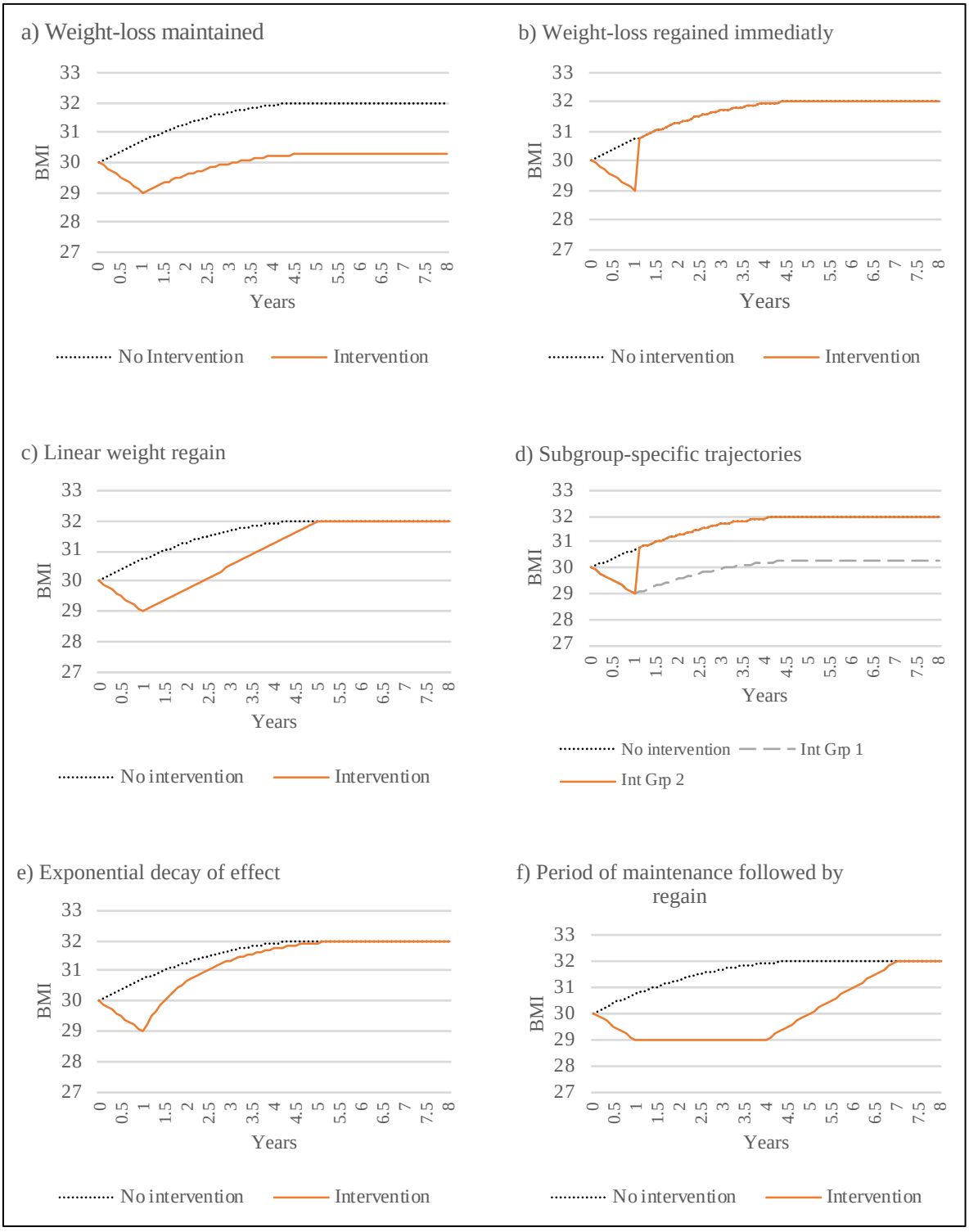

Figure 2.2. Graphical representations of categories of weight trajectory assumptions used in health economic models of overweight or obesity.

2.4.2. Evidence sources used to justify assumed weight trajectories

None of the HEMs that included assumptions that either weight loss was maintained (*n* = 12) or regained immediately (*n* = 8) cited an evidence source to justify this assumption. Of those that utilised other assumptions, three did not give an evidence source (45, 46, 51). Of the remaining 15 HEMs, seven (43, 44, 48-50, 52, 57) cited a meta-analysis, six (47, 53-55, 59, 60) cited trials, two (56, 58) cited a range of sources (including meta-analyses, trials and observational studies). The details of the evidence sources are provided in Table 2.1.

Nine of the HEMs (29-31, 34, 40, 41, 45, 46, 50) utilised a natural history to represent the weight trajectory of the control group and the intervention group once, and if, weight had been regained. The annual rates of weight gain reported for the natural history trajectories were 1kg (30, 46), 0.43kg (29), 0.46kg (34) and 0.16 BMI units (40); four studies did not report this detail (31, 39, 45, 50). These rates of regain were based on the change observed in individuals over time within trials (5, 61), a meta-analysis (62), observational studies (63, 64) or on NICE guidelines (1).

Table 2.1. Evidence sources used to inform the prediction of weight trajectory

First author	BMI trajectory assumption	Type of evidence source	Description and brief findings	Limitations
Au, N. (47)	Weight regain between week 26 and 78 in the study was extrapolated until baseline BMI was reached.	Trial (65)	The trial compared 6 months of standard behavioural therapy (SBT) with detailed meal plans and shopping lists (*n* = 163). One-year post-intervention, weight loss was 6.9kg for the intervention group compared to 3.3 kg for the SBT group.	The sample size was small and had a maximum follow-up of 18 months (12 months post-intervention).
Cobiac, L. (57)	Annual exponential decay of effect of 50% (almost no effect after 5.5 years).	Meta-analysis (6)	The review included 46 studies (11,853 participants) examining the impact of dietary counselling interventions on weight loss compared to a control group with follow-up of up to 5 years. Results suggest a regain of 0.02 to 0.03 BMI units per month post-intervention such that, on average, participants return to their baseline weight after 5.5 years	Only a single study (*n* = 51) had a follow-up of 5 years. Studies had high rates of missing data and were moderate to poor quality.
Cleghorn, C. (52)	Weight regain of 0.03 BMI unit/month (regained fully by 5 months post-intervention).			
Forster, M. (43)	Weight regain of 0.03 BMI unit/month (regained fully by 5 years post-intervention).			
Fuller, N. (48)	Weight regain of 0.03 BMI unit/ month after the 2-year follow-up.			
Retat, L. (50)	All weight loss was regained over 5 years post intervention.			
Whelan, M. (44)	Weight regain of 0.03 BMI unit/ month.			

First author	BMI trajectory assumption	Type of evidence source	Description and brief findings	Limitations
Ginsberg, G. (58)	Annual exponential decay of effect of 50%.	Meta-analysis (66)	The review included 80 studies (26,455 participants) of weight-loss interventions with at least one-year follow-up. Approximately 50% of weight loss was regained at 24, 36 and 48 months.	The meta-analysis was only conducted on 21 diet and/or exercise studies (the remainder were pharmacological interventions). The average proportion of participant dropout was 29%.
		Trial (5) (Also referenced by Gillet et al. 2012)	The Diabetes prevention programme (US) examined the effectiveness of an intensive lifestyle intervention for 3234 overweight individuals. Participants lost a mean of 7 kg by 1 year. This was gradually regained and at the 7-year follow-up, participants maintained at weight loss of 2kg.	Only individuals with impaired glucose tolerance were included. Lifestyle sessions to reinforce original weight loss were offered every 3 months, which may have increased weight loss maintenance. At the 3-years follow-up weight was collected from less than 50% of participants.
		Observational study (8) (Also reference by Roux et al. 2006)	The national weight control registry is a large (n > 4000) self-selecting sample of individuals that had successfully maintained weight loss (≥ 13.6kg) for at least a year at entry into the registry. Participants in this study reported having lost an average of 33kg from an average maximum weight of 105kg. More than 87% of participants reported maintaining a weight loss of at least 10% (of initial weight) after 10 years.	Participants were self-selecting and weight loss on entry to the registry, and weight change while in the registry was self-reported.
Gillet, M. (55)	Responders (40%) maintained weight loss until year 4 and regained all weight loss by year 8.	Trial (67)	The Finnish Diabetes Prevention Study (n = 523) examined the effectiveness of a diabetes prevention lifestyle (diet plus exercise) intervention. At the 7-	The mean follow-up was 3.2 years indicating longer follow-up was not available for many participants. Only

First author	BMI trajectory assumption	Type of evidence source	Description and brief findings	Limitations
Galani, C. (59)	Weight loss maintained until year 6 before a linear weight regain to year 10.		year follow-up, the intervention group had maintained an average weight loss of 3.1kg (maximum average weight loss reported at 2 years to be 4.2kg).	individuals with impaired glucose tolerance were included.
Galani, C. (60)	Weight loss maintained until year 6 before a linear weight regain to year 10.			
Kent, S. (49)	Weight returned to baseline weight over 5 years.	Meta-analysis (7)	The review included 45 trials (7,788 participants) of behavioural interventions focussed on weight loss maintenance. The mean difference between the intervention and control groups was significant at 24 months but not at 30 months.	Only 2 studies (n = 694) reported outcomes at 24 and 30 months. The average participant dropout was 28.4% and 20% for the weight loss and weight loss maintenance interventions respectively.
Lymer, S. (53)	Participant's weight increased by 3% annually from their lowest weight to their pre-intervention weight.	Trial (68)	In a comparison of a 12-month of a commercial weight management intervention and standard care (n = 772), there was no significant weight difference between groups at 24 months.	Follow-up was limited to 24 months (1-year post-intervention). Only 203 of 772 participants completed the 24-month visit.
Roux, L. (56)	Participants had a 20% probability of long-term weight maintenance (remain at post-intervention weight for the remainder of the time horizon) and a 67% probability of short-term weight maintenance (weight	Observational study (69)	A telephone survey of participants who had maintained a weight loss of at least 10% from their maximum weight for at least a year. Of those who had been overweight (n = 228), 62% reported losing more than 10% of their maximum weight and of this, 47-49% had maintained the weight loss for at least 1 year.	The sample size was small and all weight change was self-reported. Only 57% of people contacted agreed to take part in the survey.

First author	BMI trajectory assumption	Type of evidence source	Description and brief findings	Limitations
	maintenance for 6 months). The remainder did not lose weight.	Trials	Lowe et al., 2001 (70) examined weight loss maintenance among participants (n = 1,002) of a commercial weight loss program. At 5 years, 42.6% of participants had maintained a loss of 5% or more and 18.8% had maintained a loss of 10% or more.	All participants had already met their goal weight (determined by the participant); maintenance among participants who did not meet their goal weight was not included.
			Anderson et al., 2013 (71) assessed long-term weight maintenance after a very-low-calorie dietary intervention. Participants (*n* = 122) regained an average of 73% of their weight loss during the first 3 years. The average weight loss maintained was 23% of initial weight loss after 5 years.	The sample size was small. There were 426 participants in the program but only 154 were eligible for follow up (e.g. completed the programme and met weight loss target of 10kg) and data was only available for 122 (73%) of these.
			Gosseline & Cote, 2001 (72) report weight loss maintenance among participants (*n* = 291) of a commercial weight loss program. At a follow-up of 9-11 years, 20% maintained at least 5% of their initial weight loss.	A maximum of 55 participants completed assessments at each time point. Only participants that had reached their goal weight in the initial weight loss programme were included.
		Meta-analysis (73)	The review included 29 studies (4,298 participants) of dietary interventions. At 5 years post-intervention, average weight maintenance was 23% of initial weight loss.	Only very low energy or energy balanced dietary interventions were included. Eight (1,388 participants) of the 29 studies had a 5-year follow-up. An average of 79% of participants were available for follow-up.

First author	BMI trajectory assumption	Type of evidence source	Description and brief findings	Limitations
Segal, L. (54)	Successful participants (33%) maintained weight loss until year 4 when all weight was regained. The remainder followed the trajectory of the control group.	Trial (74)	In a feasibility trial of 370 participants with impaired glucose tolerance, participants (90% available for follow-up) maintained an average of 50% of initial weight loss after 5 years.	The sample size was small and limited to participants with impaired glucose tolerance.

BMI, body mass index; SBT, standard behavioural therapy

2.4.3. Impact of differing assumptions on outcomes

Nineteen of the HEMs conducted sensitivity analysis around the assumption of weight trajectories. In these studies other assumptions about weight trajectories were modelled to determine the magnitude of change in the outcomes. The assumption used in the main analysis and resulting ICER, and the sensitivity analysis conducted and corresponding ICER (or reported impact) are reported in Table 2.2. The findings in this table indicate that the weight trajectory assumption does impact on cost-effectiveness outcomes. In eight of these studies (24, 26, 49, 51, 52, 56-58) the sensitivity analysis had a large enough impact on the outcomes of the evaluation that the ICER crossed a known or estimated cost-effectiveness threshold in the country in which the analysis was based. This may have altered the conclusions and recommendations from the CEA. Five of these tested the scenarios in which all weight loss was either maintained for the remainder of the time horizon (52, 57, 58) or regained immediately (24, 26). Two tested a scenario in which the duration of intervention effect was reduced (49, 51) and one reduced the probability of individuals achieving weight maintenance (56). In another HEM (27) that tested an increase in the percentage of weight loss regained, the cost-recovery period increased from 6 to 13 years (ICER not reported) which may also impact the assessment of cost-effectiveness.

Table 2.2. Impact of Sensitivity analyses conducted on predicted weight trajectories within HEMs

First author	Method used to predict weight trajectory	Base case ICER	Specific method tested in sensitivity analysis	Impact on ICER
Au, N. (47)	Linear weight regain	£166/ QALY	Upper CI of treatment effect and regain	£61/QALY
			Lower CI of treatment effect and regain	£330/QALY
Bemelmans, P. (36)	Weight regained immediately	€7,400/ QALY	Permanent decrease in overweight of one percentage point and no improvement in physical activity.	€9,900/QALY
			Permanent decrease of 4% in overweight and inactivity.	€5,600/QALY
Cleghorn, C. (52)	Linear weight regain	79,700 NZD/ QALY	Weight loss maintained.	Cost-saving
Cobiac, L. (57)	Exponential decay of effect (50%)	130,000 AUD/ DALY	Rate of decay varied from no benefit after the first year to full benefit sustained for life.	Probability of cost-effectiveness: 0% to 83% (threshold: $50,000/DALY)
Finkelstein, E. (51)	Linear weight regain	$30,071/ QALY	Duration of intervention effect reduced from 3 years to 1 year.	$58,867/QALY
Forster, M. (43)	Linear weight regain	12,000 AUD/ DALY	Rate of regain halved.	3,000 AUD/DALY
Ginsberg, G. (58)	Exponential decay of effect (annual decay of 50%)	47,559 NIS/ QALY	Annual decay of intervention effect 20%.	11,812 NIS/QALY
			Annual decay of intervention effect 35%.	29,661 NIS/QALY
			Annual decay of intervention effect 65%.	65,457 NIS/QALY
			Annual decay of intervention effect 80%.	83,355 NIS/QALY
Gray, C.(34)	Weight loss maintained	£2,150/ QALY	Weight regained.	Remained cost-effective.
Gustafson, A. (23)	Weight loss maintained	$183/ LYG	50% of weight loss maintained.	$3,612/QALY
			Weight loss regained after 1 year.	$18,615/QALY
Hersey, J. (27)	Weight loss maintained	$4,400-5,600/ QALY (Cost-recovery period 6 years)	Participants regained 30% more.	Cost-recovery period increased to 13 years.
			Participants regained 30% less.	No impact on cost-recovery period.

First author	Method used to predict weight trajectory	Base case ICER	Specific method tested in sensitivity analysis	Impact on ICER
Kent, S. (49)	Linear weight regain	£12,955/ QALY	Participants maintained a 1kg lower weight than their pre-intervention weight after 5 years.	£3,203/QALY
			Weight regained immediately and then each year up to 5 years.	Cost-effective only if weight regain takes ≥ 3 years
Krukowski, R. (24)	Weight loss maintained	$2,160-3,306/ LYG	All participants returned to pre-intervention weight at 1 year.	$73,005-111,736/LYG
			Participants regained 50% of the weight at year 1 and the remaining weight by the end of the time horizon.	$6,602/LYG
Lewis, L. (40)	Linear weight regain	£12,585/ QALY	Assumed that BMI returned to pre-intervention weight after 12 months if data wasn't available.	£15,276/ QALY
Meads, D. (29)	Weight loss maintained	Dominant	All weight-loss regained by year 2.	Dominant
			All weight-loss regained by year 3.	Dominant
Miners, A. (30)	Weight loss maintained	£103,112/ QALY	Doubled the time to a 0.1 BMI increase after the treatment stops.	£122,125/ QALY
Palmer, A. (38)	Weight regained immediately	£6,381/ LYG	Intervention effective over lifetime.	£4,439/LYG
Roux, L. (56)	Subgroup-specific trajectories: probability of short- and long-term maintenance 67% and 20%	$12,640/ QALY	Probability of long-term maintenance 0%.	$36,000/QALY
			Probability of long-term maintenance 60%.	$5,000/QALY
			Probability of short-term maintenance 20%.	$130,000/QALY
			Probability of short-term maintenance 80%.	$15,000/QALY
Sacks, G. (26)	Weight loss maintained	Dominant	Effect decayed progressively down to no effect after 10 years.	$50,000 AUD/ DALY
Trueman, P. (46)	Linear weight regain	Dominant	Weight loss is maintained as a decrement below the expected weight trajectory.	Dominant

AUD; Australian Dollars, DALY; Disability Adjusted Life Years, LYG; Life Years Gained, NIS; Israeli new shekel, NZD; New Zealand Dollars, QALY; Quality Adjusted Life Years

2.4.4. Factors used to predict weight trajectories

None of the studies reported using psychosocial factors to predict weight trajectories.

2.4.5. Measurement of psychosocial factors within evidence sources informing weight trajectories

The evidence sources cited for a) estimated weight loss and b) estimated weight regain trajectory were examined to determine if any psychosocial variables had been measured. Psychosocial variables measured in either of these indicates the potential to have included these within the health economic modelling to inform predictions of weight trajectories.

a) Estimated weight-loss. Thirty HEMs cited an evidence source for estimated weight-loss that reported no measurement of psychosocial variables (24-33, 35-40, 42, 44, 46, 49-52, 54-60). Psychosocial variables were measured in evidence sources cited in eight HEMs (Table 2.2); four of these HEMs (43, 45, 48, 53) each based the estimated weight loss on a single trial but no analyses of the psychosocial variables measured in relation to the intervention or weight change were reported in the trial. Four HEMs (23, 34, 41, 47) cited five trials that included some analysis of psychosocial factors. In four of these trials, there were significant changes to psychosocial variables but no reported analysis of the association between these changes and weight loss outcomes. First, in a study that provided either a shopping list for healthy meal ingredients or the ingredients free-of-charge, there was greater adherence to self-monitoring of food intake and exercise (47, 65), and both interventions reduced the time and effort required to decide on, and plan meals. For those that were provided food free-of-charge potential financial barriers to healthy eating were reduced (47, 65). Second, a work-based dietary intervention influenced diet-related attitudes including a reduction in confusion about what to eat and an increase in the belief that food is important for health. There was no reported impact of this intervention on perceived social support or self-efficacy for increasing fruit and vegetable consumption (75). Third, a behavioural intervention aimed at low-income women improved perceived social support (76) and, fourth, an intervention for men delivered through professional football clubs improved self-esteem and positive affect (i.e. feelings and emotions) (34). One trial reported analysis of associations between psychosocial variables and BMI; following the introduction of a nutritional labelling policy, health attitudes, including beliefs about own health and desire to change health status, were not associated with a change in BMI (77).

b) Estimated weight regain trajectory. When examining the evidence sources to estimate the weight trajectory beyond the initial weight loss, two HEMs (56, 58) cited studies that included psychosocial variables. In these studies, decreases in dietary restraint (78) and increases in dietary disinhibition (78, 79), hunger (78), depression (78, 79) and binge eating (78, 79) were associated with regaining weight. Two HEMs (45, 50) cited changes in weight over time observed in the Health Survey for England (HSE) to support the use of an annual weight change for both the control group and intervention group post-regain; this is the weight trajectory expected in the absence of any intervention. The HSE is an annual repeat cross-sectional survey of around 8,000 adults and included measures of stress and eating habits. The measure of eating habits used was a descriptive measure of eating behaviour rather than the extent to which a behaviour is habitual. Both stress and eating habits have the potential to impact weight loss maintenance (13, 15, 64) but no analyses were reported to test this.

Overall, the most frequently assessed variables within trials used to estimate weight loss were depression and/or anxiety (n = 6), dietary restraint (n = 5) and social support (n = 4). There was evidence to indicate that dietary restraint, dietary disinhibition, hunger, depression and binge eating were associated with change in BMI although only three of the 13 evidence sources cited included analyses of the association between the psychosocial variables measured and weight loss outcomes.

Table 2.3. Psychosocial variables measured within evidence sources referenced in HEMs

Variables Measured	**Definition**	**Measured in evidence source cited for estimated:**	
		Weight loss	**Weight regain**
Depression	Persistent low mood and loss of interest or pleasure (80).	Ahern (45), Forster (43), Fuller (48), Gustafson (23),	Ginsberg (58), Roux (56)
Anxiety	Feelings of tension worry or unease with physical symptoms such as sweating (80).		
Dietary restraint	Conscious restriction of dietary intake with to manage weight (81).	Ahern (45), Forster (43), Fuller (48), Lymer (53)	Ginsberg (58),
Social support	The quantity and quality of people that an individual feels they can rely on and seek support from (82)	Cecchini (41), Forster (43), Fuller (48), Gustafson (23)	
Dietary disinhibition	The tendency to overeat in response to factors such as availability of palatable foods or emotional stress (81).	Forster (43), Fuller (48), Lymer (53)	Ginsberg (58),
Binge eating	The extent to which an individual consumes more than most would and feel out of control when eating (83).		Ginsberg (58), Roux (56)
Health attitudes	Beliefs, feelings, and thoughts about food (e.g. beliefs about what is healthy or belief diet is important for health (75).	Cecchini (41), Forster (43)	
Perceived stress	The extent to which situations in an individual's life are viewed as stressful (84).	Forster (43)	Ahern (45), Retat (50)
Habit	The extent to which health behaviours become automatic and part of an individual's identity (85).	Ahern (45)	Ahern (45), Retat (50)
Self-regulation	Monitoring of own health behaviour which can be autonomous (internally motivated) or controlled (externally motivated) (45).	Ahern (45)	
Problem eating behaviour	The perception of certain eating behaviours as problematic to the individual (45).	Ahern (45)	Roux (56)
Life satisfaction	The extent to which an individual is satisfied with their life (86).	Ahern (45)	
Self-monitoring	The degree to which individual records or monitors the food they consume and the exercise they do (87).	Au (47)	
Resources	The financial, cognitive and time resources that an individual has available.	Au (47)	

Self-efficacy	An individual's belief in his or her ability to execute health eating and exercise behaviours (88).	Cecchini (41)	
Outcome expectancies	An individual's belief that a certain behaviour or action will lead to a specific outcome. (89)	Cecchini (41)	
Hedonic hunger	The drive to eat for pleasure in the absence of a physiological need for food (90).		Ginsberg (58)
Self-esteem	The way an individual positively or negatively evaluates their view of themselves (91).	Gray (34)	Roux (56)
Mood	An individual's state of mind or feeling (92).		Roux (56)
Affect (Positive and Negative)	The emotions and expression of a positive (e.g. cheerfulness) or negative (e.g. sadness) nature (93).	Gray (34)	

2.5 Discussion

There was a wide range of weight trajectory assumptions made within the HEMs, which varied in complexity from simple assumptions such as regaining or maintaining all weight loss to more complex assumptions such as subgroup-specific trajectories or applying an exponential decay of intervention effect. In the absence of data, it is difficult to determine which is the most likely to be accurate. Thus, the second aim was to examine the evidence on which these assumptions are based. Fifteen of the 38 studies included in the review cited an evidence source to justify the assumption made and these sources included meta-analyses, trials, and observational studies. While many of these sources represented a large number of participants and long-term follow-up, the sample sizes decreased as the length of follow-up increased. Furthermore, some of the evidence sources were focused mainly or solely on those participants who were successful in weight loss and weight loss maintenance (67, 69, 78, 79, 94). Although in two HEMs these sources were used to inform the trajectories of successful participants only, another included it alongside other evidence sources to inform the trajectories of all participants which could result in an overestimation of effect. Others focussed on a population with impaired glucose tolerance and these may have a different weight trajectory to those who have a healthy glucose tolerance given the differences in weight loss observed between those with and without diabetes (6). In addition, the evidence sources indicated a wide range of results; reported weight regain at 5 years ranged from 0% to 50% of initial weight loss and one source reported that over 80% of participants were able to maintain a 10% (of initial weight) weight loss for 10 years (95). There was no evidence cited to support the assumptions that all participants regained weight loss immediately post-intervention or maintained all weight loss indefinitely indicating that these assumptions should not be used within HEMs unless there is strong evidence to support this. However, due to the large variation in reported weight loss maintenance, there is not a single weight trajectory assumption that can be recommended at this time. This justifies further analysis of the factors associated with weight loss maintenance to understand this variation and improve the prediction of weight trajectories.

For the third aim, we reviewed any sensitivity analyses conducted around weight trajectory assumptions. Using different weight trajectories impacted on the costs and consequences to the extent that, in almost half of the studies that conducted this type of sensitivity analysis, it would likely impact on assessments of cost-

effectiveness. This highlights that a change in the assumptions used could have a large impact on results and that results from models using different assumptions are unlikely to be comparable. Given this impact, sensitivity analysis on the weight trajectory should always be conducted in health economic modelling of obesity particularly on the time post-intervention at which a participant returns to their pre-intervention weight (if at all). This is especially important if the main assumption is that all weight loss is immediately regained post-intervention or maintained for the rest of the time horizon; there is little evidence for these assumptions and when tested in sensitivity analysis, they often resulted in large changes in outcomes. The impact that these assumptions had on outcomes further support the need to gain a greater understanding of weight trajectories.

Reviews of survival analyses used in cost-effectiveness analyses have identified similar limitations in long-term extrapolation methods. Similar to weight trajectories, the long term survival of individuals is hard to determine from short-term data, has a potentially large impact on estimates of cost-effectiveness, and methods used are not consistent and often not justified (96, 97). Hawkins and Grieve (2017) state that considering causal assumptions is essential to improving the accuracy of cost-effectiveness analyses; in survival analyses, these may be factors such as time take for illness to progress to a more severe state (97) whereas for the assumptions made about weight trajectories, these may be psychosocial factors.

The fourth and fifth aims of this review were to examine the use of psychosocial variables to predict weight trajectories and the potential role of psychosocial factors in HEMs. None of the HEMs utilised any psychosocial variables in the prediction of individual weight trajectories. However, psychosocial variables were measured within the evidence sources that informed weight trajectories. Furthermore, analyses conducted within these evidence sources indicated that the weight-loss interventions were associated with improvement in self-monitoring, financial and time resources, attitudes and social support and that decreased dietary restraint, and increased dietary disinhibition, hunger, depression and binge eating were associated with weight regain. The variables could have been included in the HEMs which would not only add to the understanding of why an intervention is effective, which can inform future intervention design, but also aid in the prediction of weight trajectories within HEMs. Weight trajectories may be different depending on whether psychosocial factors (that promote weight loss maintenance) have changed during an intervention. For example, in a trial of two weight loss programmes, despite equivalent outcomes at the end of the 12-week treatment period, the

intervention that focused more on habit formation was associated with greater weight loss maintenance after 6 months (98). Including psychosocial variables would enable weight trajectory to be based, in part, on change in psychological variables and thus these long-term differences would be represented. Similarly, an individuals' observed shift in psychosocial variables can be used to inform their long-term weight trajectories which may better reflect the heterogeneity that is observed in the evidence sources cited by the HEMs. Thus, including psychosocial variables has the potential to improve the accuracy of estimates of long-term weight trajectories and therefore the accuracy of cost-effectiveness estimates.

There are some limitations of this review. First, although PRISMA guidelines were followed, we did not measure quality or risk of bias for the studies; the review was focussed on a specific aspect of HEMs on which there are no current guidelines; as a result, the review focussed on description of the method rather than the quality. Secondly, a formal assessment of the evidence used to support assumptions was not conducted, as this was not in the scope of the review. The type of evidence cited, and brief details have been included but future research could apply a formal assessment which would help to determine which assumption is best supported by evidence. Thirdly, although the search was extensive, it focussed on academic journals and thus there may have been eligible HEMs generated for organisations such as governments, local authorities or charities that were not included. Also, the criteria that weight loss must be an aim of the intervention may have excluded HEMs of interventions of prevention programmes that measured and predicted weight trajectories despite weight loss not being an explicit aim. Similarly, the restriction to English-language journals may have excluded models using alternative methods. Finally, in considering the impact of the different trajectories, the review was limited to the types of sensitivity analysis conducted by the studies. The extent to which the weight trajectory tested in sensitivity analysis diverged from the base case assumption varied and alternative comparisons of assumptions may have led to different conclusions.

2.5.1 Conclusion

The current review has highlighted that (i) there is no consistent assumption made about weight trajectories beyond the weight loss intervention, (ii) the evidence of long-term weight maintenance is limited, and results are highly variable, and (iii) the assumption used has the potential to impact assessments of cost-effectiveness. Furthermore, (iv) despite evidence indicating that psychosocial variables are associated with weight loss

maintenance, they have not been used to inform the prediction of weight trajectories. This is despite the finding that (v) psychosocial variables have been measured within cited evidence sources. Future research should investigate how psychosocial variables measured within trials and observational studies can be used within HEMs to increase the accuracy of predicted weight trajectories and estimates of cost-effectiveness.

2.6 Contribution to thesis

This chapter confirmed that estimating long-term weight trajectories presents a challenge when conducting health economic modelling of a behavioural weight management intervention. This reflects the weight management literature where understanding the extent of weight loss maintenance post weight loss remains difficult due to the lack of long-term follow-up. This indicates the need to explore other methods that could contribute to accurate predictions of weight loss and weight loss maintenance when estimating cost-effectiveness. The finding that psychosocial variables were not included in the health economic models despite the data being available in some cases, provides evidence that there is the potential to incorporate these variables. Incorporating psychological variables has been identified as an avenue for future research in public health economic modelling methods and this review contributes to the rationale for considering how psychological variables can be included in health economic models of obesity, particularly in the prediction of weight trajectories. In the next chapters, I investigate what psychological factors explain the effectiveness of a weight management intervention (Chapter 3) and then incorporate these into a health economic model of obesity to inform predictions of weight trajectories (Chapter 4).

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2.8 Supplementary Material

Table 2.4. Full search strategy

Search terms (AND, OR, NOT) and truncation (wildcard characters like *)	***(Obes* OR Overweight) AND (weight loss OR calorie restriction OR diet,reducing OR weight maintenance OR life?style OR healthy lifestyle OR health diet OR health promotion OR weight reduction programs OR weight management OR eating behaviour OR diet OR health diet OR portion size OR serving size OR exercise OR physical activity) AND cost: OR cost benefit analys: OR health care costs) NOT (child)*** ***(((((((obesity[Title/Abstract] OR Overweight[Title/Abstract])) AND ("caloric restriction"[Title/Abstract] OR "calorie restriction"[Title/Abstract] OR diet[Title/Abstract] OR weight maintenance[Title/Abstract] OR weight loss[Title/Abstract] OR weight reduction[Title/Abstract] OR management[Title/Abstract] OR "eating behaviour"[Title/Abstract] OR "eating behavior"[Title/Abstract] OR "health* diet"[Title/Abstract] OR "portion size"[Title/Abstract] OR "serving size"[Title/Abstract] OR exercise[Title/Abstract])) AND (cost[Title/Abstract] OR cost benefit analysis[Title/Abstract] OR health care costs[Title/Abstract] OR economic[Title/Abstract]))) humans***
Databases searched	*Medline, Pubmed, Cochrane, NHS EE, Embase, PSYCinfo, Cinahl, Econlit*
Part of journals searched	*Title, abstract, keyword, subject heading word.*
Years of search	*Up until 24th November2017*
Language	*English*
Types of studies to be included	*Heath economic evaluation of non-pharmaceutical non-surgical obesity interventions tha include some health economic modelling*
Inclusion criteria (why did you include it?	*Health economic evaluation* *Includes modelling of outcomes beyond available data* *Incudes modelling of at least one behavioural/public health intervention (including disease prevention programmes)* *Weight or BMI is an outcome* *Aimed at adults (18 -65)*
Exclusion criteria (why did you rule it out?	*Health economic evaluation of solely drug and pharmaceutical interventions* *Aimed at children or older adults 65+* *Aimed exclusively at population with health condition (e.g. post MI or post-natal)* *If weight or BMI is not measured as an outcome*

Table 2.5. Data extraction form

Column Headings
First author
Country
Type of model
Time horizon
Intervention type
Method/assumption used to predict weight trajectory
Sensitivity analysis on trajectory (1 row for each type if more than one)
Impact on CE outcomes
Any mention of psychosocial variables throughout paper (if yes list what variables and what section of paper)
Reference to psychosocial variable in assumptions of weight trajectory (if yes, list the variables and context)
Analysis conducted between intervention and psychosocial variables
Analysis conducted between psychosocial variables and weight trajectory
Evidence sources cited to justify assumptions made about weight trajectories (1 row per evidence source if more than one)
Author and reference (NA if none)
Type of evidence source (e.g. trial, meta-analysis)
Psychosocial variables measured
Analysis conducted between intervention and psychosocial variables
Analysis conducted between psychosocial variables and weight trajectory

Table 2.6. Final papers

First author	Year	Title
Ahern, A.	2017	Extended and standard duration weight-loss programme referrals for adults in primary care (WRAP): a randomised controlled trial.
Au, N.	2013	The cost-effectiveness of shopping to a predetermined grocery list to reduce overweight and obesity
Avenell, A.	2004	Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement.
Bemelmans, P.	2008	The costs, effects and cost-effectiveness of counteracting overweight on a population level. A scientific base for policy targets for the Dutch national plan for action.
Cecchini, M.	2010	Tackling of unhealthy diets, physical inactivity, and obesity: health effects and cost-effectiveness.
Cleghorn, C.	2019	Health benefits and cost-effectiveness from promoting smartphone apps for weight loss: Multistate life table modelling.
Cobiac, L.	2010	Cost-effectiveness of Weight Watchers and the Lighten Up to a Healthy Lifestyle program
Dalziel, K.	2007	Time to give nutrition interventions a higher profile: cost-effectiveness of 10 nutrition interventions
Finkelstein, E.	2019	Incremental cost-effectiveness of evidence-based non-surgical weight loss strategies
Forster, M.	2011	Cost-effectiveness of diet and exercise interventions to reduce overweight and obesity
Fuller, N.	2013	Cost effectiveness of primary care referral to a commercial provider for weight loss treatment, relative to standard care: a modelled lifetime analysis
Galani, C.	2007	Modelling the lifetime costs and health effects of lifestyle intervention in the prevention and treatment of obesity in Switzerland.
Galani, C.	2008	Uncertainty in decision-making: value of additional information in the cost-effectiveness of lifestyle intervention in overweight and obese people
Gillet, M	2012	Non-pharmacological interventions to reduce the risk of diabetes in people with impaired glucose regulation: a systematic review and economic evaluation.
Ginsberg, G.	2012	Economic effects of interventions to reduce obesity in Israel
Gray, C.	2018	Long-term weight loss trajectories following participation in a randomised controlled trial of a weight management programme for men delivered through professional football clubs: a longitudinal cohort study and economic evaluation

First author	Year	Title
Gustafson, A.	2009	Cost-effectiveness of a behavioural weight loss intervention for low-income women: The Weight-Wise Program.
Hersey, J. C.	2012	The efficacy and cost-effectiveness of a community weight management intervention: A randomized controlled trial of the health weight management demonstration.
Kent, S.	2019	Is doctor referral to a low-energy total diet replacement program cost-effective for the routine treatment of obesity?
Krukowski, R.	2011	Comparing behavioral weight loss modalities: incremental cost-effectiveness of an internet-based versus an in-person condition
Lewis, L.	2014	The cost-effectiveness of the LighterLife weight management programme as an intervention for obesity in England
Lymer, S.	2018	The population cost-effectiveness of weight watchers with general practitioner referral compared with standard care
Meads, D.	2014	The cost-effectiveness of primary care referral to a UK commercial weight loss programme
Michaud, T.	2017	Cost-effectiveness and return on investment of a scalable community weight loss intervention
Miners, A.	2012	An economic evaluation of adaptive e-learning devices to promote weight loss via dietary change for people with obesity
Olsen, J.	2005	Cost-effectiveness of nutritional counselling for obese patients and patients at risk of ischemic heart disease
Palmer, A.	2000	Applying some UK Prospective Diabetes Study results to Switzerland: the cost-effectiveness of intensive glycaemic control with metformin versus conventional control in overweight patients with type-2 diabetes
Retat, L.	2019	Screening and brief intervention for obesity in primary care: cost-effectiveness analysis in the BWeL trial
Roux, L.	2006	Economic evaluation of weight loss interventions in overweight and obese women
Sacks, G.	2011	'Traffic-light' nutrition labelling and 'junk-food' tax: a modelled comparison of cost-effectiveness for obesity prevention.
Segal, L.	1998	Cost-effectiveness of the primary prevention of non-insulin dependent diabetes mellitus.
Smith, K. J.	2010	Cost-effectiveness analysis of efforts to reduce risk of type 2 diabetes and cardiovascular disease in southwestern Pennsylvania, 2005-2007

First author	Year	Title
Smith, K.J.	2016	Cost effectiveness of an internet-delivered lifestyle intervention in primary care patients with high cardiovascular risk.
Su, W.	2016	Return on Investment for Digital Behavioral Counselling in Patients with Prediabetes and Cardiovascular Disease
Thorpe, K.	2011	Enrolling People with Prediabetes Ages 60-64 In A Proven Weight Loss Program Could Save Medicare $7 Billion Or More.
Trueman, P.	2010	Long-term cost-effectiveness of weight management in primary care.
Whelan, M.	2014	Feasibility, effectiveness, and cost-effectiveness of a telephone-based weight loss program delivered via a hospital outpatient setting
Wilson, K.	2014	Cost-effectiveness of a community-based weight control intervention targeting a low-socioeconomic-status Mexican-origin population

CHAPTER 3: INVESTIGATING THE MECHANISMS OF ACTION OF A WEIGHT MANAGEMENT INTERVENTION

This chapter reports the analysis of an data from a trial of a weight management intervention. The intervention was found to be effective and cost-effective in previous analysis but the work in this chapter explores the mechanisms of actions of this intervention to gain an understanding of how the intervention achieves the observed effect on BMI. This has the potential to inform future research and will also inform development of a health economic model to include psychological factors in the subsequent chapters.

The chapter was accepted for publication in *Annals of Behavioural Medicine* in 2021.

Bates, S., Norman, P., Breeze, P., Brennan, A., & Ahern, A. (2021). Mechanisms of action in a behavioural weight-management programme: latent growth curve analysis. Accepted for publication in *Annals of Behavioural Medicine*.

This articles will be published open access following the requirement of the Wellcome Trust who financially supported this work. The conditions of the open access publishing allows use of the final published PDF, original submission or accepted manuscript in this thesis (including in any electronic institutional repository or database). The content of the chapter is the same as the accepted version of the manuscript other than section 3.6.

The paper in the chapter was written with 4 co-authors; Amy Ahern, Penny Breeze, Alan Brennan and Paul Norman. Sarah Bates conceived the idea, conducted the analysis and wrote the manuscript. Penny Breeze, Alan Brennan and Paul Norman supervised the work. Amy Ahern gave permission to use the data that was analysed. Amy Ahern, Penny Breeze, Alan Brennan and Paul Norman provided feedback on the manuscript.

Ethical approval

Ethical approval for the extended and standard duration weight-loss programme referral for adults in primary care (WRAP) trial was received from NRES Committee East of England Cambridge East and local approvals

from NRES Committee North West Liverpool Central and NRES Committee South Central Oxford. This trial was registered with Current Controlled Trials, number ISRCTN82857232. All participants in the original trial gave written informed consent. Approval to conduct the secondary data analysis conducted in this chapter was given by Amy Ahern on behalf of the WRAP Investigator Committee and the Senior Data Manager. Data were robustly anonymised and transferred and stored securely. This ethics approval included the use of the WRAP sample population to simulate the baseline population for the health economic modelling in Chapters 4 and 6. I signed a University Research Ethics Committee-approved self-declaration to confirm that the research involves only existing anonymised data (ID: 021946); Appendix 2.

MECHANISMS OF ACTION IN A BEHAVIOURAL WEIGHT-MANAGEMENT PROGRAMME: LATENT GROWTH CURVE ANALYSIS

3.1 Abstract

Background. A greater understanding of the mechanisms of action of weight-management interventions is needed to inform the design of effective interventions.

Purpose. To investigate whether dietary restraint, habit strength or diet self-regulation mediated the impact of a behavioural weight-management intervention on weight loss and weight loss maintenance.

Methods. Latent growth curve analysis (LGCA) was conducted on trial data in which adults (*N*=1267) with a Body Mass Index (BMI) ≥ 28kg/m² were randomised to either a brief intervention (booklet on losing weight), a 12-week weight-management programme or the same programme for 52 weeks. LGCA estimated the trajectory of the variables over 4 time-points (baseline and 3, 12 and 24 months) to assess whether potential mechanisms of action mediated the impact of the weight-management programme on BMI.

Results. Participants randomised to the 12- and 52-week programmes had a significantly greater decrease in BMI than the brief intervention. This direct effect became non-significant when dietary restraint, habit strength and autonomous diet self-regulation were controlled for. The total indirect effect was significant for both the 12- (estimate=-1.33, se=0.41, p=0.001) and 52-week (estimate=-2.13, se=0.52, p<0.001) programme. Only the individual indirect effect for dietary restraint was significant for the 12-week intervention whereas all three indirect effects were significant for the 52-week intervention.

Conclusions. Behaviour change techniques that target dietary restraint, habit strength and autonomous diet self-regulation should be considered when designing weight loss and weight loss maintenance interventions. Longer interventions may need to target both deliberative and automatic control processes to support successful weight management.

Keywords: weight management, mediation, restraint, habit, self-regulation

3.2 Introduction

Approximately two thirds of adults in the UK and US are classed as being overweight or obese based on their Body Mass Index (BMI) and there is little evidence that the prevalence is decreasing (1, 2). Behavioural weight-management programmes are the first-line treatment for people classed as overweight or obese (3) and although there is evidence that these are effective (4), the results are heterogenous between and within studies (5). In a systematic review, the average weight loss across randomised controlled trials of non-surgical weight loss interventions varied from -4.03kg to -21.3kg (6). There is also variability in evidence for the duration of the intervention effect. A systematic review of trials with a follow-up of at least 16 weeks found evidence for significant intervention effects ranging from 18 months to 5 years from baseline (7).

The heterogeneity in the size and duration of treatment effect may be due to differences in the behaviour change techniques (BCTs) used in an intervention and the mechanisms of actions targeted. For example, in a previous trial, an intervention that used BCTs such as developing implementation intentions to target habit formation resulted in greater weight loss than an intervention that used BCTs such as education about misinformation to target unhealthy relationships with food (8). Given the similarities in the duration and mode of delivery, the findings indicate that the different BCTs used, and mechanisms of action targeted, resulted in differences in weight change. Identifying relevant mechanisms of action associated with the desired outcome will enable the evidence-based selection of BCTs to include in an intervention (9). This is particularly important for weight loss maintenance as weight regain post-intervention is commonly reported (e.g. (7)). Thus, a greater understanding of the mechanisms of action associated with short and longer-term weight loss is needed to inform the design of effective interventions, through the selection of appropriate BCTs, that result in both weight loss and weight loss maintenance.

There are many potential mechanisms of action for weight-management interventions. A common focus of these interventions is to create healthy eating behaviours by restricting the amount and types of food and drinks consumed (10). Efforts to restrict food intake such as using strategies to prevent overeating (e.g., portion control or avoiding unhealthy foods), adjusting eating behaviour after over consuming and being conscious of food choices in order to control weight are often referred to as dietary restraint (11). A recent review of studies

that measured dietary restraint found that restraint was associated with weight loss (12); specifically, higher dietary restraint was associated with a lower weight in populations with obesity and increases in dietary restraint were associated with greater weight loss. In studies that have examined weight loss maintenance, increases in dietary restraint during weight loss have also been found to predict weight loss maintenance (13) and decreases in dietary restraint have been found to be associated with greater weight regain over 18 months (14) to 10 years (8). Although there is evidence from observational and randomised controlled trials that changes in dietary restraint are associated with weight control (12, 15), there has been less research on dietary restraint as a mechanism of action (i.e., mediator) of weight-management interventions. In a review, only one study had conducted formal mediation analysis (16), reporting that dietary restraint mediated the impact of a weight-management intervention on weight loss over 24 months (17). In a more recent study, dietary restraint was not found to mediate the effect of a weight-management intervention; however, the intervention included meal plans and pre-packaged food which may have limited the opportunity for participants to practice restrained eating (18).

Continued dietary restraint may lead to healthy dietary behaviours becoming habitual which, in turn, may aid the maintenance of weight loss. Habits can be defined as learned stimulus-response associations, such that when a stimulus is encountered, an individual responds automatically with a certain behaviour or set of behaviours (19, 20). Habits are formed when a behaviour, such as monitoring diet, eating fruit and vegetables or taking part in physical activity, is repeated frequently in the same context such that a cognitive association is made between the situation and behaviour (21). Habit strength has been associated with eating behaviours in observational studies (22, 23) and decreases in BMI during a weight loss intervention (24). In addition, in a weight loss maintenance intervention, increases in healthy eating habits were associated with decreases in BMI over 1 year (25). Although there has been some research on the benefits of habit-based interventions (9, 26), there is little research on whether habit strength is a mechanism of action of effective interventions. In one study, the effect of a brief habit-based weight loss intervention was mediated by automaticity (27). However, this analysis was conducted over a short time period (3 months) and only one item was used to assess automaticity.

The motivation that drives behaviour change is also a key factor in weight loss and weight loss maintenance (28). Autonomous regulation occurs when engaging in a behaviour is autonomously motivated; that is, the behaviour is perceived as valued, important to the individual, consistent with intrinsic goals or outcomes and part of the individual's identity (29). It is predicted that those with higher autonomous self-regulation are more likely to adhere to the behaviour change desired (30), and this is supported by findings that increased autonomous self-regulation is associated with adherence to self-monitoring behaviour (31), weight loss (31, 32), and weight loss maintenance (33). In contrast, controlled regulation is driven by external pressures such as a reward or avoidance of negative consequences. Although there is evidence that controlled regulation results in success in the short term (34), it is predicted that without autonomous regulation, positive changes in behaviours and weight loss will not be maintained (28). In a systematic review of mediators of weight loss (16), only one study examined the mediating role of autonomous self-regulation (35); an intervention aimed at promoting autonomous regulation resulted in greater weight loss than a general health education programme and intervention effects on 3-year weight change were partially mediated by autonomous self-regulation at 2 years (33) supporting the proposition that autonomous diet self-regulation contributes to weight loss maintenance (28).

Overall, although there is evidence that dietary restraint, habit strength and autonomous self-regulation are associated with weight control, there have been few formal mediation analyses examining whether change in these factors mediate the impact of effective interventions. In addition, of those mediation analyses that have been conducted, traditional regression methods have been used which only examine two time points. This results in the loss of information or requires several analyses between each set of time points. Using only two timepoints, especially the start and end of a study means that the model does not represent the trajectory of weight throughout the intervention and follow-up (36). Latent growth curve analysis (LGCA) enables analysis of the full trajectory of a variable over time. This is particularly important when individual changes follow a non-linear trajectory which is likely in a weight-management intervention in which a greater change during the active intervention than during follow-up is often expected (6). LGCA also enables variables to be both outcomes and predictors so that the trajectory of a potential mediator can be conditional on demographics factors while also being a predictor of an outcome. This method allows a greater understanding of the complex associations between treatment, mechanisms of action and outcomes over time (36).

3.2.1 The present study

Secondary mediation analysis was conducted on data from the Weight loss Referrals for Adults in Primary care trial (the WRAP trial) which examined the effectiveness and cost-effectiveness of a 52-week referral to an open-group behavioural weight-management programme (WW, formerly Weight Watchers) compared to a 12-week referral to the same programme and a brief intervention (written materials on how to lose weight) (37). Participants assigned to the 12- and 52-week weight-management programmes lost significantly more weight than the control group at 3 and 12 months and those assigned to the 52-week programme lost significantly more weight than the 12-week programme and the brief intervention at 12 and 24 months. The full results are reported in Ahern et al (37). The aim of the present study was to investigate whether the trajectories of dietary restraint, habit strength, and autonomous, controlled and amotivation self-regulation of diet mediated the effect of the weight-management programme on BMI trajectory over 24 months using latent growth curve analysis; a method that incorporates the full trajectory of the mediators and BMI.

3.3 Method

3.3.1 Participants

Eligible participants were aged 18 years or older with a BMI of 28kg/m^2 or above and were recruited through general practice records in England. Eligible individuals were identified by their primary care providers. Patients who were pregnant or were planning pregnancy within 2 years, who had past or planned bariatric surgery, were already participating in a structured monitored weight-management programme, were taking part in other research that would impact on the study outcomes, had a diagnosed eating disorder, or were unable to understand study information were excluded. Practices also excluded patients considered ineligible for other reasons not stated above such as terminal illness or a mental health diagnosis. Eligible participants were then invited to take part in the study by letter and asked to contact a study coordinator for a telephone screening if interested in participating. Eligible and willing participants were given an appointment where weight and height were measured to confirm eligibility. All participants gave written informed consent (37).

3.3.2 Interventions

Participants were randomly assigned to either a brief intervention, a 12-week referral to an open-group behavioural weight-management programme (WW, formerly Weight Watchers) or a 52-week referral to the same programme in a 2:5:5 allocation stratified by centre and gender using a randomisation sequence generated by the trial statistician.

The brief intervention included recognition of the problem by the GP in the form of a letter and written information on self-help weight loss strategies (British Heart Foundation Booklet: So you want to lose weight…for good). At the baseline visit, participants were read a scripted introduction that drew attention to each section of this booklet. The 12- and 52-week behavioural weight-management programmes were group-based and led by an individual who had personal experience of successful weight management. It included one-to-one discussions with participants at their first session and during the part of the session when participants were weighed (38). Sessions were held once a week at community-based venues and were an hour long. The core programme material consisted of a food points-based system (calculated based on the participant's age, gender, height, weight and activity) and strategies to tackle hunger, increase physical activity, manage eating out and keeping motivated. Sessions also included information about recipes, health and nutrition, and physical activity. Weight loss goals were between 0.5 and 1kg per week based on a deficit of 500kcal per day. Participants were encouraged to be physically active and work towards a goal of 10,000 steps per day. The intervention used food and activity diaries, goal setting, evaluation of progression and the provision of rewards for reaching weight loss targets. Using the taxonomy described by Michie et al. (39), the intervention content has retrospectively been categorised into the following BCTs: provide general information on behaviour-health link, prompt intention formation, prompt review of behavioural goals, prompt self-monitoring of behaviour, provide feedback on performance, provide contingent rewards, set graded tasks, provide opportunities for social comparison, instruction on how to perform a behaviour, information from a credible source (i.e. someone with experience of successful weight management), social support, relapse prevention and restructuring the food environment (40, 41).

Participants assigned to the behavioural weight-management programmes were given vouchers to attend weekly sessions and use online tools for the duration of their intervention. Those allocated to the 12-week

referral received vouchers to attend 12 group sessions and access to internet resources for 16 weeks and those allocated to the 52-week referral received vouchers for 52 sessions and access to internet resources for 12 months (42). The vouchers covered the full cost of the sessions and access to online resources.

3.3.3 Measures

Body mass index (BMI) and potential mediators were collected at baseline and 3, 12 and 24 months.

BMI

Height was measured at baseline to the nearest 0.1cm using a stadiometer and weight was measured to the nearest 0.1kg using a 4-point segmental body composition analyser at all time points. This was used to calculate BMI (kg/m^2).

Dietary restraint

A 14-item subscale of the Three Factor Eating Questionnaire (12, 43) was used to assess two types of restraint: rigid control which refers to an all-or-nothing perception of weight control and flexible control which refers to more adaptability in eating behaviours to control weight. In the current study the two types of restraint were highly correlated (r = .89) so the total subscale score was used (alpha = .86). This reflects findings from other studies in which dieting behaviour and weight loss are associated with similar increases in both rigid and flexible dietary restraint (44, 45). The measure includes items such as *'I deliberately take small helpings as a measure of weight control*'. Eight items have a true/false response option and the remaining six items are presented with a 4-point Likert scale. Higher scores on this measure represent greater control over dietary behaviours (11, 43).

Self-report habit index

The self-report habit index (46) was used to measure habit strength. The measure includes items assessing behavioural frequency, automaticity and identity (alpha = .89). The statement '*Watching what I eat is something*' was followed by 12 items such as '*I do frequently'* or '*would require effort not to do it'*. The items were accompanied by 7-point Likert scales from agree to disagree. Higher scores indicate that the behaviour is more habitual.

Diet self-regulation

The measure of diet self-regulation was adapted from the Treatment self-regulation questionnaire (47) to assess self-regulation of eating a healthy diet. In the measure "*The reason I would eat a healthy diet is*" is followed by 15 items split into three subscales. The autonomous self-regulation subscale (alpha = 0.81) includes 6 items such as "*Because it is consistent with my life goals*". The controlled self-regulation subscale (alpha = 0.88) includes 6 items such as "*Because I want others to approve of me*". The amotivation self-regulation subscale (alpha = 0.79), a measure of the absence of motivation, included 3 items such as "*I don't really think about it*". All items were presented with a 7-point Likert scale from not at all true to very true.

3.3.4 Statistical Analysis

To examine the longitudinal associations between the potential mediators and BMI, latent growth curve analysis (LGCA) was conducted. This type of analysis, in which a curve is fitted to the variable at each of the four time points, allows examination of the trajectory of variables over the two years. More detail about this analysis method can be found in the Supplementary Material. All analyses were conducted using Mplus8, Version 1.6 (1). Maximum likelihood estimation was used for all models. The analysis was conducted in three stages.

Step 1. Fit a latent growth curve to each variable

Scores at baseline, 3, 12 and 24 months were used to fit a curve to BMI, dietary restraint, habit strength and the three subscales of diet self-regulation; autonomous, controlled and amotivation. The intercept factor represented the values at baseline and the slope and quadratic factors represented the change in variables between baseline and 24 months. The means of each variable over the four time points were examined to determine the likely shape of the curve (i.e., linear or quadratic). In line with recommendations, the first model fitted was the simplest, a single growth factor with a variance of 0 then increasingly complex models were fitted and compared (48). At each stage, if the simpler model had a better or equal fit to the more complex model it was chosen for analysis. An example of the path diagram for the unconditional model is in the Supplementary Material (Figure 3.6). Once the best fitting unconditional model was chosen, variables were added to form the conditional model (36). Age, gender and treatment group were included as control variables

for each latent growth factor. For the BMI curve, income and education were also controlled based on evidence that these demographic factors are associated with BMI (49). These additional factors were not included in the curve for the potential mediators due to the lack of evidence supporting an association. Path diagrams for the conditional models are in the Supplementary Material (Figures 3.7 and 3.8). A piecewise analysis was also fitted, splitting the trajectories of BMI and potential mediators into two latent growth curves based on the initial change (baseline to either 3 or 12 months depending on the trajectory of the variable; Figures 3.1 and 3.2) and the subsequent return towards baseline values. This analysis was conducted to determine if piecewise models resulted in a better fit to the variables, and to explore the relationships between BMI and potential mediators at different time points in the trial.

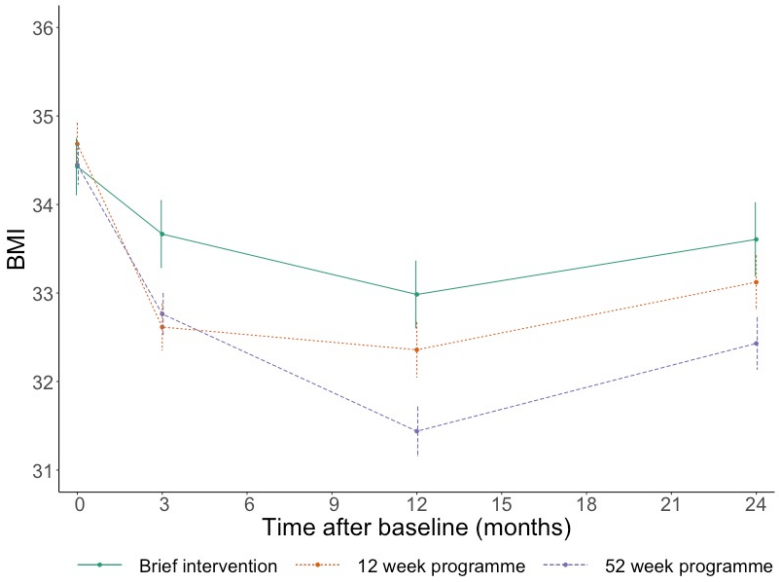

Figure 3.1. Mean change in BMI in each treatment group over 24 months

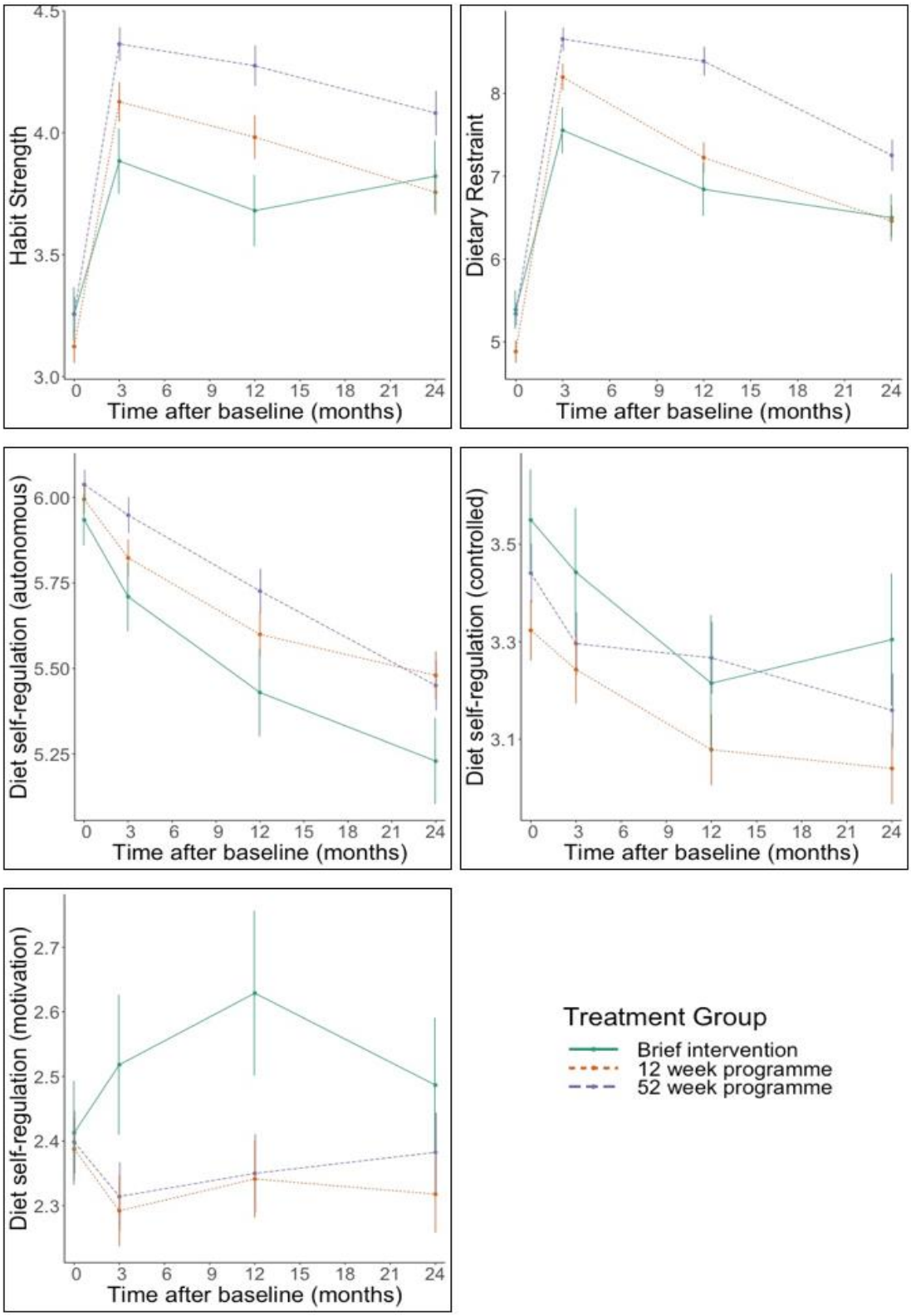

Figure 3.2. Mean change in habit strength, dietary restraint and diet self-regulation subscales in each treatment group over 24 months

Step 2. Examine associations between change in potential mediator variables and change in BMI

Parallel processes models were developed for each of the potential mediator variables and BMI. These models allow examination of the correlation between the growth curves fitted in step one. Specifically, the curve fitted to the potential mediators in the previous step were (individually) combined with the curve fitted to the BMI trajectory to determine the correlations between the latent growth factors of the two variables.

Step 3. Mediation models

If the trajectory of a potential mediator was associated with group allocation (identified in step one) and with the BMI trajectory (step 2), then it was included in the full mediation model. The curves fitted to the potential mediators and BMI in step one were combined in a single model in which the trajectory of BMI was conditional on the trajectory of potential mediators. The significance of the individual indirect effects of each mediator, total indirect effect and the direct effect between the intervention and the BMI was examined to determine whether the intervention effect was mediated.

Model fit

Model fit was checked at each stage. The criteria used to make a judgement on model fit were a Comparative Fit Index (CFI) above or equal to 0.95, Root Mean Square Error of Approximation (RMSEA) and Standardised Root Mean-square Residual (SRMR) below or equal to 0.08 (36). A non-significant value of the chi-square (χ^2) statistic is often used to judge model fit; however, due to the large sample size, which often results in a significant value even with a good model fit (48), this criterion was not used in this study. The fit of each model was assessed using all criteria.

3.3.5 Missing Data

The percentage of participants who completed the assessments at 3, 12 and 24 months was 79, 65 and 68% respectively. The percentage of missing data for each treatment group and specifically for BMI and the measures are reported in Supplementary Material (Tables 3.7 and 3.8). The pattern of missing data was assessed and was treated as missing not at random (MNAR). There was an increasing number of missing values at later time points and it is probable that drop-out was linked to treatment effectiveness (50). Multiple imputation was conducted using R. For each variable, the missing values were predicted; the variables selected

for prediction were based on the strategy outlined by van Buuren et al (51). A prediction matrix (Supplementary Material, Figure 3.5) shows the variables that were used to predict missing values for each variable. Full details of the method used are in the Supplementary Material. Convergence plots confirmed that convergence had been achieved and strip plots showed that the imputed values did not go out of the range of the actual values and that they followed the same distribution.

3.4 Results

3.4.1 Baseline Characteristics

Between 18 October 2012 and 10 February 2014, 1954 participants were screened and 1267 were eligible and were randomly allocated to a condition (37). The baseline characteristics of the participants (*N=1267*) including psychological variables are in Table 3.1. Additional participant characteristics can be found in the original reporting of the study (37). The change in both BMI and the psychological/behavioural variables are shown in Figures 3.1 and 3.2. There were no significant differences between the treatment groups at baseline on BMI or the potential mediators determined by one-way analysis of variance (ANOVA) tests. BMI and the mediator variables showed change between baseline and 3 or 12 months before a stabilisation or return towards baseline between 12 and 24 months. Autonomous diet self-regulation decreased over the 24 months for all intervention groups.

Table 3.1. Baseline characteristics of participants in the WRAP trial (N = 1267)

	Treatment Group					
	Brief intervention		**12-Week intervention**		**52-Week intervention**	
	n	%	*n*	%	*n*	%
Gender						
Female	143	68	357	68	358	68
Male	68	32	171	32	170	32
Education						
None	7	3	25	5	27	5
GCSE/A-level/equivalent	108	51	247	47	265	50
University degree or higher/ equivalent	81	38	199	38	174	33
Missing	15	7	54	10	60	11
Income						
Under £20 000	65	33	124	25	138	28
£20 - £49 999	66	33	173	35	176	35
£50 000+	41	21	91	18	84	17
Prefer not to say or missing	27	13	111	22	100	20
	M	*SD*	*M*	*SD*	*M*	*SD*
Age	51.91	14.07	53.60	12.27	53.29	13.98
BMI	34.43	4.63	34.68	5.39	34.45	5.05
Dietary restraint	5.39	3.26	4.88	3.03	5.34	3.06
Habit strength	3.24	1.38	3.08	1.29	3.14	1.38
Diet self-regulation						
Amotivation	2.41	1.14	2.39	1.10	2.40	1.09
Autonomous	5.93	1.07	5.99	0.92	6.04	0.97
Controlled	3.55	1.47	3.32	1.39	3.44	1.36

3.4.2 Latent Growth Curve Analysis

Step 1. Fit a latent growth curve to each variable

A latent growth curve was fitted to the four time-points (baseline, 3, 12 and 24 months) for BMI, dietary restraint, habit strength and the three subscales of diet self-regulation (autonomous, controlled and amotivation). A quadratic growth curve was the best fitting model for all variables other than the amotivation subscale of diet self-regulation for which an intercept only model was the best fit. For the other four potential mediators (dietary restraint, habit strength and autonomous and controlled diet self-regulation) the model was able to converge and fitted best when the variance of the quadratic factor was set to 0. The model for BMI fitted well without this restriction. The results from the increasingly complex unconditional models are reported in Supplementary Material (Tables 3.10-3.15). Once the best fitting unconditional model was established, the conditional factors were added. The values for each of the latent growth factors along with fit statistics of the conditional model are shown in Table 3.2. The model fit for all variables was good for all the criteria other than the model for BMI which did not meet the cut-off criteria for CFI and RMSEA. However, the values were close to the criteria indicating that the model provided a reasonable description of the data.

Table 3.2. Model fits to trajectory of BMI and psychological/behavioural variables

Variable	Intercept	Slope	Quadratic	CFI	RMSEA	SRMR
BMI	36.16 (1.02)***	0.84 (0.95)	0.03 (0.32)	0.93	0.12	0.02
Dietary restraint	2.82 (0.37)***	2.68 (0.59)***	-0.87 (0.19)***	0.97	0.05	0.04
Habit strength	1.94 (0.19)***	0.79 (0.27)**	-0.21 (0.11)	0.97	0.05	0.04
DSR Autonomous	5.75 (0.13)***	-1.16 (0.33)***	0.36 (0.13)**	0.96	0.05	0.02
DSR Controlled	3.10 (0.17)***	-0.08 (0.30)	0.09 (0.13)	0.99	0.03	0.02
DSR Amotivation	2.39 (0.12)***	NA	NA	0.96	0.04	0.05

Note. * $p < .05$. ** $p < .01$. *** $p < .00$. BMI, Body Mass Index. CFI, comparative fit index. RMSEA, Root mean square error of approximation. SRMR, Standardized Root Mean Square Residual. DSR, Diet self-regulation.

Table 3.3 shows the full details of the associations between the latent growth factors of each variable and age, gender and treatment group in the conditional models. There were significant effects of both the 12- and 52-week programme on the slope and quadratic of the BMI trajectory, controlling for age, gender, income and education. There were significant effects of both the 12- and 52-week programme on the slope and quadratic factors of dietary restraint and habit strength but only the 52-week intervention significantly impacted autonomous diet self-regulation. Age and gender were controlled for in all models. Gender was associated with the slope and quadratic of dietary restraint and controlled diet self-regulation, and age was associated with the slope and quadratic of autonomous diet self-regulation.

There were significant associations between the BMI intercept and slope (estimate = -2.31, *SE* = 0.77, *p* = .002), intercept and quadratic (estimate = 0.72, *SE* = 0.30, *p* = .02) and slope and quadratic growth factors (estimate = -2.81, *SE* = 0.30, *p* < .001) indicating a higher BMI at baseline was associated with a steeper decline in BMI, and a steeper return towards the baseline BMI. There were also significant correlations between the intercepts and slopes of dietary restraint (estimate = 0.40, *SE* = 0.12, *p* = .001) and controlled diet self-regulation (estimate = -0.05, *SE* = 0.02, *p* = .02) indicating that higher baseline values resulted in a lower slope (lesser increase) for controlled diet self-regulation and a higher slope (greater increase) for dietary restraint. The correlations between the intercept and slope of autonomous diet regulation (estimate = 0.03, *SE* = 0.02, *p* = .10) and habit strength (estimate = -.04, *SE* = 0.05, *p* = 0.41) were non-significant.

Piecewise latent growth curves were fitted to the trajectories of BMI and the potential mediators; however, this resulted in a poorer fit than the quadratic model. Full results are in the Supplementary Material (Tables 3.16-3.19).

Table 3.3. Coefficients of age, gender, and group allocation on trajectories of BMI and potential mediators

Variable	Gender (reference group male)	Age	Treatment Group (reference brief intervention)	
			12-week group	52-week group
BMI				
Intercept	1.18 (0.31)***	-0.04 (0.01)**		
Slope	-0.52 (0.27)	-0.03 (0.01) **	-0.91 (0.38)**	-1.82 (0.39)***
Quadratic	0.11 (0.10)	0.01 (0.003)	0.37 (0.13)**	0.66 (0.13) ***
Dietary Restraint				
Intercept	1.56 (0.18)***	0.02 (0.01)***		
Slope	-0.86 (0.24)**	0.01 (0.01)	0.87 (0.29)**	1.50 (0.31)***
Quadratic	0.23 (0.08)**	-0.003 (0.003)***	-0.30 (0.10)**	-0.47 (0.10)***
Habit				
Intercept	0.24 (0.09)**	0.02 (0.003)***		
Slope	0.06 (0.11)	-0.004 (0.004)	0.36 (0.14)*	0.57 (0.14)***
Quadratic	-0.03 (0.04)	0.002 (0.002)	-0.16 (0.06)*	-0.23 (0.06)***
Diet self-regulation Autonomous				
Intercept	0.27 (0.06)***	-0.001 (0.002)		
Slope	-0.24 (0.13)	0.01 (0.01)*	0.21 (0.16)	0.40 (0.17)*
Quadratic	0.09 (0.05)	-0.01 (0.002)*	-0.06 (0.07)	-0.15 (0.07)*
Diet self-regulation Controlled				
Intercept	0.17 (0.08)*	0.003 (0.003)		
Slope	-0.38 (0.13)**	-0.001 (0.01)	0.12 (0.13)	0.29 (0.17)
Quadratic	0.12 (0.05)*	-0.001 (0.002)	-0.05 (0.06)	-0.12 (0.07)
Diet self-regulation Amotivation				
Intercept	-0.07 (0.03)	0.02 (0.04)*		

Note. * $p < .05$. ** $p < .01$. *** $p < .001$. BMI, Body Mass Index.

Step 2. Examine associations between change in potential mediator variables and change in BMI

The associations between each of the latent growth factors of the potential mediator variables and the latent growth factors of BMI along with the model fit statistics are in Table 3.4. There were negative associations between the slopes of BMI and three potential mediator variables; dietary restraint (estimate = -0.60, *SE* = 0.20, $p = 0.003$), habit strength (estimate = -0.36, *SE* = 0.08, $p < .001$) and autonomous diet self-regulation (estimate = -0.87, *SE* = 0.25, $p < .001$). Increases in these potential mediators were associated with decreases in BMI. At baseline, a higher controlled diet self-regulation score was associated with a higher BMI (estimate = 0.71, *SE* = 0.19, $p < .001$) but the association between the slopes was non-significant (estimate = -0.02, *SE* = 0.06, $p = .74$). The amotivation subscale of diet self-regulation was specified as an intercept only model so the correlation of the change over time in this variable with change in BMI could not be examined. Although the curve of the potential mediator variables were quadratic, the quadratic growth factors were fixed to 0 and therefore the correlation between this and the BMI growth factors could not be calculated. Although three models fell slightly below the criteria recommended for the CFI, all were close and met other measures of fit.

Table 3.4. Correlations between the latent growth factors of BMI and potential mediators

Variable	**BMI growth factors**			**Fit statistics**		
	Intercept	**Slope**	**Quadratic**	**CFI**	**RMSEA**	**SRMR**
Dietary Restraint						
Intercept	-0.57 (0.36)	-0.28 (0.36)	0.10 (0.12)	0.94	0.08	0.03
Slope	0.20 (0.22)	-0.60 (0.20)**	0.11 (0.07)			
Habit strength						
Intercept	-0.35 (0.19)	0.05 (0.17)	-0.01 (0.06)	0.95	0.08	0.03
Slope	0.12 (0.10)	-0.36 (0.08)***	0.08 (0.03)**			
Autonomous diet Self-regulation						
Intercept	0.22 (0.14)	0.10 (0.11)	-0.03 (0.04)	0.93	0.08	0.06
Slope	-0.45 (0.31)	-0.87 (0.25)***	0.25 (0.09)**			
Controlled diet Self-regulation						
Intercept	0.71 (0.19)***	-0.03 (0.15)	0.02 (0.05)	0.94	0.07	0.02
slope	-0.12 (0.08)	-0.02 (0.06)	-0.001 (0.02)			

Note. * $p < .05$. ** $p < .01$. *** $p < .001$. BMI, Body Mass Index. CFI, comparative fit index. RMSEA, Root mean square error of approximation. SRMR, Standardized Root Mean Square Residual.

In the piecewise analyses, associations between the slopes of the mediators in the intervention (0-12 months) and maintenance phases (12-24 months) were examined. In the intervention phase, the BMI slope was associated with the slopes of dietary restraint, habit strength and autonomous diet self-regulation. The BMI slope in the maintenance phase was associated with the slope of autonomous diet self-regulation in the intervention phase and the slope of habit in the maintenance phase. However, the fit of the piecewise models was poor based on model fit statistics (Supplementary Material, Table 3.16). Therefore, these results should be interpreted with caution and a full mediation model was not examined.

Step 3. Mediation models

In step 1 it was determined that there were treatment effects of both the 12- and 52- week intervention on BMI trajectory compared to the control group. Of the potential mediators, dietary restraint, habit strength and autonomous diet self-regulation were associated with both treatment group (step 1) and BMI trajectory (step 2). The amotivation and controlled subscales of diet self-regulation did not fit these criteria and therefore were not included.

Mediation models were tested to determine whether the impact of the intervention on BMI slope was mediated by the slope of dietary restraint, habit strength and autonomous diet self-regulation (the variance of the quadratic variables was restricted to 0 and therefore could not be included as a mediator). The results of the separate models for each of the potential mediators are in Supplementary Material (Table 3.21) and indicate that dietary restraint and habit strength were significant mediators of the 12-week intervention and that all three variables were significant mediators of the 52-week intervention. A full mediation model with all three mechanisms of action was then tested. When fitted, the total effects of both interventions on BMI slope were significant and the direct effects became non-significant (Table 3.5). The total indirect effect via the three mediator variables was significant; for the 12-week intervention effect, only the individual indirect effect of dietary restraint was statistically significant whereas for the 52-week intervention the individual indirect of all three variables were significant. Effect sizes were larger for the 52-week programme than the 12-week programme on all mediators but only significantly larger for dietary restraint and habit strength. Model fit statistics indicate an adequate fit on RMSEA (0.06) and SRMR (0.06) measures and was close to the fit criteria

for CFI (0.94). The results of this are shown in Table 3.5 and a simplified model is included in Figure 3.3 (full model tested is presented in Supplementary Material, Figure 3.11).

Table 3.5. Total, direct and indirect effects via mediating variables of the 12- and 52-week intervention on BMI

	12-week intervention			**52-week intervention**		
Effects	**Estimate**	**SE**	***p***	**Estimate**	**SE**	***p***
Total impact of intervention on BMI	-0.69	0.36	0.04	-1.72	0.38	<.001
Direct effect of intervention on BMI when mediators included	0.64	0.54	0.23	0.42	0.63	0.51
Total indirect effect of mediating variables	-1.33	0.41	0.001	-2.13	0.52	<.001
Indirect Effect of Mediators						
Dietary restraint	-0.61	0.27	0.02	-0.98	0.39	.008
Habit strength	-0.56	0.29	0.06	-0.88	0.25	.018
Autonomous diet self-regulation	-0.17	0.54	0.23	-0.27	0.62	.048

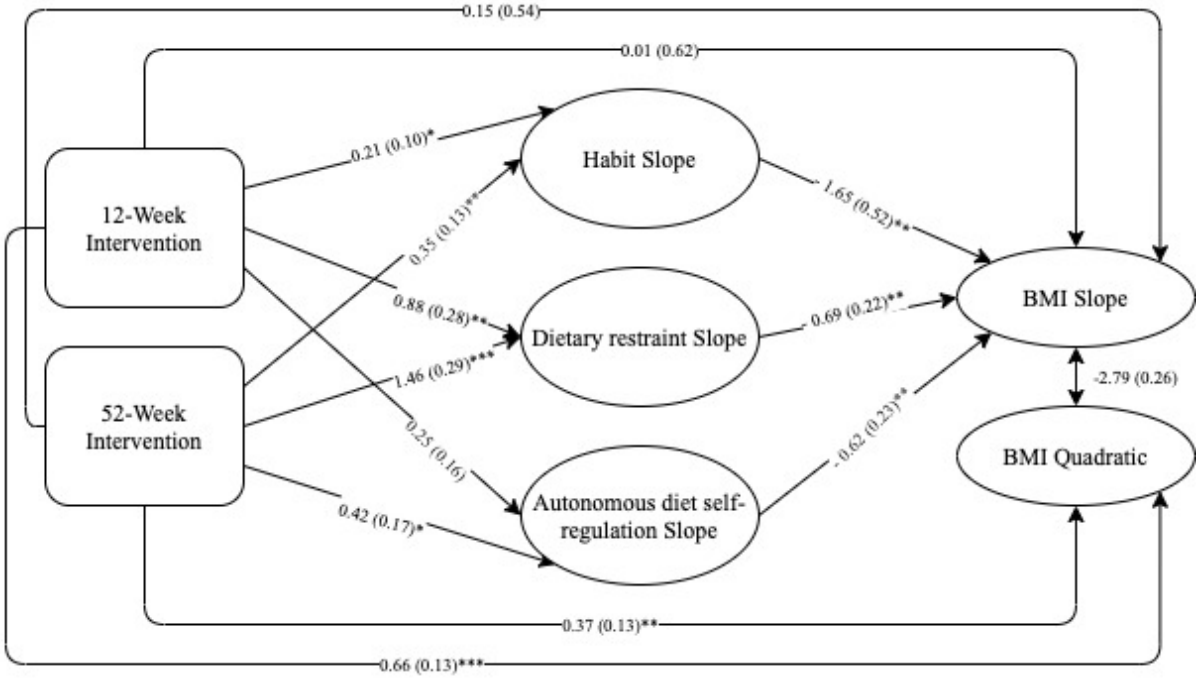

Figure 3.3. Mediation path diagram

3.5 Discussion

Dietary restraint, habit strength and autonomous diet self-regulation mediated the effect of a weight-management programme on BMI. The 12- and 52-week programmes were both associated with increases in dietary restraint and habit strength and the 52-week programme was also associated with a lower reduction in autonomous diet self-regulation. These changes were associated with decreases in BMI over the 2 years. When controlling for change in habit strength, dietary restraint and autonomous diet self-regulation, the impact of both the 12- and 52-week programme on the slope of BMI became non-significant. Although the combined indirect effect was significant for both the 12- and 52-week intervention, for the shorter intervention, only the individual direct effect of dietary restraint was significant, whereas the indirect direct effect of all three variables were significant for the 52-week intervention.

This intervention included several BCTs and so it is not possible to establish which specific BCTs or combination of BCTs resulted in the increases in dietary restraint and habit strength observed during the 12- and 52-week weight-management programmes. However, the intervention included several BCTs that have been linked with behavioural regulation, including self-monitoring of behaviour and outcomes, through food and activity diaries and regular weight measurement, goal setting and action planning (52, 53). Behavioural regulation is defined as behavioural, cognitive, and/or emotional skills for managing or changing behaviour (52, 53). Given that dietary restraint can be considered as behavioural and cognitive control of eating behaviour, these BCTs may have contributed to the observed increase in dietary restraint.

The BCTs that may have contributed to the increase in habit strength are social support, restricting the food environment and general information on behaviour-health link. These have all been linked to behavioural cueing, a construct that promotes formation of habits (52, 53). However, the finding that habit strength was a significant independent mediator for the 52-week intervention but not the 12-week intervention indicates that the intervention length might be an influential moderating factor. This may be linked to a higher ‘dose’ of the BCTs in the 52-week intervention compared to the 12-week intervention due to the longer duration which may help the formation of stronger habits to support weight maintenance. This formation of stronger habits may be particularly important as piecewise analysis indicated that a reduction in habit strength following the

intervention was associated with an increase in BMI. Given that the content of the weight-management programmes were the same other than their length, the 52-week intervention provided participants with continued social support from the group leader and other attendees as well as more opportunity to perform behaviours frequently in a stable context compared to the 12-week intervention; this may have enabled the transition of diet monitoring behaviour from deliberative to automatic control (54) which, in turn, supported weight loss maintenance. Such an interpretation is in line with dual-process theories. These theories outline deliberative (or reflective) processes which involve conscious and rational decision-making and automatic (or impulsive) processes which involve non-conscious, learned reactions (55-57). This is particularly important in health behaviours when individuals aiming to perform healthy behaviours often have to overcome unhealthy habitual behaviours and make conscious and reasoned healthier decisions (56). These findings support the use of long-term interventions that may facilitate the transition from deliberative attempts to control eating (dietary restraint) to more automatic and less effortful self-regulation of eating behaviour (habit strength).

Although autonomous self-regulation was identified as an independent significant mediator for the 52-week intervention, all groups actually experienced a decrease in autonomous motivation throughout the trial and follow-up. This indicates that although the lesser reduction experienced by the individuals in the 52-week intervention compared to the other two groups was beneficial (for weight loss), all interventions (including the brief intervention) had a negative effect on autonomous self-regulation. It is possible that this, and other, weight-management interventions may have a negative impact on autonomous self-regulation through implicitly promoting the message that participants need to be told what to do by people with expertise in order to manage their weight (28). This is supported by qualitative findings from the WRAP trial that suggested that participants felt a sense of obligation to the leader of the group sessions (58). The weight loss and weight loss maintenance achieved in both the 12- and 52-week intervention may have been greater if autonomous self-regulation had been maintained or increased during the intervention.

The findings have implications for the content of future interventions. Given that dietary restraint, habit strength and autonomous diet self-regulation mediated the effect of the weight-management programme on weight loss and maintenance over two years, researchers should consider including BCTs that are hypothesised to target these mechanisms of action in future interventions. Recent research that has sought to link specific

BCTs and mechanisms of action could be used to identify further BCTs to increase dietary restraint, habit strength and autonomous diet self-regulation (52, 53). For example, expert consensus exercises have indicated that the BCTs of introducing prompts and cues for a desired behaviour and avoiding or reducing exposure to cues for an unhealthy behaviour may be linked to behavioural cueing (52), a mechanism of action that is likely to support the formation of new habits. Similarly, self-monitoring and goal setting have been linked to behavioural regulation (53) and could be used as strategies to support dietary restraint. Although a range of BCTs have been linked with motivation as a mechanism of action, including the use of rewards and the consideration of pros and cons (52, 53), particular attention needs to be given to how to specifically target autonomous motivation. For example, interventions implementing an autonomy-supportive environment, in which individuals are encouraged to engage in health-related behaviours for their own reasons, are supported in overcoming barriers to change, and are made to feel accepted and respected, have been found to be associated with higher autonomous self-regulation, a healthier diet and greater weight loss in a meta-analysis (59). In contrast, techniques such as the use of rewards, may foster more extrinsic or controlled forms of motivation which, although they may promote initial behaviour change, may not be sufficient to support the maintenance of behaviour change (60, 61). In addition, given that the longer duration of intervention was associated with larger changes in dietary restraint and habit strength, researchers should consider interventions that provide support over an extended period of time to promote sustained changes in those mechanisms of action that contribute to weight loss maintenance.

A key strength of this study compared to previous studies was the use of latent growth curve analysis to disentangle the complex system of interactions between behavioural weight-management interventions, mechanisms of action and the trajectory of weight change. This method enabled a mediation analysis that accounted for changes at every time point rather than just two time points that are often considered in traditional regression methods. This is particularly important as changes in the mediators and BMI were non-linear and an analysis assuming a linear trajectory may not have captured the full impact of the mediating variables. This method also enabled growth factors to be both outcomes and predictors. For example, the model tested enabled the slope of the habit strength to be an outcome conditional on treatment group, age and gender, and a predictor of the BMI trajectory simultaneously. These results largely support previous research that indicates dietary restraint, habit strength and self-regulation are potential mediators for the effect of a behaviour

weight-management programme on weight loss and weight loss maintenance (8, 15, 17, 23, 31, 32). In particular, the findings add to the small number of formal mediation analyses on these factors (17, 27, 33) and, using a complex method examining the mediating action of the three variables simultaneously, provide evidence that these are relevant mechanisms of action for weight management.

There were some study limitations which need to be taken into consideration when interpreting the findings. First, it was not possible to include the associations between the quadratic growth factors of the mediators and the trajectory of BMI due to non-convergence of the individual latent growth curves (conducted in step 1 of the analysis) when allowing the variance of the quadratic factors to vary between individuals. Thus, the rate of acceleration/deceleration of change in BMI was not conditional on acceleration/deceleration of change (quadratic) of the mediating variables. Including this would have resulted in a greater understanding of the associations between the mediators and BMI. However, even without this, the model fit was adequate. Second, the attrition rate was over 30% at 12 and 24 months which could have introduced some bias; however, multiple imputation was used which is a valid general method for managing missing data in RCTs (62). Finally, although participants were referred to the commercial weight loss programme and the cost of sessions was covered for a set period of time (either 12 or 52 weeks), attendance at weekly sessions was not recorded consistently throughout the trial. Due to the large proportion of missing data on attendance (40%) it was not included as a covariate in the analysis. Therefore, the potential impact of attendance on both the mediators and BMI was not controlled for.

In conclusion, dietary restraint, habit strength and autonomous diet self-regulation were all identified as mechanisms of action for the effective 52-week weight-management programme. The finding that habit strength was only a significant mediator of the 52-week programme suggests that longer interventions may provide the consistency of support required for behaviours to move from deliberative to habitual control. BCTs that target dietary restraint and habit strength and maintain or increase autonomous diet-self regulation should be considered when designing weight loss and weight loss maintenance interventions.

3.6 Contribution to thesis

In this chapter, I used complex mediation methods to understand the mechanisms of action of a widely available weight management programme available commercially and through GP referral. The findings indicated that dietary restraint, habit strength and autonomous diet self-regulation were mechanisms of action and these findings can be used to inform the design of future weight management intervention. The work in this chapter adds to the limited number of mediation analyses used to detect mechanisms of action of weight management interventions. Furthermore, given that in this chapter I found that dietary restraint, habit strength and autonomous diet self-regulation are modifiable determinants of BMI, these are potentially suitable psychological factors to incorporate into a health economic model. This will be explored in the next chapter (Chapter 4).

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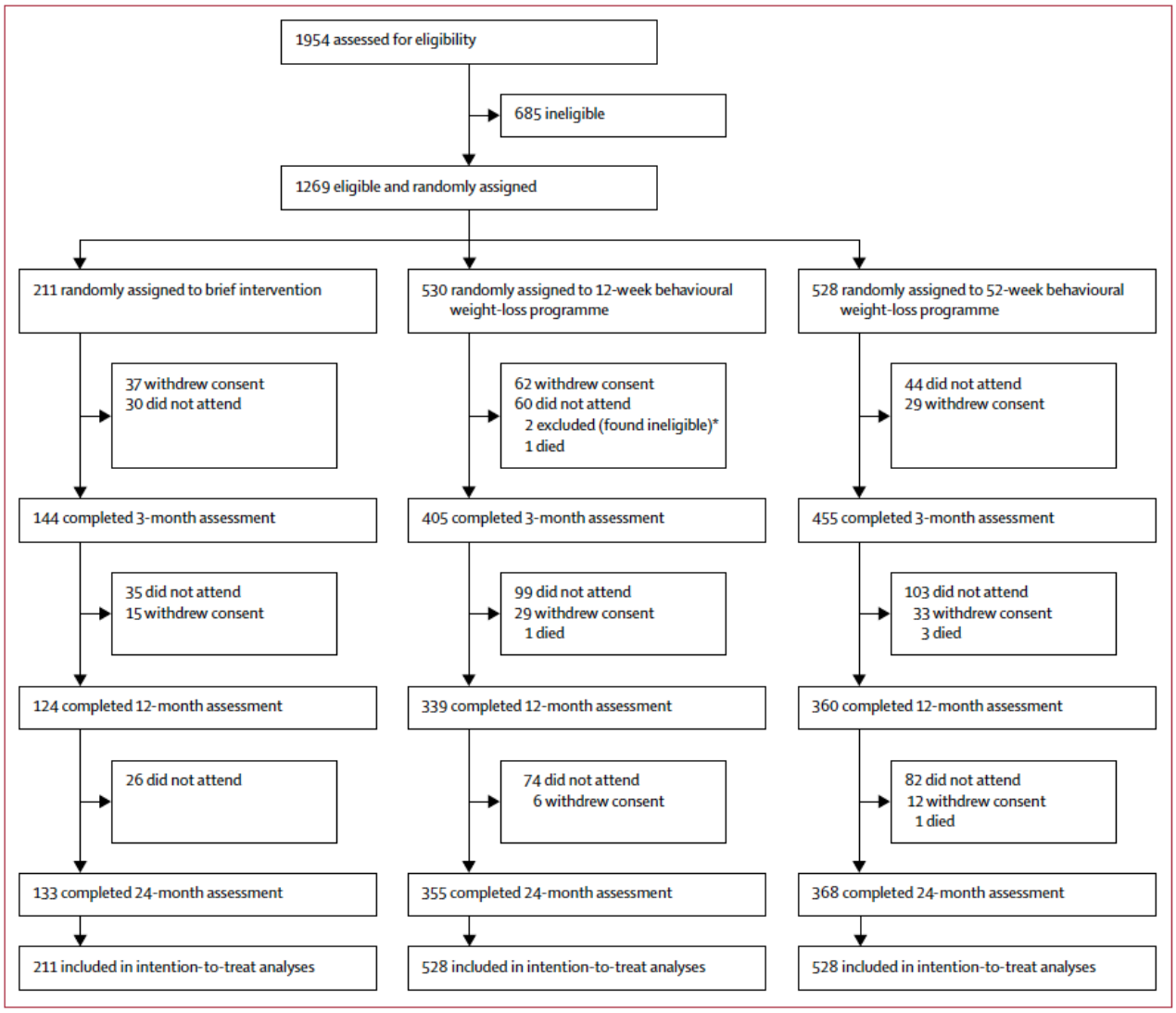
3.8 Supplementary Material

3.8.1 Participants



*Excluded from intention-to-treat analyses.

Figure 3.4. Trial profile published in Ahern AL, Wheeler GM, Aveyard P, et al. Extended and standard duration weight-loss programme referrals for adults in primary care (WRAP): a randomised controlled trial. The Lancet. 2017; 389:2214-2225.

3.8.2 Descriptive Analysis

Table 3.6. Mean values of psychological variables in each treatment group at each time points

Time	Treatment group	Dietary restraint		Diet self-regulation						Habit	
		Mean	sd	Autonomous		Controlled		Motivation		Mean	sd
				Mean	sd	Mean	sd	Mean	sd		
Baseline	BI	5.39	3.26	5.93	1.07	3.55	1.47	2.41	1.14	3.24	1.38
	12 weeks	4.88	3.03	5.99	0.92	3.32	1.39	2.39	1.10	3.08	1.29
	52 weeks	5.34	3.06	6.04	0.97	3.44	1.36	2.40	1.09	3.14	1.38
3 months	BI	7.55	3.13	5.71	1.15	3.44	1.49	2.52	1.23	3.64	1.33
	12 weeks	8.20	3.10	5.82	1.04	3.24	1.34	2.29	1.05	3.72	1.32
	52 weeks	8.66	2.89	5.95	1.07	3.30	1.33	2.31	1.09	3.84	1.31
12	BI	6.84	3.28	5.43	1.32	3.21	1.43	2.63	1.31	3.51	1.28
months	12 weeks	7.23	3.22	5.60	1.17	3.08	1.29	2.34	1.06	3.66	1.33
	52 weeks	8.39	3.14	5.73	1.17	3.27	1.34	2.35	1.10	3.87	1.32
24	BI	6.50	3.00	5.23	1.32	3.30	1.43	2.49	1.10	3.67	1.42
months	12 weeks	6.46	3.35	5.48	1.23	3.04	1.28	2.32	1.04	3.55	1.39
	52 weeks	7.25	3.39	5.45	1.31	3.16	1.36	2.38	1.10	3.71	1.33

3.8.3 Missing Data

Method

Forty imputations were generated based on the rule of thumb that number of imputations should match the average percentage rate of missingness (Bodner, 2008). In this case the amount of missing data was highest at year 3 (35%) and so the number of imputations was rounded up to 40 to ensure that there was a sufficient amount. The method chosen for the continuous variable was predictive mean matching which is a semi-parametric method which restricts the imputed values to the observed values and preserves non-linear relationships between the variables used to impute the missing data. Multinomial logit model were used for the categorial variables (Buuren & Groothuis-Oudshoorn, 2010). As recommended (Bodner, 2008), 30 iterations were conducted for each imputation.

Variables used for prediction

It was assumed that gender and age predicted the missing data of the potential mediator variables as it is recommended that covariates used in analysis are also used in prediction of missing data. These, income and education predicted the missing data of the BMI variable based on evidence that these factors impact on BMI (Tyrrell et al., 2016). Treatment group was also used to impute missing values of BMI and psychological variables at 3, 12 and 24 months and missing values of variables and each time point were predicted by values of that variables at other time points. Any variables that were correlated (with a correlation of at least .30) and had enough usable cases to predict missing values in the other variable were also retained as predictors.

Table 3.7. Percentage of participants that completed each assessment after baseline

Time after baseline	Brief intervention	12-week intervention	52-week intervention	All groups
3 months	68	77	86	79
12 months	59	64	68	65
24 months	63	67	70	68

Table 3.8. The percentage of missing data at each time point for each measure

Time	Treatment group	BMI	Dietary restraint	Diet self-regulation			Habit
				Autonomous	Controlled	Amotivation	
Baseline	BI	0.00	3.32	3.79	3.32	3.32	3.32
	12 weeks	0.00	2.27	2.65	2.27	2.46	2.65
	52 weeks	0.00	2.27	2.27	2.46	2.65	3.03
3 months	BI	31.75	37.91	39.34	38.39	38.86	38.86
	12 weeks	23.30	28.03	28.79	28.98	28.98	29.17
	52 weeks	13.83	17.61	19.51	19.32	19.32	19.32
12 months	BI	41.23	49.76	49.29	49.76	50.24	49.76
	12 weeks	35.80	39.39	39.39	39.77	39.96	39.96
	52 weeks	31.82	36.17	36.55	36.74	36.74	36.93
24 months	BI	36.97	45.50	45.50	46.92	47.39	46.92
	12 weeks	32.77	39.58	39.77	41.10	41.10	41.48
	52 weeks	30.30	38.07	38.45	38.07	38.07	38.26

Table 3.9. The percentage of missing data across all groups

Time	BMI	Dietary restraint	Diet self-regulation			Habit
			Autonomous	Controlled	Motivation	
Baseline	0.00	2.62	2.91	2.68	2.81	3.00
12 weeks	22.96	27.85	29.21	28.89	29.05	29.12
52 weeks	36.28	41.78	41.75	42.09	42.31	42.22
3 months	33.35	41.05	41.24	42.03	42.19	42.22

	SerNo	TXGROUP	Sex	INCOME	EDU	AGE	BMI.0	DRES.0	HABIT.0	DSRA.0	DSRC.0	DSRM.0	BMI.3	DRES.3	HABIT.3	DSRA.3	DSRC.3	DSRM.3	BMI.12	DRES.12	HABIT.12	DSRA.12	DSRC.12	DSRM.12	BMI.24	DRES.24	HABIT.24	DSRA.24	DSRC.24	DSRM.24
TXGROUP	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Sex	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
INCOME	0	1	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
EDU	0	1	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
AGE	0	1	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
BMI.0	0	0	1	1	1	1	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0
DRES.0	0	0	1	1	0	1	0	0	0	0	0	0	0	1	1	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0
HABIT.0	0	0	1	1	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0
DSRA.0	0	0	1	1	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0
DSRC.0	0	0	1	1	0	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	1	1	0	0	0	0	1	0
DSRM.0	0	0	1	1	0	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	1	1	0	0	0	0	1	1
BMI.3	0	1	1	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0
DRES.3	0	1	1	1	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0
HABIT.3	0	1	1	1	0	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0
DSRA.3	0	1	1	1	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
DSRC.3	0	1	1	1	0	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0
DSRM.3	0	1	1	1	0	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1
BMI.12	0	1	1	1	0	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
DRES.12	0	1	1	1	0	1	0	1	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0
HABIT.12	0	1	1	1	0	1	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
DSRA.12	0	1	1	1	0	1	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0
DSRC.12	0	1	1	1	0	1	0	0	0	0	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0
DSRM.12	0	1	1	1	0	1	0	0	0	0	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	1
BMI.24	0	1	1	1	0	1	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
DRES.24	0	1	1	1	0	1	0	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
HABIT.24	0	1	1	1	0	1	0	0	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
DSRA.24	0	1	1	1	0	1	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0
DSRC.24	0	1	1	1	0	1	0	0	0	0	1	1	0	0	0	0	1	1	0	0	0	0	1	0	0	0	0	0	0	0
DSRM.24	0	1	1	1	0	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0

Figure 3.5. Prediction matric used in multiple imputation

3.8.4. Latent growth curve analysis

In latent growth curve analysis (LGCA), the value for each individual (i) at each time point (t) can be represented by a linear (Eq. 1) or quadratic (Eq. 2) equations where $\mathbb{I}, \mathbb{S}$ and $\mathbb{Q}$ are the intercept, slope and quadratic latent growth factors respectively assuming that the error term is normally and independently distributed.

$$Variable_{it} = \mathbb{I}_i + \mathbb{S}_i\, t + \varepsilon_{it} \quad (1)$$

$$Variable_{it} = \mathbb{I}_i + \mathbb{S}_i\, t + \mathbb{Q}\, t^2 + \varepsilon_{it} \quad (2)$$

The growth factors of each individual is used to estimate the average growth factors and an aggregated error variance for each as well as correlation between the growth factors (1).

Analysis Strategy

First, we fitted an unconditional model. We tested increasingly complex models starting with a model in which its assumed that all participants have the same intercept and then testing each of the hypothesis below following recommendations in the literature (2).

1) There will be variation between individual in the level of the variable
2) There will be a change in the variables over the course of two years
3) There will be variation in individuals in the extent of change in the variable over the two years
4) There will be a non-linear (quadratic) change in the variable over the two years
5) There will be a variation in individuals in the extent of non-linear (quadratic) change in the variable over the 2 years.

The factor loadings (represented as coefficients) for the intercept were set to 1. The coefficient of the slopes reflect the time points at which the data was collected in months (0, 3, 12, 24) and similarly the quadratic represent the acceleration or deceleration of changes and the loading and the squared values of those used for the slope (0, 9, 144, 576) (1).

For each of them the nested $\mathcal{X}^2$ difference test ($\mathcal{X}^2_{\text{DIFF}}$) was used to compare models (the more complex model to the previous one tested). A significant value on this test indicates that the more complex model is a better fit than the less complex model. If the value is not significant then both models fit equally well and thus the

simple model is considered the preferred option (1). However, all model fit indices will be considered when deciding on the best fitting model. An example of a growth model with the maximum amount of growth factors possible for this data set (intercept, slope and quadratic) is shown in Figure 3.6.

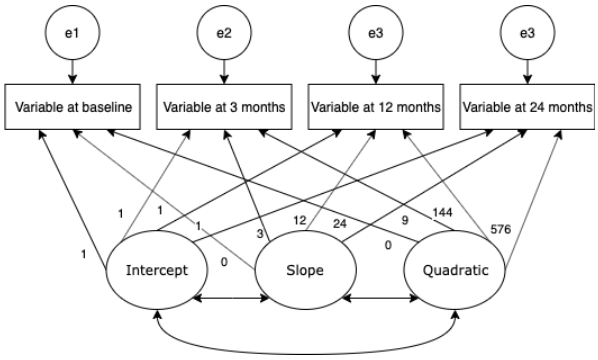


Figure 3.6. Unconditional latent growth curve model

Once model fit was established for the unconditional model, a conditional model was fitted (2). These included age and gender for all variables and education and income for BMI. Treatment group was included as a covariate for the slope and quadratic (due to randomisation, no impact of group allocation on intercept was modelled). All variables were treated as time-invariant; although age is a time-variant variable in reality, as the trial was only two years long, we used starting age as a time-invariant variable to avoid additional complexity in the model. For the psychological variables, the estimates of each of the growth factors in show in equations 3-5 where α, β and γ are the coefficients linking the age, sex and treatment group to the growth factor. The same for the BMI variables in in equations 6-8 where ρ and ν are the coefficients linking income and education to the latent growth factors. Conditional growth models for potential mediators and BMI are shown in Figure 3.7 and 3.8 respectively.

$$\mathbb{I}_i = \mu_{00} + \alpha_0 Age_i + \beta_0 Sex_i \quad (3)$$

$$\mathbb{S}_i = \mu_{00} + \alpha_1 Age_i + \beta_1 Sex_i + \gamma_1 TG \quad (4)$$

$$\mathbb{Q}_i = \mu_{00} + \alpha_2 Age_i + \beta_2 Sex_i + \gamma_2 TG \quad (5)$$

$$\mathbb{I}_i = \mu_{00} + \alpha_0 Age_i + \beta_0 Sex_i + \rho_0 Income_i + \nu_0 Education_i \quad (6)$$

$$\mathbb{S}_i = \mu_{00} + \alpha_1 Age_i + \beta_1 Sex_i + \rho_0 Income_i + \nu_0 Education_i + \gamma_1 TG \quad (7)$$

$$\mathbb{Q}_i = \mu_{00} + \alpha_2 Age_i + \beta_2 Sex_i + \rho_0 Income_i + \nu_0 Education_i + \gamma_2 TG \quad (8)$$

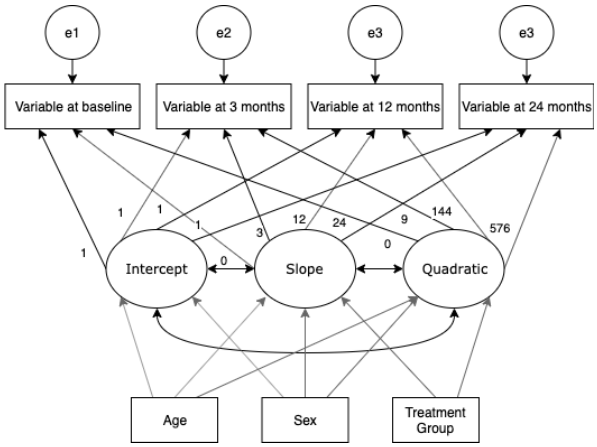


Figure 3.7. Mediator conditional growth curve model

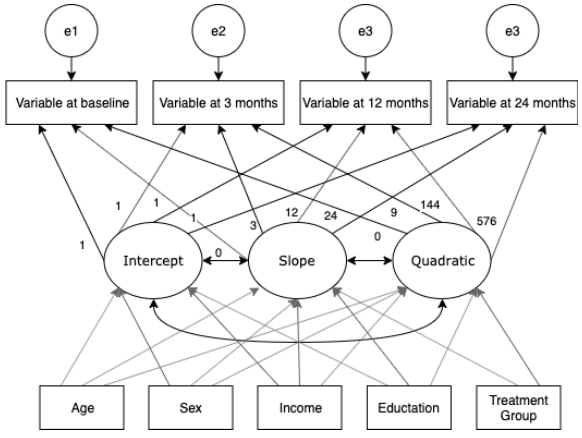


Figure 3.8. BMI conditional growth curve model

Piecewise growth curve model

Piecewise growth curve model were also fitted to the trajectories of each of the mechanisms of action and BMI as a secondary analysis. This enables a single intercept with two slopes which can be used to represent the intervention stage (up to 12 months) and the maintenance stage (12-24 months). Ideally piecewise analysis requires at least 5 time points such that three time points can be used for each curve (1). However piecewise analysis can be conducted on fewer time points, although the requires restriction on some parameters (for example, limiting the variance of, or covariance between, growth factors to zero) to allow the model to be fitted (3). These were fitted at each stage following the same procedure as described in the analysis strategy however based on the findings from the latent growth curve analysis, it was assumed that there were two slope factors. The piecewise model was fitted with each of 3 and 12 months as the points that the slopes meet to test which was the better fit (steps 1 and 2). The slope of the first slope was varied first as the change in the variable was the focus and greater variation change was expected in this phase when the intervention took place. The model with the better fit was taken through to the next stage:

1) Intercept and both slopes fixed to zero, slope 1 is 0-3 months, slope 2 is 3-24 months
2) Intercept and both slopes fixed to zero, slope 1 is 0-12 months, slope 2 is 12-24 months
3) Intercept and slope 2 fixed to zero
4) Intercept fixed to zero

The unconditional and conditional examples of a piecewise model are shown in Figures 3.9 and 3.10.

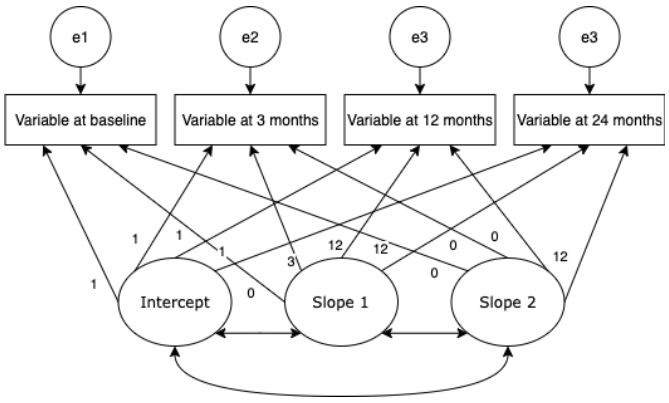


Figure 3.9. Mediator unconditional piecewise growth curve model

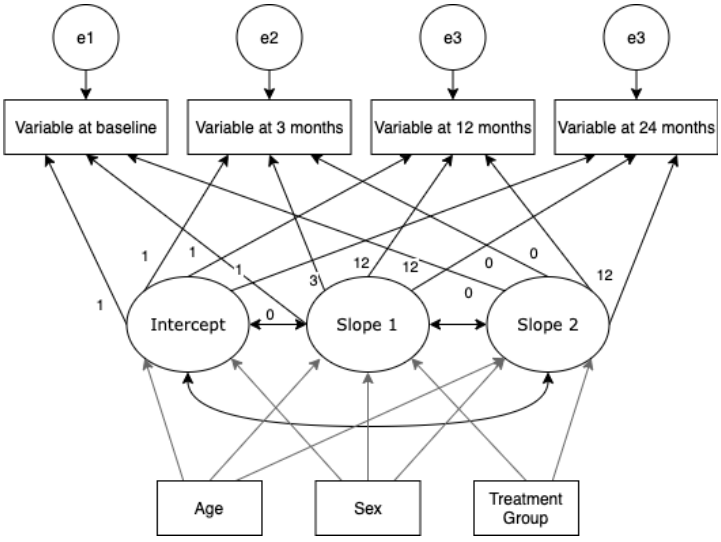


Figure 3.10. Mediator conditional piecewise growth curve model

Benefits of the method

LGCA as a method has many benefits over traditional regression methods, an alternative analysis method for this type of research question. Standard regression methods tend to use just two time points, the baseline and the last time point. The last time point is regressed on the predictors while controlling for the baseline value; thus, the analysis examines predictors of residual values (final value with the effect of the baseline value removed) (1). When there are more time points available, as in the data set from the WRAP study, the information available about values about time points between the first and last is lost. In addition, if the trajectory of variables is not linear, the impact of covariate may not be detected (1). This is important for this analysis as the intervention takes place within the first year and therefore it is reasonable to expect an initial change from baseline and a return towards the baseline value. This does not reflect a linear trajectory.

Another benefit of LGCA is that it is possible to investigate the different growth parameters in one analysis (2). Although in this analysis, we were most interested in the change over time (slope and quadratic factors), we were also able to account for any association between the change in the outcome variable (BMI) and baseline values of the predictors (intercept) as well as the impact of the change in predictors on the change in BMI. This allows a more complete picture of the association between the predictors and the outcome. In addition, the growth factors can be used as predictor or outcomes. In the mediation model, slopes of the

psychological variables were an outcome (predicted by demographic variables and group allocation) and predictors (of change in BMI).

Finally, the ability of enabling a time-varying variable (in this case the slope of the mediator) to be a predictor of another time-varying variable (slope and quadratic of BMI) in both the parallel processing model (step 2) and the full mediation would be challenging to do with other regression models.

Limitations

There are some limitations of this method. The shape of the curve is expected to be the same for all individuals and so although the covariate can reflect the magnitude of the growth factors, they cannot be used to predict shape. This is a limitation in this study as the three groups had different intervention time periods and therefore different curve shapes was possible (1). However, as can be seen in Figure 1 in the main paper, the trajectory of change in the groups seem to follow a similar shape but with different magnitudes and thus we don't expect this limitation to have had a large impact. The analysis is based on the assumption that variables are univariate and multivariate normally distributed (2). This was initially a concern because the variables used were not normally distributed. However, we used a method of estimation method of that is robust to non-normal distributions and found that the results did not differ significantly from the standard methods. Finally, it's acknowledged that the fit of a model isn't easy to asses as there is not a single measure of fit and researchers must make a decision. Therefore, throughout the results, we included model fit statistics and have highlighted when some are below recommended cut off values.

Considerations

1) Measurement issues

Often in LGCA, the observation between time points will be correlated such that time points closer together will have a stronger correlation than time points further apart (4). However, in this study, this may not be the case as we could expect more change between baseline and 3 months in which all participants have an intervention of some kind than between year 1 and 2 when there is no reported intervention. Thus, in this LGCA we've not added correlation paths between adjacent and nearly adjacent variables. Another potential measurement issue is the assumption of homoscedasticity over time (5). That is, is it expected that at each time

point the residual variance around an observation will be the same (i.e. the is the same around of variation among individuals at each time point). Thus, changes observed between time points can be assumed to be changes in in these variables rather than changes in residual variance. When fitting a curve to each of the variables, we fixed variances for each time to be equal. For each variable we also checked whether the model fit was better without this fixing to determine any problems with this assumption.

2) Sample size

The sample size in terms of the number of time points and number of participants has an impact on LGCA. The number of time points determine the complexity of the growth curve through the number of growth factors. The number of growth factors much be at least one less than the number of time points. In the case, because there were four time points, the maximum number of growth factors was three (intercept, slope and quadratic). There are no clear guidelines on the number of time points needed (6). Some suggest that four to five measurements are sufficient and but that this is conditional on effect size, sample size and sample size (7), others recommends that a limited number occasions avoid high levels of complexity that can make achieving an adequate fit challenging (2). The important point is that the time points should adequately cover the time of interest. In this case, the time points were before intervention, after one group finished their intervention, after the second group finished the intervention and then one year later which covers the points in time where the most change was expected to occur.

In terms of the number of subjects, again there is not clear guidelines for this although at least 100 are preferred (8),(9) and our sample exceeded this substantially. However, as the sample size increases, there is a greater probability of rejecting the models based on the significance of the Chi square statistic and therefore this model fit statistic was not used.

3.8.5. Results

In Tables 3.10-3.15 below the first model tested (0) will be the base model in which it's assumed that all participants have the same intercept and no change over time. Models 1-5 represent increasingly complex models tested (outlined in previous section). A conditional model (adapted from the best fitting unconditional

model) was then fitted. Finally, we checked the homoscedasticity assumption by removing the restriction of equal variances across timepoints.

Tables 3.16-3.19 show the model statistics for the piecewise models fitted to BMI and each of the mediators. Models 1-4 are those described previously in the analysis section. A conditional model (adapted from the best fitting unconditional model) was then fitted. Unlike the previous analyses, the homoscedasticity was assumed throughout the models. This is based on the finding that assuming the same variance across time points did not negatively impact model fit in the previous section and because the piecewise model required more parameters to be fixed to avoid oversaturation on the model.

Table 3.10. Latent growth curve analysis of BMI

Model	Fit statistics					Intercept		Slope		Quadratic		Covariance		
	Chi-Square (df)	Change in Chi-Square (df)	RMSEA	CFI	SRMR	mean	variance	mean	variance	mean	variance	Intercept, slope	Intercept, quadratic	Slope, quadratic
0	3903.24 (12)		0.51	0.00	0.62	33.38								
1	1005.78 (11)	2897.46 (1)***	0.27	0.62	0.20	33.38	24.34							
2	932.43 (10)	73.35 (1)***	0.27	0.64	0.17	33.69	25.27	-0.32						
3	715.38 (8)	217.05 (2)***	0.26	0.73	0.11	33.69	24.21	-0.32	0.89			0.24		
4	384.31 (7)	331.07 (1)***	0.21	0.85	0.06	34.22	24.56	-2.69	1.08	0.98		0.05		
5	224.35 (4)	159.96 (3)***	0.21	0.92	0.03	34.22	25.32	-2.69	10.342	0.98	1.00	-2.05*	0.64*	-3.08*
Conditional	364.35 (15)	NA	0.14	0.93	0.02	36.16	24.50	0.84	9.52	0.03	0.92	-2.15*	0.67*	-2.82*
Check homoscedasticity	391.21 (12)		0.16	0.93	0.03	36.24	24.62	0.45	7.65	0.11	1.38	-2.09	0.68	-2.68

RMSEA; Root Mean Square Error of Approximation, CFI; Comparative Fit Index, SRMR; Standardized Root Mean Square Residual

Table 3.11. Latent growth curve analysis of habit strength

Model	Fit statistics					Intercept		Slope		Quadratic		Covariance		
	Chi-Square (df)	Change in Chi-Square (df)	RMSEA	CFI	SRMR	mean	variance	mean	variance	mean	variance	Intercept, slope	Intercept, quadratic	Slope, quadratic
0	1134.12 (12)		0.27	0.0	0.39	3.84								
1	340.49 (11)	793.63 (1)***	0.15	0.5	0.17	3.84	1.16							
2	299.61 (10)	40.99 (2) ***	0.15	0.6	0.17	3.70	1.17	0.14						
3	127.62 (8)	171.99 (2)***	0.12	0.8	0.11	3.40	1.22	0.28	0.01			-0.02		
4	32.95 (7)	94.67 (2)***	0.07	0.9	0.05	3.26	1.21	0.99	0.09	-0.30		-0.04		
5	Not converged													
Conditional	41.52 (13)	NA	0.05	0.9	0.04	1.94	1.14	0.79	0.10	-0.21		-0.06		
Check homoscedasticity	47.77 (10)	NA	0.05	0.9 8	0.03	2.28	1.09	0.63	-0.06	-0.17		-0.03		

RMSEA; Root Mean Square Error of Approximation, CFI; Comparative Fit Index, SRMR; Standardized Root Mean Square Residual

Table 3.12. Latent growth curve analysis of dietary restraint

Model	Fit statistics					Intercept		Slope		Quadratic		Covariance		
	Chi-Square (df)	Change in Chi-Square (df)	RMSEA	CFI	SRMR	mean	variance	mean	variance	mean	variance	Intercept, slope	Intercept, quadratic	Slope, quadratic
0	1345.75 (12)		0.30	0.00	0.40	6.96								
1	756.84 (11)	588.91 (1)***	0.23	0.05	0.25	6.96	4.50							
2	311.20 (10)	445.64 (2)***	0.16	0.62	0.14	5.69	4.80	0.70						
3	292.71 (8)	18.49 (2)***	0.18	0.64	0.14	5.69	4.31	0.71	-0.09			0.20		
4	34.09 (7)	258.62 (1)***	0.07	0.96	0.05	5.15	4.14	3.41	0.13	-1.13		0.43*		
5	Not converged													
Conditional	45.15 (13)	NA	0.05	0.97	0.04	2.82	3.72	2.68	0.15	-0.87		0.40**		
Check homoscedasticity	38.77 (10)	6.38 (3)*	0.04	0.98	0.03	2.82	3.53	2.68	0.37	-0.86		0.43**		

RMSEA; Root Mean Square Error of Approximation, CFI; Comparative Fit Index, SRMR; Standardized Root Mean Square Residual

Table 3.13. Latent growth curve analysis of autonomous diet self-regulation

Model	Fit statistics					Intercept		Slope		Quadratic		Covariance		
	Chi-Square (df)	Change in Chi-Square (df)	RMSEA	CFI	SRMR	mean	variance	mean	variance	mean	variance	Intercept, slope	Intercept, quadratic	Slope, quadratic
0	381.88 (12)		0.16	0.47	0.52	0.81								
1	359.40 (11)	22.48 (1)***	0.16	0.50	0.44	5.71	0.62							
2	154.57 (10)	204.83 (1)***	0.11	0.79	0.34	5.95	0.64	-0.24						
3	55.22 (8)	99.35 (2)***	0.07	0.93	0.18	5.95	0.52	-0.24	0.09			0.03		
4	43.72 (7)	11.50 (1)***	0.06	0.95	0.16	5.89	0.52	-0.43	0.09	0.08		0.03		
5	Not converged													
Conditional	52.49 (13)	NA	0.05	0.96	0.02	5.75	0.51	-1.16	0.09	0.36		0.03		
Check homoscedasticity	45.57 (10)	6.92 (3)*	0.05	0.96	0.07	5.76	0.53	-1.19	0.11	0.37		0.01		

RMSEA; Root Mean Square Error of Approximation, CFI; Comparative Fit Index, SRMR; Standardized Root Mean Square Residual

Table 3.14. Latent growth curve analysis of controlled diet self-regulation

Model	Fit statistics					Intercept		Slope		Quadratic		Covariance		
	Chi-Square (df)	Change in Chi-Square (df)	RMSEA	CFI	SRMR	mean	variance	mean	variance	mean	variance	Intercept, slope	Intercept, quadratic	Slope, quadratic
0	1616.59 (12)		0.33	0.00	0.42	3.27								
1	59.23 (11)	1557.36	0.06	0.96	0.03	3.27	1.18							
2	25.60 (10)	33.63 (1)***	0.04	0.99	0.03	3.63	1.19	-0.09						
3	14.63 (8)	10.97 (2)**	0.03	1.00	0.02	3.36	1.27	-0.09	0.04			-0.06		
4	9.04 (7)	5.59 (1)*	0.02	1.00	0.02	3.39	1.27	-0.22	0.04	0.06		-0.06		
5*	5.36 (4)	3.68 (3)	0.02	1.00	0.01	3.39	1.27	-0.22	-0.04	0.06	-0.03	-0.05	0.00	0.05
Conditional	14.76 (13)	NA	0.02	1.00	0.02	3.10	1.26	-0.08	-0.09	0.09	-0.03	-0.04	-0.1	0.07
Check homoscedasticity	11.08 (10)	3.68 (2)	0.02	1.00	0.02	3.08	1.22	-0.06	-0.17	0.09	-0.05	0.04	-0.03	0.10

*This model was not significantly better fitting than the previous, more simple, model and therefore the previous model was selected for the next step of the analysis.

RMSEA; Root Mean Square Error of Approximation, CFI; Comparative Fit Index, SRMR; Standardized Root Mean Square Residual

Table 3.15. Latent growth curve analysis of amotivation diet self-regulation

Model	Fit statistics					Intercept		Slope		Quadratic		Covariance		
	Chi-Square (df)	Change in Chi-Square (df)	RMSEA	CFI	SRMR	mean	variance	mean	variance	mean	variance	Intercept, slope	Intercept, quadratic	Slope, quadratic
0	802.96 (12)		0.23	0.00	0.32	2.39								
1	28.40 (11)	774.56 (1)***	0.04	0.97	0.04	2.39	0.59							
2*	27.20 (10)	1.2 (1)	0.04	0.97	0.04	2.38	0.59	0.02						
Conditional	48.83 (17)	NA	0.04	0.96	0.04	2.39	0.59							
Check homoscedasticity	42.79 (14)	6.04 (3)	0.04	0.96	0.05	2.40	0.60							

*This model was not significantly better fitting than the previous, more simple, model and therefore the previous model was selected for the next step of the analysis.

RMSEA; Root Mean Square Error of Approximation, CFI; Comparative Fit Index, SRMR; Standardized Root Mean Square Residual

Table 3.16. Piecewise latent growth curve analysis of BMI

Model	Fit statistics					Intercept		Slope		Slope 2		Covariance		
	Chi-Square (df)	Change in Chi-Square (df)	RMSEA	CFI	SRMR	mean	variance	mean	variance	mean	variance	Intercept, slope	Intercept, slope 2	Slope 2, slope 2
1 (slope 1: 0-3)	3598.23 (10)		0.53	0.00	0.61	34.54		-5.81		0.180				
2 (slope 1: 0-12)	**3512.69 (10)**		**0.53**	**0.00**	**0.61**	**34.08**		**-1.35**		**0.741**				
3 (slope 1: 0-12)	2758.75 (9)	753.94 (1)***	0.49	0.29	0.99	34.06		-1.35	18.75	0.741				
4 (slope 1: 0-12)	2360.54 (7)	398.21 (2)***	0.52	0.21	0.61	34.06		-1.35	13.47	0.74	6.71			0.08
5 (slope 1: 0-12)	374.69 (4)	1985.85 (3)***	0.27	0.86	0.04	34.06	24.97	-1.35	3.80	0.741	0.67	-0.95*	0.20	0.08
Conditional	545.51 (16)	NA	0.16	0.90	0.02	36.01	24.16	2.07	3.46	0.83	0.61	-0.034**	0.20*	0.15

Table 3.17. Piecewise latent growth curve analysis of habit strength

Model	Fit statistics					Intercept		Slope		Slope 2		Covariance		
	Chi-Square (df)	Change in Chi-Square (df)	RMSEA	CFI	SRMR	mean	variance	mean	variance	mean	variance	Intercept, slope	Intercept, slope 2	Slope 2, slope 2
1 (slope 1: 0-3)	1008.93 (10)		0.28	0.00	0.36	3.26		2.97		-0.11				
2 (slope 1: 0-12)	1107.99 (10)		0.29	0.00	0.36	3.59		0.45		-0.18				
3 (slope 1: 0-3)	810.01 (9)	397.98 (1)***	0.21	0.38	0.34	3.26		297	12.64	-0.11				
4 (slope 1: 0-3)	Not converged													
5 (slope 1: 0-3)	Not converged													
Conditional	484.79 (15)	NA	0.16	0.57	0.21	1.94		2.47	11.67	-0.01				

Table 3.18. Piecewise growth curve analysis of dietary restraint

Model	Fit statistics					Intercept		Slope		Slope 2		Covariance		
	Chi-Square (df)	Change in Chi-Square (df)	RMSEA	CFI	SRMR	mean	variance	mean	variance	mean	variance	Intercept, slope	Intercept, slope 2	Slope 2, slope 2
1 (slope 1: 0-3)	740.49 (10)		0.24	0.00	0.32	5.15		10.30		-0.67				
2 (slope 1: 0-12)	944.33 (10)		0.27	0.00	0.38	6.30		1.42		-0.97				
3 (slope 1: 0-3)	325.35 (9)	618.98 (1)***	0.17	0.44	0.26	5.15		10.30	54.16	-0.67				
4 (slope 1: 0-3)	Not converged													
5 (slope 1: 0-3)	Not converged													
Conditional	319.61 (15)	NA	0.13	0.65	0.16	2.85		8.12	49.63	-0.37				

Table 3.19. Piecewise growth curve analysis of autonomous diet self-regulation

Model	Fit statistics					Intercept		Slope		Slope 2		Covariance		
	Chi-Square (df)	Change in Chi-Square (df)	RMSEA	CFI	SRMR	mean	variance	mean	variance	mean	variance	Intercept, slope	Intercept, slope 2	Slope 2, slope 2
1 (slope 1: 0-3)	952.34 (10)		0.27	0.00	0.49	6.00		-0.58		-0.20				
2 (slope 1: 0-12)	954.46 (10)		0.27	0.00	0.47	5.98		-0.32		-0.15				
3 (slope 1: 0-3)	Not converged													
4 (slope 1: 0-3)	Not converged													
5 (slope 1: 0-3)	Not converged													
Conditional	319.61 (15)	NA	0.20	0.37	0.39	2.85		8.12	49.63	-0.37				

Table 3.20. Associations between the latent growth factors of BMI and potential mediators

Variable	BMI growth factors		Fit statistics		
	Slope	Slope 2	CFI	RMSEA	SRMR
Dietary Restraint					
Slope	-0.45 (0.13) **	-0.51 (2.54)	0.72	0.14	0.12
Slope 2		-1.70 (5.84)			
Habit strength					
Slope	-0.61 (0.19)**	0.26 (0.14)	0.76	0.14	0.12
Slope 2		-0.56 (0.15)**			
Autonomous diet Self-regulation					
Slope	-1.17 (0.50)*	0.74 (0.30)*	0.61	0.13	0.17
Slope 2		1.63 (1.25)			

Note. * $p < .05$. ** $p < .01$. *** $p < .001$. BMI, Body Mass Index. CFI, comparative fit index.

RMSEA, Root mean square error of approximation. SRMR, Standardized Root Mean Square Residual.

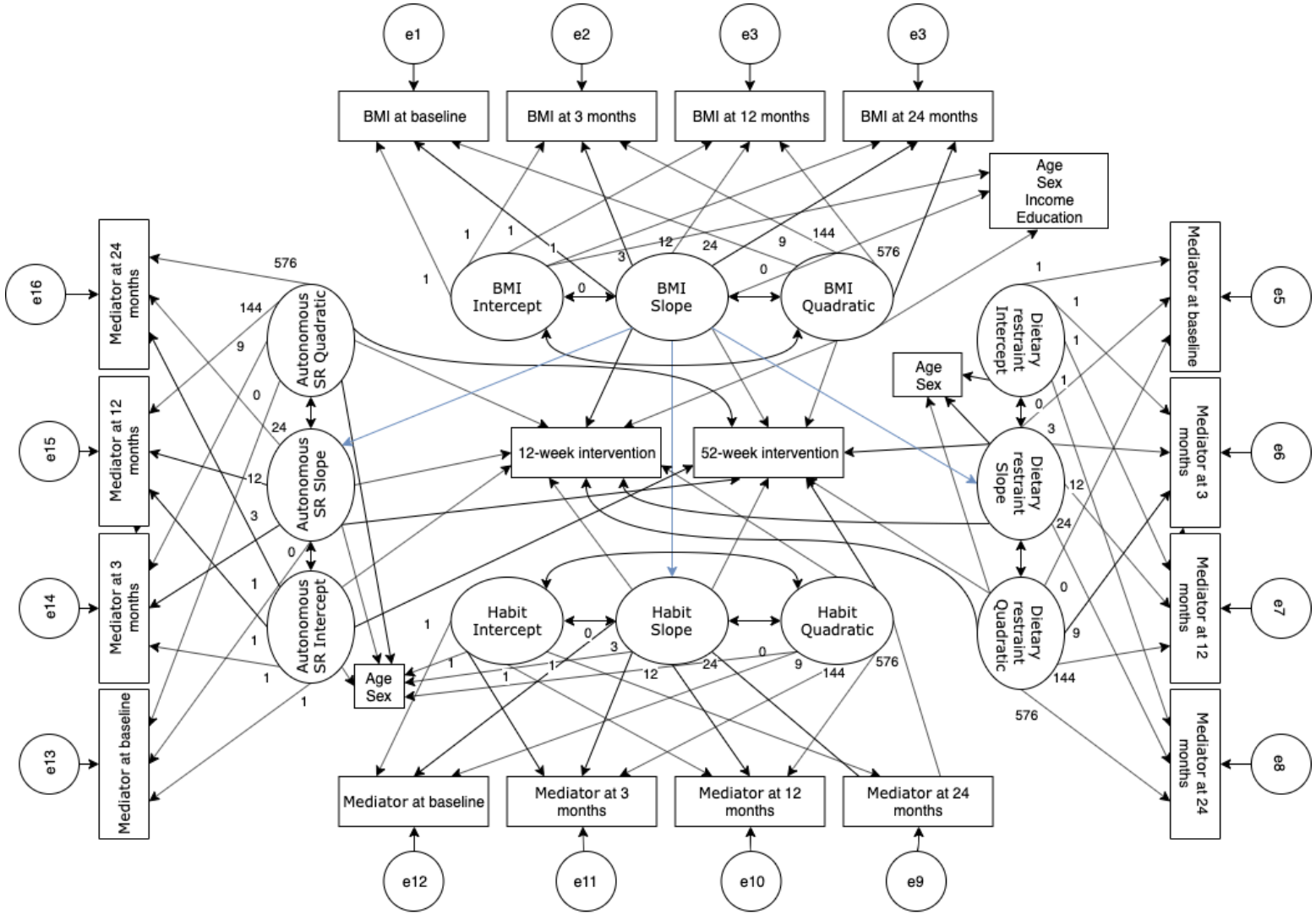


Figure 3.11. Full mediation model tested

Table 3.21. Total, direct and indirect effects via mediating variables of the 12- and 52-week intervention on BMI for each mediator (tested in separate models)

	Total impact of intervention on BMI			Total indirect effect of mediating variables			Direct effect of intervention on BMI when mediator included		
Effect	Estimate	SE	P value	Estimate	SE	P value	Estimate	SE	P value
Habit strength									
12-week intervention	-0.68	0.37	0.06	-0.599	0.30	0.04	-0.08	0.45	0.86
52-week intervention	-1.72	0.38	<0.001	-1.08	0.39	0.01	-0.65	0.53	0.22
Dietary restraint									
12-week intervention	-0.68	0.37	0.06	-0.83	0.34	0.014	0.14	0.51	0.78
52-week intervention	-1.72	0.38	<0.001	-1.41	0.47	0.003	-0.31	0.60	0.60
Autonomous diet self-regulation									
12-week intervention	-0.68	0.37	0.06	-0.21	0.17	0.21	-0.442	0.39	0.26
52-week intervention	-1.72	0.38	<0.001	-0.39	0.18	0.03	-1.32	0.40	0.001

Table 3.22. Standardised total, direct and indirect effects via mediating variables of the 12- and 52-week intervention on BMI

	12-week intervention			52-week intervention		
Effect	Estimate	SE	P value	Estimate	SE	P value
Total impact of intervention on BMI	-0.15	0.06	0.01	-0.28	0.06	<0.001
Total indirect effect of mediating variables	-0.17	0.06	0.002	-0.29	0.07	<0.001
Direct effect of intervention on BMI when mediators included	0.02	0.08	0.78	0.002	0.10	0.983
Indirect Effect of Mediator						
Habit	-0.05	0.03	0.07	-0.09	0.04	0.02
Restraint	-0.10	0.04	0.027	-0.16	0.06	0.009
DSR	-0.02	0.02	0.154	-0.04	0.02	0.048

3.8.6. References

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CHAPTER 4: INCORPORATING PSYCHOLOGICAL MECHANISMS OF ACTION INTO A HEALTH ECONOMIC MODEL OF OBESITY

This chapter reports the adaptation of an existing health economic model of obesity to include the three mechanisms of action identified in Chapter 2. Specifically, dietary restraint, habit strength and autonomous diet self-regulation were incorporated into the School of Public Health Research Health economic model. The aims were then to 1) compare simulated BMI and cost-effectiveness when these mechanisms were incorporated, to model specifications without these mechanisms and 2) explore the additional subgroup and sensitivity analyses that can be conducted using the newly adapted model. A version of this paper was presented at the Health Economists Study Group (HESG) Winter 2021.

USING A HEALTH ECONOMIC MODEL THAT INCORPORATES PSYCHOLOGICAL MECHANISMS OF ACTION TO ESTIMATE COST-EFFECTIVENESS OF A BEHAVIOURAL WEIGHT MANAGEMENT INTERVENTION

4.1 Abstract

Objectives. Incorporating psychological mechanisms of action (MoA) of weight-management interventions into health economic modelling could result in better representation of heterogeneity in weight change and cost-effectiveness estimates and thus more efficient allocation of resources. The aim of the study was to incorporate psychological MoAs of a weight-management intervention into a health economic model and examine (i) if Body Mass Index (BMI) over 2 years can be simulated using MoAs, (ii) how cost-effectiveness estimates based on MoAs compare to those generated when treatment effect on BMI is entered directly, (iii) if baseline levels of MoAs impact cost-effectiveness and (iv) sensitivity analysis around duration of effect based on MoAs.

Methods. Analysis of a randomised controlled trial, in which participants (*N*=1,267) were randomised to either a brief intervention, a 12-week weight management intervention or the same intervention for 52 weeks, indicated that dietary restraint, habit strength and autonomous diet self-regulation were significant MoAs. These three MoAs were incorporated into the School for Public Health Research microsimulation model. Estimated BMI at years 1 and 2 and long-term cost-effectiveness were compared for three model specifications: applying mean change in BMI in each treatment group (Mean change), change in BMI in each treatment group adjusting for demographic factors (Demographic-adjusted) and treatment effect based on demographic factors and change in psychological MoAs (Demographic plus MoA-adjusted). Cost-effectiveness outcomes for individuals high and low on these variables, for each variable individually and three variables together, were compared. Two sensitivity analyses were conducted based on hypothesised trajectories of mechanisms of action.

Results. There were no significant differences between the simulated mean and distribution of BMI of the three model specifications, and those observed in the study data. Cost savings of the 12- and 52-week interventions compared to the brief intervention, were lower for the Demographic-adjusted and Demographic plus MoA-adjusted models compared to the Mean change model and QALYs were higher. There were small differences in incremental costs and QALYs when comparing individual that were high or low on each or all mechanisms of action. Sensitivity analysis indicated that sustained changes in mechanisms of action results in larger cost savings and higher incremental QALYs.

Conclusions. Although limited to one study and three variables, this research demonstrates how mechanisms of action identified in mediation analysis of behavioural weight management interventions can be used to reliably estimate BMI within health economic modelling. While our findings do not indicate that including psychological mechanisms of action in a health economic model of obesity provides a predictive advantage compared to standard methods of inputting intervention effect, it does enables subgroup and sensitivity analysis based on psychological mechanism of action which have the potential to have an impact on cost-effectiveness and funding decisions.

4.2 Introduction

Behavioural weight management interventions are the first-line treatment recommended for people who are above a healthy Body Mass Index (BMI) (1) but they vary in content and effectiveness (2). This has led to an increased emphasis in the field of behaviour change science, on reporting the content of behavioural interventions and the underlying theory that inform their design (3-5). More recently this has been conceptualised as description of the behaviour change techniques used in an intervention and the targeted mechanisms of action ("the processes through which a behaviour change technique affects behaviour") (5). It is argued that an intervention is more likely to be effective at changing behaviour and ultimately improving health, if it targets and changes known influential mechanisms of action (e.g., dietary restraint (6)). Therefore, a greater understanding of the relationship between an intervention, the mechanisms of action and weight change, could inform the design of effective interventions and enhance understanding of why certain interventions work and for whom (7, 8).

Including relevant mechanisms of action in health economic modelling of behavioural weight management interventions has two potential benefits. First, it may result in better representation of the heterogeneity in weight change and cost-effectiveness leading to more efficient allocation of resources. Heterogeneity is widely reported; in a systematic review of trials of weight management interventions, mean weight change at 12 months ranged from +0.30kg to -7.6kg across studies (2). Furthermore, while another systematic review found that, on average, weight loss was regained by five years after the start of an intervention (9), there is evidence from an observational study that some individuals are able to maintain weight loss for up to ten years (10). Allowing change in BMI to be conditional on change in mechanisms of action may result in better prediction of BMI for individuals in a population compared to methods commonly used such as entering a mean change in BMI in weight for all simulated individuals or entering a change in BMI based on demographic factors such as age and gender (11, 12). Including relevant mechanisms of action would also enable subgroup analysis based on these factors, which could be used to allocate resources if commissioners are budget constrained. Subgroup analysis is often conducted to examine the impact of demographic and health-related factors (e.g. age, gender and baseline BMI) on cost-effectiveness (11). However, given strong evidence that psychological

variables are important determinants of weight management (13-15), there is justification to examine whether cost-effectiveness is dependent on the levels of psychological determinants of weight change at baseline. Finally, the inclusion of mechanisms of action may provide an opportunity to estimate long-term trajectories based on psychological theory. Estimating duration of effect of an intervention is often challenging as trial follow-ups are often limited to one or two years (9) and assumptions are made about the time taken for individual to regain weight lost (12). Using research that has investigated the role of psychological factors in weight loss maintenance (14) to guide sensitivity analysis, has the potential to inform more accurate estimates of long-term cost-effectiveness in the population of interest and ultimately support more efficient allocation of resources (16).

A second benefit of including relevant mechanisms of action in health economic modelling of behavioural weight management interventions is that it may facilitate consideration of cost-effectiveness in the design phase of a behavioural intervention through pre-trial modelling. Pre-trial modelling is recommended as it enables the researcher to consider the likelihood of the intervention being cost-effective based on known intervention costs and estimated effects, and thus can inform decisions about the intervention design and whether proceeding to a trial is justified (17, 18). Estimations of intervention effect are more likely to be accurate if they're specific to the intervention and based on the mechanisms of action targeted within the intervention (7). Entering this estimate of intervention effect on mechanisms of action would enable a more theory-based and intervention-specific estimate of long-term costs, benefits and cost-effectiveness. Despite the potential benefits, a recent systematic review found that no health economic models incorporated psychological mechanisms of action (12). Therefore, at present, there isn't evidence that change in BMI within health economic models can be reliably predicted from change in mechanisms of action.

Therefore, the aim of the current study was to examine the feasibility of estimating change in BMI and long-term cost-effectiveness using change in mechanisms of action. To do this, psychological mechanisms of action of a behavioural weight management intervention were incorporated into an existing health economic microsimulation model based on a three-arm randomised controlled trial (RCT). In this trial, dietary restraint, habit strength and autonomous diet self-regulation were identified as mechanisms of actions of a 12- and 52-

week weight management intervention compared to a brief intervention (Chapter 3). The aim can be divided into two parts. First, the aim was to compare a model specification in which BMI was simulated based on mechanisms of action, to commonly used methods to input intervention effect. Specifically the objectives were:

1) To validate prediction of BMI at year 1 and 2 based on demographic factors, baseline BMI and change in known mechanisms of action (dietary restraint, habit strength and autonomous diet self-regulating) compared to (a) the BMI in the original RCT, (b) entering mean change in BMI for each treatment group and (c) entering change in BMI for each treatment group adjusting for demographic factors and baseline BMI.
2) To compare the cost-effectiveness estimates generated when BMI was predicted based on the demographic factors, baseline BMI and mechanisms of action to those generated when entering BMI using two methods: (a) entering mean change in BMI for each treatment group and (b) entering change in BMI for each treatment group adjusting for demographic factors and baseline BMI.

The second aim was to explore the impact of additional analyses based on the mechanisms of action incorporated into the health economic model. The objectives were:

3) To investigate cost-effectiveness of the intervention in subgroups based on baseline scores on the mechanisms of action.
4) To examine different assumptions of duration of effect based on psychological theory (sensitivity analysis).

4.3 Method

4.3.1 Case Description

The mechanisms of action included in the health economic model in this study were based on the weight-loss programme referrals for adults in primary care (WRAP) randomised controlled trial (19). In this trial, participants (N = 1,267) with a BMI of 28 or over were randomised to either a control group in which they were given a self-help booklet (brief intervention), a 12-week commercial weight management programme or

52 weeks of the same programme (vouchers provided). The participants completed assessments at pre-randomisation (baseline) and at 3, 12, and 24 months after starting the intervention. At these time points weight and height were measured, BMI was calculated, and participants completed measures of hypothesized mechanisms of action of the intervention (i.e. dietary restraint, habit strength and diet self-regulation). Participants in the weight management interventions (12- and 52-week) lost more weight than the brief intervention at 3 and 12 months. At 24 months, there was a significant difference between the 52-week intervention and the brief intervention but not between the 12-week intervention and the brief intervention. Latent growth curve mediation analyses was conducted to determine the association between the treatment group, the potential mechanisms of action (dietary restraint, habit strength and autonomous, controlled and amotivation diet self-regulation) and BMI ((20); Chapter 3). The trajectories of dietary restraint, habit strength and autonomous diet self-regulation mediated the impact of both the 12- and 52-week intervention on BMI; that is, when the change in these variables was controlled for, there was no longer a significant impact of the interventions on the slope of BMI. This indicated that the interventions were effective through the impact they had on these three variables (i.e. mechanisms of action). Only dietary restraint was an independent mechanism of action for the 12-week intervention whereas all three were significant independent mechanisms of action for the 52-week intervention. These three variables were incorporated into the health economic model.

4.3.2 School of Public Health Research (SPHR) diabetes prevention model

In the present study, the School of Public Health Research (SPHR) diabetes prevention model was adapted to incorporate the three mechanisms of action: dietary restraint, habit strength and autonomous diet self-regulation. In the SPHR model, annual change in BMI (natural history) and associated changes in other metabolic factors (blood glucose, systolic blood pressure (SBP) and cholesterol) are based on analysis of the Whitehall II prospective cohort study (21). Based on this analysis, it is assumed that reductions in BMI results in improvements in blood glucose, systolic blood pressure (SBP) and cholesterol. These metabolic factors impact on whether an individual receives a diagnosis of diabetes, experiences a cardiovascular event, cancer, osteoarthritis or diabetes-related complications. For each simulated individual in the model, each year their BMI updates (increases, decreases or stays the same), which then impacts on their other metabolic factors and

their individual risk of disease diagnosis and/or health event. Specifically, within the SPHR model, BMI is a risk factor for cardiovascular disease, cancer (breast and colon) and osteoarthritis. BMI is also an indirect risk factor for type 2 diabetes through the association with HbA1c.

The impact of a weight management intervention is implemented in the model by entering a change in BMI, often observed in a trial. This change in BMI then impacts on the other metabolic factors and the risk of healthcare events and conditions as described above. In the base case scenario, it is assumed that all weight is regained to the natural history trajectory (based on the Whitehall trajectories previously described) in the absence of the intervention after 5 years.

The model is an individual simulation model that runs in annual cycles with a lifetime time horizon such that costs, and effectiveness are measured over the lifetime of all simulated individuals. Effectiveness is measured in Quality Adjusted Life Years (QALYs). A national health service (NHS) and personal social services (PSS) perspective is used. This model has been used to assess the cost-effectiveness of diabetes prevention programmes (22, 23). This health economic model was suited for this study because individual BMI trajectories are modelled for each simulated individual in the model. This enabled adaptation of the BMI trajectories such that they were conditional on individual factors including demographic factors and mechanisms of action. This model is also built in the software R which had the capability to incorporate the analysis on the mechanism of action in Chapter 3. Full details of the model and model parameters can be found in Appendix 3 and 4.

Summary School of Public Health Research (SPHR) diabetes prevention model

The School of Public Health economic model is an existing health economic model that has been adapted for the thesis and is used in Chapters 4-6. Because of the manuscript format of the chapters, the model is described briefly in each chapter, and the full details of the model have been included in Appendix 3. This was previously described in the Supplementary Material of a published article. For the purposes of the thesis, this section will include a summary of the model structure.

At the first stage in the model, the age of the simulated individual is updated. In the second stage, the number of GP visits is estimated and is conditional on demographic variables and comorbidities such as diabetes and cancer based on an analysis of the South Yorkshire Cohort study (24). The number of GP visits was used to estimate healthcare utilisation and the likelihood that the individual will have a healthcare screening. The third stages estimates the change in BMI and in stages 4, 5 and 6, the individuals glycaemia, blood pressure and cholesterol are updated. The changes in these metabolic factors are conditional on several individual characteristics including age, sex, ethnicity, smoking, family history of CVD, and family history of type 2 diabetes based on an analysis of the Whitehall II cohort (21). Change in glycaemia, blood pressure and cholesterol (stages 4-6) are influenced by the changes in BMI (stage 3). Trajectories of glycaemia, cholesterol and blood pressures differ depending on whether the simulated patient has a diagnoses of type 2 diabetes, are receiving statin or are receiving anti-hypertensive treatment respectively. In stage 7, the simulated individual may have opportunistic screening. It's assumed that the individual are identified as eligible for antihypertensive treatment or statins or get a diagnoses of type 2 diabetes at opportunistic screening if they attend at least one GP visit (estimated in stage 2) and if they meet certain criteria such as a history of cardiovascular disease.

In stages 8 to 14, the individual may experience cardiovascular outcomes, diabetes related complications, cancer, osteoarthritis, depression, dementia, and updated cognitive decline

associated with dementia diagnosis. The risk of cardiovascular events (stage 8) including mortality (stage 9) is based on the QRISK2 model, a validated model in which cardiovascular risk is estimated based on ethnicity, smoking status, age, BMI, ratio of total/HDL cholesterol, Townsend score, atrial fibrillation, rheumatoid arthritis, renal disease, hypertension, diabetes, and family history of cardiovascular disease (25). The risk of diabetes related complications (stage 10) including renal failure, amputation, foot ulcer, amputation and blindness) were based on the UKPDS data based on factors including age, glycaemia, blood pressure, medication history and BMI (26).

The risk of breast and colon cancer (stage 11) were estimated using the European Prospective Investigation of Cancer (EPIC) cohort (27) but included a risk adjustment such that individuals with a higher BMI have a greater risk. The risk of osteoarthritis (stage 12) was based on history of type 2 diabetes and BMI based on a longitudinal study of inhabitants of a town in Italy (33) as no UK studies were available. Individuals can develop depression at any cycle. The incidence of depression (stage 14) was based on a US cohort study (35). It was assumed that diagnosis of diabetes and/or CVD increased the incidence of depression in individuals who do not have depression at baseline.

Cancer mortality rates and other all-cause mortality (including diabetes risk were based on the 2014 Office of National statistics report.

4.3.3 Model Comparisons

Intervention effect (on BMI) can be entered into the model using several different methods including mean change in BMI or change in BMI conditional on demographic factors. Using the results from the mediation analysis (Chapter 3), BMI and cost-effectiveness outcomes were estimated based on changes in mechanisms of action (dietary restraint, habit strength, and autonomous diet self-regulation).

To determine whether using change in these mechanisms of actions reliably simulated BMI, the outcomes were compared to the actual trial data and two commonly used methods of inputting intervention effect; first, by inputting the mean change in BMI observed in each treatment group for all individuals and second, by inputting the change in BMI conditional on treatment group, baseline BMI and demographic factors (age, gender, education and income). The latter was based on the same latent growth curve analysis used in the mediation analysis (Chapter 3), but without the psychological mechanisms of actions, and enables heterogeneity to be represented based on demographic factors such as age and gender and reflects the non-linear change in BMI observed during the original trial.

Mean specification

The changes in BMI at years 1 and 2 in the 12- and 52-week treatment group were based on the corresponding mean change observed in the original WRAP study outlined in the case description (19). All individuals in each group have the same change in BMI.

Demographic-adjusted specification

Change in BMI in years 1 and 2 is based on the change in BMI in the trial adjusting for the impact of demographic factors and baseline BMI. Thus, heterogeneity in the impact of the intervention on BMI is based on treatment allocation and demographic factors (age, gender, education and income). A quadratic latent growth curve was fitted to BMI. A quadratic growth curve was fitted as it resulted in the best fit of the curve to the data when compared to a linear alternative. This also reflects the observation that there was a change in BMI between baseline and year 1 and then a return towards the baseline BMI by year 2. The growth factors of

BMI (intercept, slope and quadratic) were conditional on age, gender, education and income. The coefficients of these factors are reported in Table 4.6 of Supplementary Material.

Demographic plus MoA-adjusted specification

Change in BMI in years 1 and 2 is conditional on demographic factors, baseline BMI and the change in dietary restraint, habit strength, restraint and autonomous diet self-regulation. Heterogeneity in the impact of the intervention on BMI is based on demographic factors (age, gender, education and income) and change in mechanisms of action.

The change in BMI was based on the mediation model. In the mediation analysis, a latent growth curve was fitted to the change in dietary restraint, habit strength and autonomous diet self-regulation over the trial period of two years. A quadratic growth curve was fitted as it resulted in the best fit of the curve to the data when compared to a linear alternative. This also reflects the observation that for each variable there was a change between baseline and year 1 and then a return towards the baseline value by year 2. The growth factors (intercept, slope and quadratic) of the mechanisms of action were conditional on age and gender and the slope and quadratic growth factors were conditional on treatment group. As in the Demographic-adjusted model specification, a quadratic latent growth curve was fitted to the BMI trajectory and the growth factors were conditional on age, gender, education and income. However, in this specification, the slope of BMI was also conditional on the slope of dietary restraint, habit strength and autonomous diet self-regulation, treatment group and baseline BMI. This enabled the impact of an intervention on BMI to be entered through the impact on dietary restraint, habit strength and autonomous diet self-regulation.

More details about the mediation analysis on which the Demographic plus MoA-adjusted model specification is based, including the equations used to estimate BMI, and a diagram of the relationship between the growth factors and mechanisms of action have been previously reported in Chapter 3 (20).

Outcomes

The model specifications were compared on simulated BMI at years 1 and 2, lifetime costs and QALYs and net monetary benefit, assuming a cost-effectiveness threshold of £20,000 per QALY, for each treatment group (12- and 52-week weight management interventions) compared to the brief intervention.

Trajectory of comparison group

Usually, in the absence of an intervention, the BMI of a simulated individual follows a trajectory based on the analysis of the Whitehall II prospective cohort study (21). This is the natural history BMI trajectory simulated for each individual in the general population and is the trajectory that individuals are expected to follow if there is no intervention at all. In the WRAP trial (19), the comparison group had a brief intervention in which participants were given a self-help booklet. Because the participants in this group experienced some weight loss, the trajectory for weight change in the comparator group in the model was changed to reflect that of the brief intervention during the trial. For all model specifications and treatment groups, it was assumed that all individuals, at 5 years into the model, returned to the BMI trajectory (linearly) that they would have been on if they had followed the Whitehall trajectories from the first year.

Population

The baseline model population used in this study is the sample recruited in the randomised controlled trial (WRAP trial) on which the mediation analysis was conducted (Chapter 3) (19). Baseline characteristics are reported in Tables 4.8 and 4.9 of the Supplementary Material. Simulated individuals were randomly sampled with replication from the trial population to create a baseline population for the model. Ordinarily, the Health Survey for England (28), a repeat cross-sectional survey of around 8000 adults that are representative of the population in England, is used as the baseline population for the SPHR diabetes prevention model. However, this population does not include the relevant psychological mechanisms of action (dietary restraint, habit strength and autonomous diet self-regulation) which are required for the Demographic plus MoA-adjusted model specification.

In the WRAP data, there was some baseline information about the participants that was not collected in the original trial or was not available for the analysis, but that was required in the SPHR to inform the individual risk factors for the various conditions in the model. Information that were required for the model but were not available included past cardiovascular disease including angina, myocardial infarction, trans ischaemic attack, stroke, atrial fibrillation, and depression. For these conditions a baseline prevalence rate of zero was assumed. Although all participants were overweight and thus might be at greater risk of cardiovascular disease, the general practitioners were asked to exclude anyone with a condition that prevented them from taking part in the trial. Therefore it was determined that, in the absence of other data, this was an appropriate assumption for this sample at baseline.

Sensitivity analysis

Probabilistic Sensitivity Analysis (PSA) (described in the Chapter 1; Section 1.2) was conducted in all analyses across the three model specifications to ensure that parameter uncertainty was taken into account in the outcomes. The model was run one thousand times each with 5000 simulated individuals selected at random. Credible intervals, the central portion of the 1000 results that contain 95% of the values, were reported.

4.3.4 Subgroup analysis based on baseline levels of mechanism of action

The Demographic plus MoA-adjusted specification was used to examine subgroups based on the score on the mechanisms of action at baseline. Increases in each of these variables had a positive impact on BMI and therefore the impact of starting either low or high on this variable was examined to investigate whether the baseline level impacted cost-effectiveness. In the original latent growth curve analysis (Chapter 3), the change in BMI over time was not dependent on the intercepts of the mechanisms of action, based on initial results demonstrating no significant association between change in BMI and baseline level of mechanisms of action. However, subgroup analysis was conducted to determine if the baseline mechanisms of action impacted on cost-effectiveness by a pathway not detected within the latent growth curve analysis such as through associations with baseline demographic and metabolic variables. For each of the mechanisms of action (dietary restraint, habit strength and autonomous diet self-regulation), individuals were divided into those who scored

in the top quartile (high) and those who scored in the bottom quartile (low) at baseline. This resulted in three comparisons. In a fourth comparison, individuals who were high on all three variables to those low on all three variables.

While the option of examining each combination of high or low scores of the three variables (e.g. high habit, low dietary restraint, high autonomous diet self-regulation) was considered, this resulted in small group numbers for some scenarios which may have impacted reliability of results.

4.3.5 Sensitivity analysis based on estimated trajectories of mechanisms of action

Sensitivity analysis was conducted on the trajectories of BMI. In the base-case analysis using the Demographic plus MoA-adjusted model specification, it was assumed that for the first two years the change in BMI was based on change in mechanisms of action. It was then assumed that all participants in all groups regained to the natural history trajectory by 5 years, that is, the weight trajectory that they would have followed in the absence of an intervention. However, there is a lack of evidence of long-term weight loss maintenance (9) and it is therefore advised that the duration of intervention effect, or the time to weight regain, is varied in sensitivity analysis (Chapter 2). Without the mechanisms of action in the model, sensitivity around the duration of effect is based on assumptions about BMI only. However, inclusion of the mechanisms of action enables change in BMI to be estimated on mechanisms of action. Although there is limited evidence on long-term weight trajectories, it is possible to make some estimates about the trajectories of mechanisms of action based on theories of behaviour change maintenance. In the sensitivity analysis, the duration of effect was varied depending on the potential trajectory of mechanisms of action.

In both of the sensitivity analyses, the BMI is conditional on the mechanisms of action beyond the 2 years and uses two main assumptions. The first assumption is that after first 2 years, instead of assuming that BMI return to the natural history trajectory between 2 and 5 years (base-case assumption), the trajectory of mechanisms of action is extrapolated beyond the 2 years and the BMI continues to be conditional on this change in mechanisms of action. This assumes that the mechanisms of action return towards the baseline value. It is

assumed that an individual follows the BMI trajectory predicted by the mediation analysis from baseline to the point at which the individual reaches the natural history trajectory (that would have been followed in the absence of an intervention). The other assumption used in the sensitivity analyses is that the change in the mechanisms of action is maintained beyond the intervention and the BMI trajectory is predicted accordingly. This assumes that the behaviour change techniques used in the intervention resulted in sustained changes in the mechanisms of action beyond the two years.

In the first sensitivity analysis, it was assumed that the mechanisms of action followed the trajectory predicted by the mediation analysis for participants in both the brief intervention and the 12-week intervention. This assumed that the return to baseline that had been observed towards the end of the trial continued until the BMI reached the BMI trajectory that they would have been on in the absence of the intervention. This resulted in a regain to the original weight trajectory at an average of 3 years after baseline for both the brief and 12-week intervention groups. However it is assumed that the mechanisms of action in the 52-week intervention were maintained following the intervention. This was based on the hypothesis that the behaviour change techniques implemented over a longer period of time (52 vs 12 weeks) enabled participants to develop and maintain dietary restraint (29), and that greater increases in habit over time increased the likelihood of habits becoming stable (30). Furthermore although self-regulation had reduced during the intervention, there is evidence that an extended care model of treatment results in sustained motivation (31). This still resulted in weight regain between years 2 and 5 and, so although this was an alternative assumption compared to the base-case analysis, it still resulted in a regain to the original weight trajectories 5 years which matches the assumption made in the base case analysis.

In the second sensitivity analysis, it was assumed that the three mechanisms of action were maintained for both the 12- and 52-week intervention but not for the brief intervention. This was based on the hypothesis that both the 12 and 52-week interventions were sufficient to evoke sustained changes in mechanisms of action compared to the brief intervention which was a booklet only. Using this assumption resulted in a regain to the original weight trajectory at an average of 4 years after baseline for the 12-week intervention. The time to regain to the original trajectory was 3 and 5 years for the brief intervention and 52-week intervention

respectively as in the first sensitivity analysis. Table 4.1 outlines the sensitivity analyses and Figure 4.1 shows the BMI trajectory for each treatment group in each sensitivity analysis.

Table 4.1. Scenarios tested in sensitivity analysis

	Mechanisms of action trajectory	Years to regain
Sensitivity analysis 1		
Brief intervention	Followed trajectory predicted by the mediation analysis	3
12-week intervention	Followed trajectory predicted by the mediation analysis	3
52-week intervention	Maintained until BMI trajectory returns to original trajectory	5
Sensitivity analysis 2		
Brief intervention	Followed trajectory predicted by the mediation analysis	3
12-week intervention	Maintained until BMI trajectory returns to original trajectory	4
52-week intervention	Maintained until BMI trajectory returns to original trajectory	5

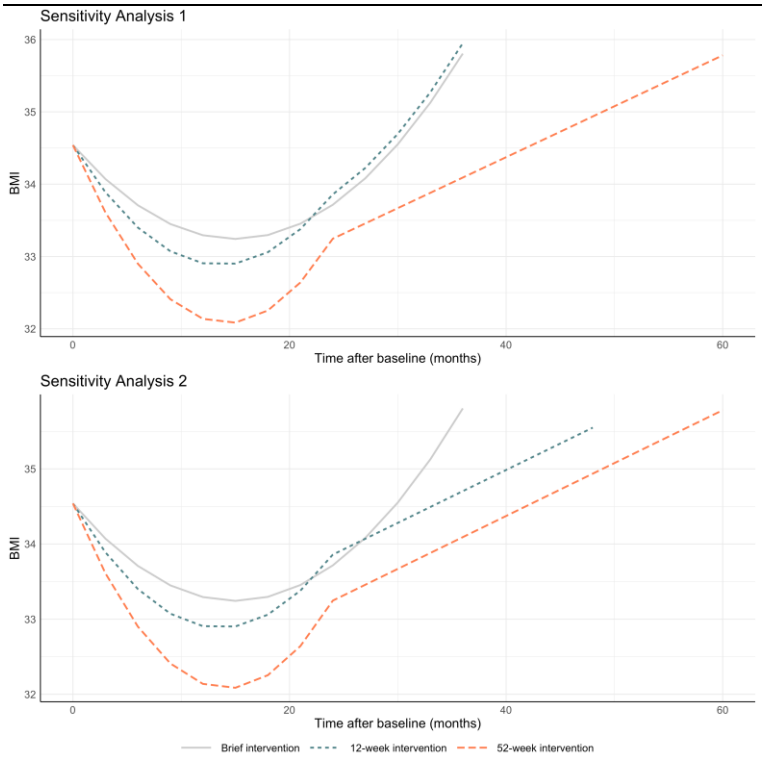

Figure 4.1. Trajectory of BMI for each treatment groups in each sensitivity analysis

4.4 Results

4.4.1 Comparing models

Validation of each model in terms of population level BMI prediction at years 1 and 2

Figure 4.2 shows the mean estimated BMI for the 12- and 52-week interventions at years 1 and 2 for all model specifications alongside the mean BMI observed in the study data. For both interventions, mean BMI at year 1 and 2 generated by the Mean, Demographic-adjusted and Demographic plus MoA-adjusted model specifications were within the confidence interval of the actual mean. The Demographic plus MoA-adjusted model specification resulted in a larger variation in BMI compared to the Mean and Demographic-adjusted suggesting that adding the mechanisms of action increased the variation in BMI.

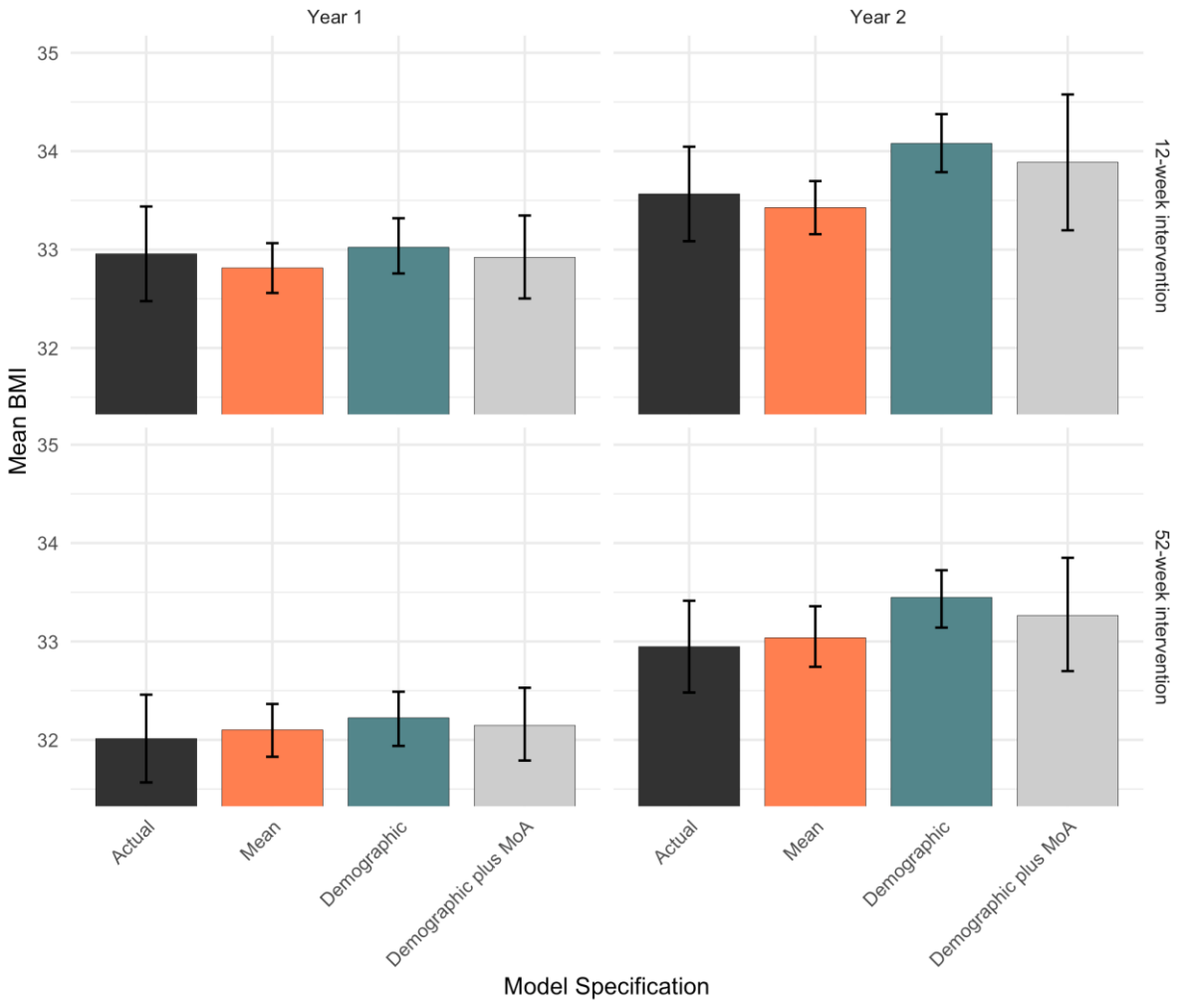

Figure 4.2. Estimated mean BMI at year 1 and 2 for the 12 and 52-week interventions using each model specification and mean BMI of the original study sample

The distribution of BMI at year 1 and 2 in each treatment group is shown in the density plots in Figure 4.3. The estimated distribution of each model specification are represented by lines overlaid on the density plot of the actual population. Chi-squared tests used to compare the estimated and actual distributions at each time point, indicated that there were no significant differences between the distributions estimated by each model specification and the actual study data. Combined with Figure 4.2, these results indicate that the mean and distributions of BMIs at years 1 and 2 can be predicted by the Mean, Demographic-adjusted and Demographic plus MoA-adjusted model specifications.

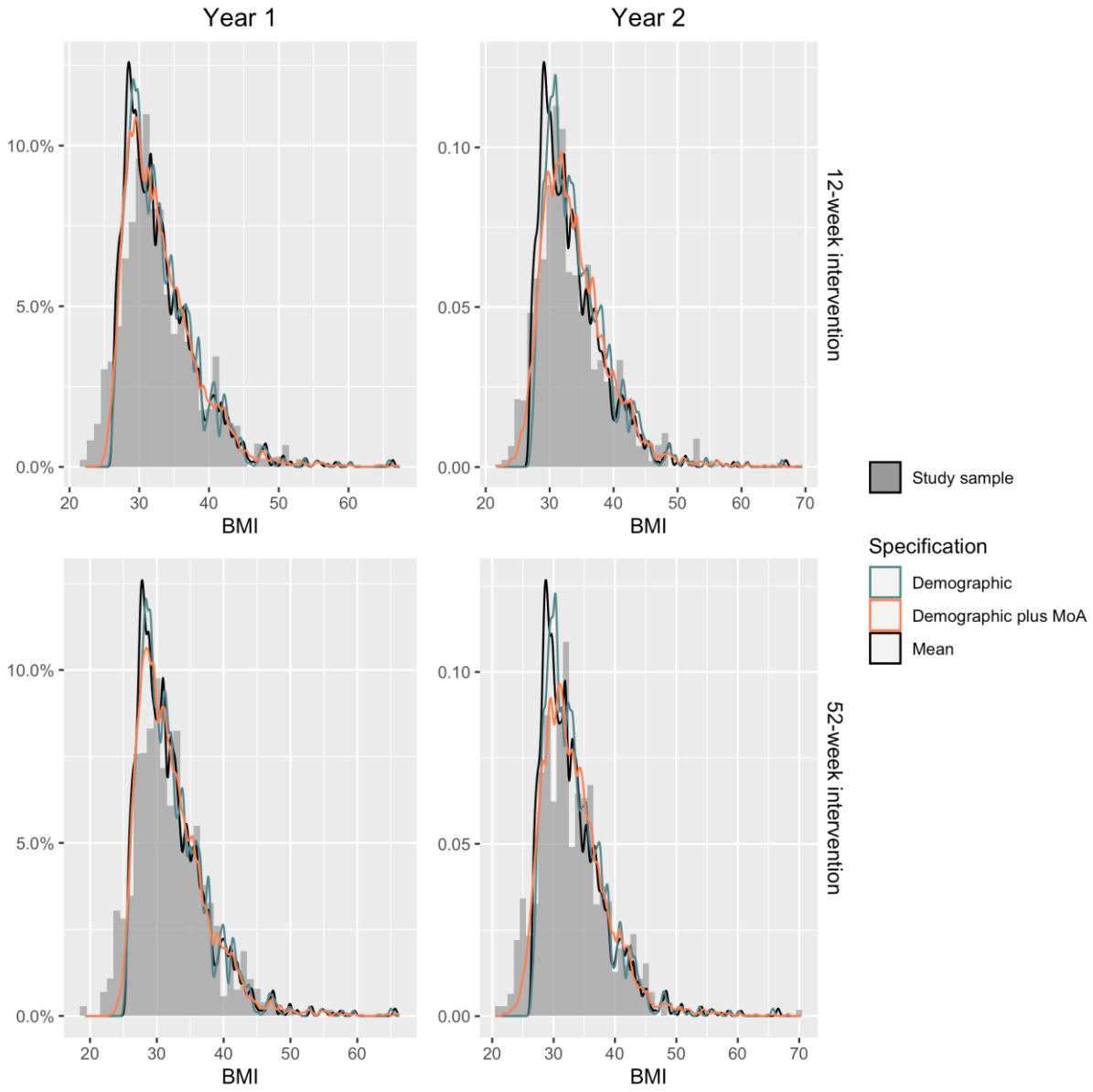

Figure 4.3. Density plots of the actual and estimated distribution of BMI at year 1 and year 2 for the two intervention arms in the WRAP trial

Costs and Quality adjusted life years (QALYs)

Table 4.2 shows the costs and QALYs for each treatment group for each model specification, and the percentage differences between both the Demographic-adjusted and Demographic plus MoA-adjusted model specification and the Mean specification. This indicates that there were only small differences between the costs and QALYS between model specifications (all under 0.5%).

Table 4.2. Absolute costs and QALYs per person for a 12-week and 52-week behavioural weight management programme using three model specifications.

	Costs (£)	QALYs
12-week intervention		
Absolute results for each intervention		
Mean	28701.72 (22167.47, 39459.01)	10.8240 (10.1379, 11.4979)
Demographic-adjusted	28911.03 (22335.85, 39853.46)	10.8037 (10.1147, 11.4719)
Demographic plus MoA-adjusted	28852.68 (22047.34, 39821.22)	10.8020 (10.1341, 11.4007)
Percentage difference from Mean model specification (%)		
Demographic adjusted	0.35 (0.33, 0.37)	-0.19 (-0.19, -0.18)
Demographic plus MoA-adjusted	0.73 (0.71, 0.75)	-0.19 (-0.26, -0.12)
52-week intervention		
Absolute results for each intervention		
Mean	28554.44 (22020.35, 39302.24)	10.8375 (10.1473, 11.5036)
Demographic adjusted	28680.24 (22127.40, 39419.27)	10.8248 (10.1367, 11.4923)
Demographic plus MoA-adjusted	28629.21 (21928.63, 39689.02)	10.8211 (10.1449, 11.4177)
Percentage difference from Mean model specification (%)		
Demographic adjusted	0.44 (0.42, 0.46)	-0.12 (-0.12, -0.11)
Demographic plus MoA-adjusted	0.28 (0.13, 0.42)	-012 (-0.21, -0.07)

All results are displayed with credible intervals, the central portion of the 1000 results that contain 95% of the values.

Table 4.3 shows the incremental costs, QALYs and net monetary benefit per person for all model specifications. In all model specifications, the brief intervention had greater costs and lower QALYs than both the 12- and 52-week intervention. There were greater cost savings and incremental QALYs for the Mean model specification than both the Demographic-adjusted and the Demographic plus MoA-adjusted model specifications and the Demographic plus MoA-adjusted model specifications had greater cost savings and incremental QALYs than the Demographic-adjusted.

Table 4.3. Incremental costs and QALYs for a 12-week and 52-week behavioural weight management programme using three model specifications

	12-week vs. brief intervention	52-week vs. brief intervention
Costs		
Mean	-274.51 (-577.53, -77.41)	-280.30 (-678.06, -24.94)
Demographic-adjusted	-70.31 (-281.31, 86.68)	-159.60 (-501.12, 64.97)
Demographic plus MoA-adjusted	-98.58 (-397.80, 164.29)	-180.55 (-562.40, 85.94)
QALYs		
Mean	0.0274 (0.0109, 0.0473)	0.0409 (0.0184, 0.0676)
Demographic-adjusted	0.0083 (-0.0053, 0.0248)	0.0295 (0.0104, 0.0538)
Demographic plus MoA-adjusted	0.0105 (-0.0076, 0.0323)	0.02958 (0.0068, 0.0560)
NMB		
Mean	822.82 (363.03, 1428.72)	1098.81 (476.59, 1818.25)
Demographic-adjusted	236.57 (-146.62, 700.24)	748.65 (221.49, 1390.06)
Demographic plus MoA-adjusted	309.05 (-225.80, 951.41)	772.08 (115.59, 1495.41)

NMB; Net monetary benefits based on a cost-effectiveness threshold of £20 000 per incremental QALY

Cost-effectiveness planes (Figure 4.4) show the incremental costs and QALYs comparing a) the 12-week intervention to the brief intervention and b) the 52-week intervention to the brief intervention for both model specifications. There was overlap in incremental costs and QALYs across the model specifications. However, despite similar estimates of BMI at the population level, the heterogeneity introduced by adjusting BMI for demographic factors or estimating BMI based on mechanisms of action results in lower costs savings and incremental QALYs. Cost-effectiveness curves indicated that at all cost-effectiveness thresholds up to £50,000, the 52-week intervention had the highest probability of being cost-effective (Figure 4.9).

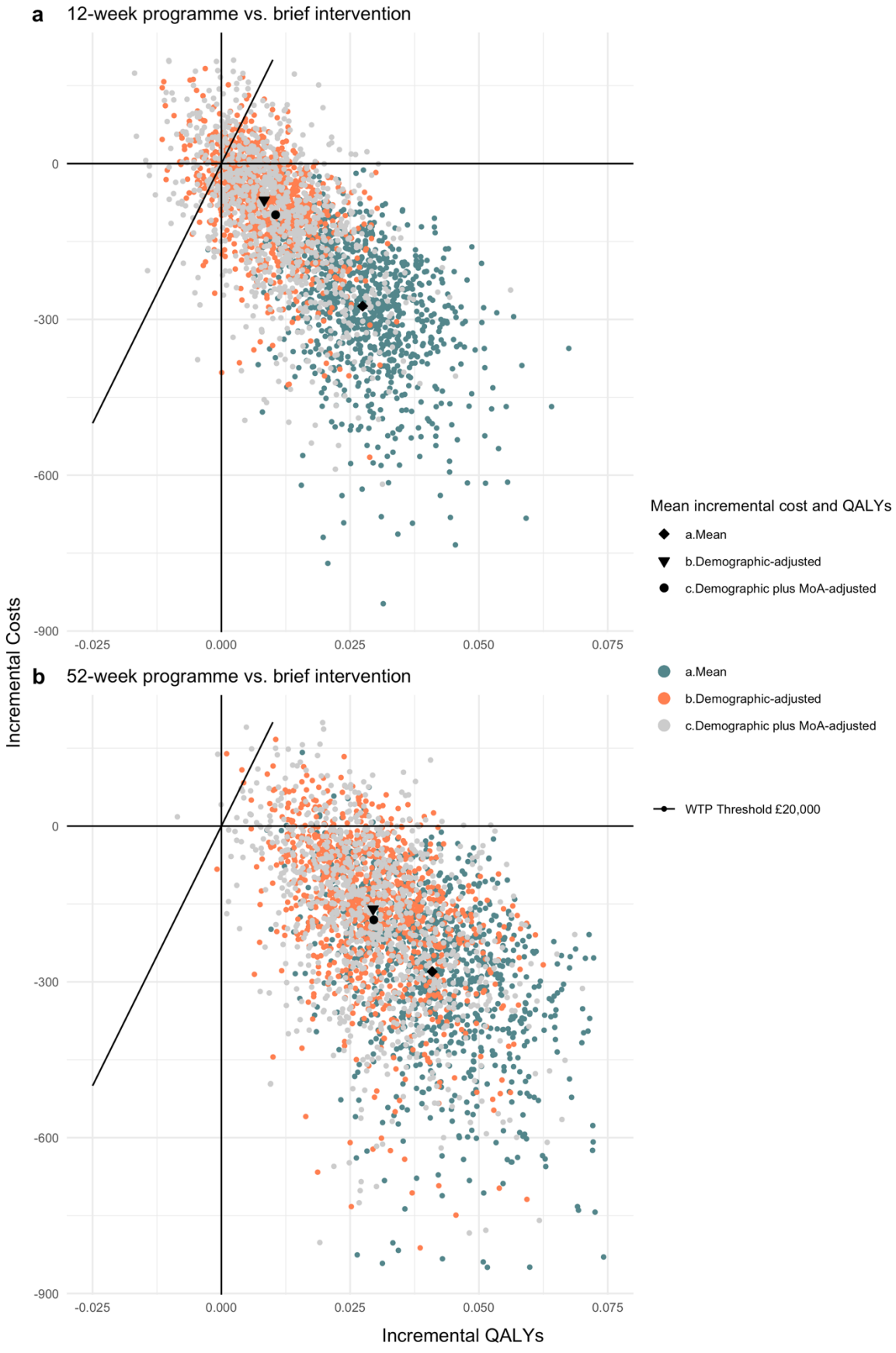

Figure 4.4. Incremental costs and QALYs of the 12- and 52-week intervention compared to the brief intervention

4.4.2 Subgroup analysis based on baseline levels of mechanism of action

Cost-effectiveness of the interventions for individuals with high (highest quartile) or low (lowest quartile) baseline scores on habit strength, dietary restraint and autonomous diet self-regulation were examined. Table 4.10 in the Supplementary Material shows the number of the baseline population in each of the subgroups. Figure 4.5 shows the average total costs and QALYs per person for each subgroup and each intervention. Although all groups had very similar costs and QALYs, individuals with low habit strength had higher costs and higher QALYs than those with high habit strength, individuals with high dietary restraint had slightly higher costs and lower QALYs than those with low dietary restraint and individuals with high autonomous diet self-regulation had higher costs and lower QALYs than those with low autonomous diet self-regulation. The direction of difference was the same across all treatment groups. Individuals high on the three mechanisms of action had higher costs and lower QALYs than individuals low on the three variables across all treatment groups.

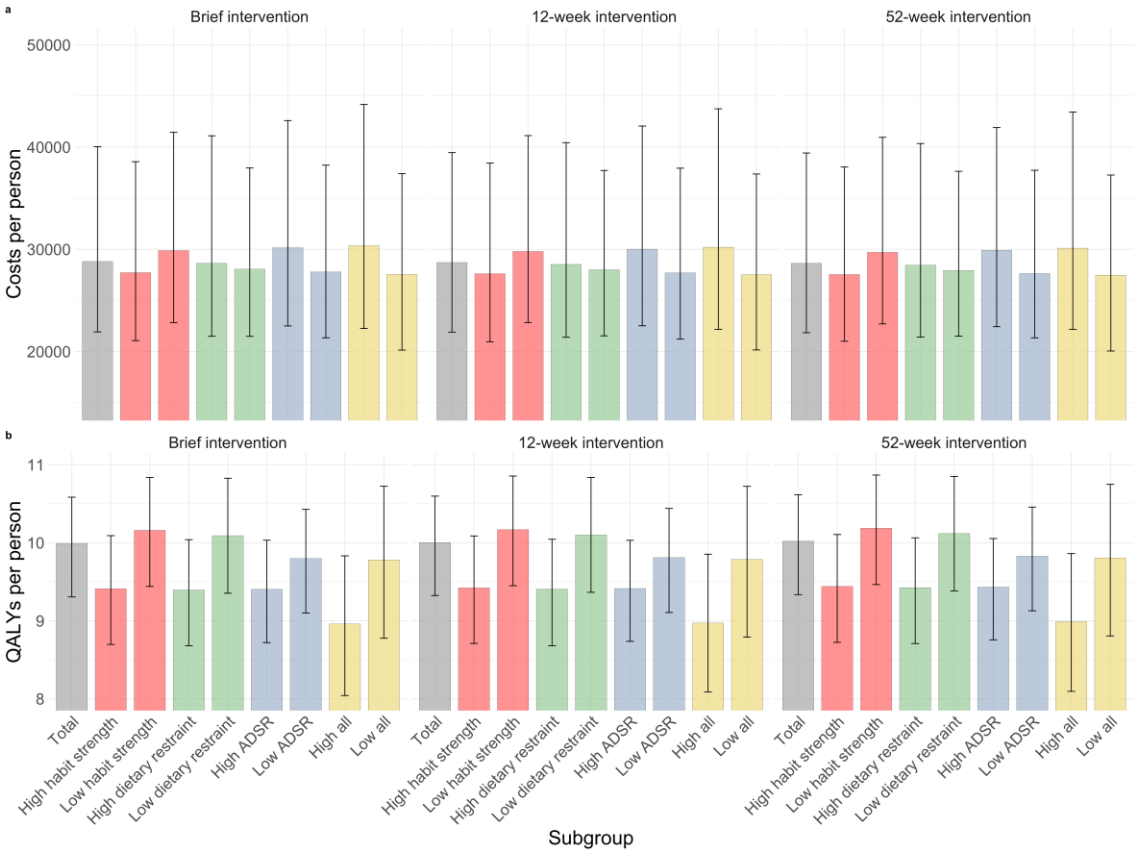

Figure 4.5. Average total costs and QALYs per person for each treatment group, for 8 subgroups, based on baseline scores of habit strength, dietary restraint and diet self-regulation

The incremental costs and QALYs and net monetary benefit are presented in Table 4.4, which shows the 12- and 52- week interventions each compared to the brief intervention. There were only small differences in incremental costs and QALYs across all of the subgroups and cost-effectiveness planes (Supplementary Material, Figure 4.7 and 4.8) show that the distribution of PSA model runs were similar. Cost-effectiveness acceptability curves indicate that for all subgroups, the 52-week intervention has the highest probability of being the most cost-effective treatment option (Figure 4.10). However, high baseline levels of habit strength, dietary restraint and autonomous diet self-regulation were all associated with higher net monetary benefits than low baseline levels of the mechanisms of action. Similarly, there was a higher net monetary benefits for individuals high on all mechanisms of action than those low on all mechanisms of action.

Table 4.4. Psychological MoA Model results for 8 subgroups: Incremental costs and QALYs for the 12-week and 52-week behavioural weight management intervention based on dietary restraint, habit strength and autonomous diet self-regulation

	Costs	QALYs	NMB
12-week intervention vs brief intervention			
Total	-98.58 (-398.75, 156.80)	0.0105 (-0.0077, 0.0322)	309.05 (-229.96, 949.58)
Habit strength			
High	-108.78 (-529.82, 223.82)	0.0117 (-0.0147, 0.0426)	343.22 (-352.73, 1187.99)
Low	-88.78 (-561.40, 297.61)	0.0089 (-0.0143, 0.0377)	267.58 (-414.43, 1106.69)
Dietary restraint			
High	-112.20 (-581.25, 272.64)	0.0114 (-0.0139, 0.0442)	340.74 (-395.31, 1205.31)
Low	-58.66 (-490.53, 359.01)	0.0093 (-0.0158, 0.0387)	243.82 (-448.84, 1049.47)
Autonomous diet self-regulation			
High	-130.16 (-588.16, 261.73)	0.0105 (-0.0134, 0.0385)	340.45 (-345.51, 1167.99)
Low	-84.09 (-483.62, 252.75)	0.0112 (-0.0131, 0.0392)	308.75 (-356.43, 1105.68)
All mechanisms of action			
High	-155.08 (-1074.12, 601.47)	0.0126 (-0.0277, 0.0697)	407.27 (-828.26, 1892.32)
Low	-31.02 (-801.25, 709.87)	0.0072 (-0.0494, 0.0678)	174.45 (-1296.58, 1677.79)
52-week intervention vs brief intervention			
Total	-180.55 (-564.91, 85.16)	0.0296 (0.0067, 0.0555)	772.08 (112.40, 1483.20)
Habit strength			
High	-183.34 (-658.02, 210.71)	0.0310 (-0.0001, 0.0680)	802.67 (-31.23, 1748.31)
Low	-176.23 (-662.01, 213.53)	0.0272 (0.0000, 0.0605)	719.27 (-97.52, 1608.12)
Dietary restraint			
High	-187.52 (-698.75, 216.87)	0.0299 (0.0001, 0.0669)	784.86 (-65.55, 1825.60)
Low	-130.05 (-637.76, 265.74)	0.0284 (0.0008, 0.0600)	698.77 (-51.73, 1590.04)
Autonomous diet self-regulation			
High	-232.74 (-806.95, 194.42)	0.0287 (0.0014, 0.0615)	805.83 (8.85, 1724.49)
Low	-149.76 (-639.98, 187.09)	0.0301 (0.0007, 0.0649)	750.77 (-38.87, 1663.41)
All mechanisms of action			
High	-249.08 (-1349.66, 542.03)	0.0304 (-0.0131, 0.0907)	856.17 (-443.02, 2521.97)
Low	-86.20 (-1028.56, 655.90)	0.0259 (-0.0295, 0.0987)	604.11 (-833.90, 2241.14)

QALYs; Quality Adjusted Life Years, NMB; Net Monetary Benefit.

4.4.3 Sensitivity analysis based on estimated trajectories of mechanisms of action

Sensitivity analyses of two scenarios in which the duration of the intervention effect, time to weight regain to original trajectory, were varied based on the expected trajectory of the mechanisms of action, were conducted. This indicated that, when individuals in both the brief intervention and the 12-week intervention return to the non-intervention trajectory after 3 years, both the cost savings and QALYs gained were larger when comparing both interventions (sensitivity analysis 1) to the brief interventions (Figure 4.6). This costs saving of the 12-week intervention compared to the brief intervention was even higher when it was assumed that the individuals in the 12-week intervention returned to the non-intervention trajectory after 4 years (scenario 2).

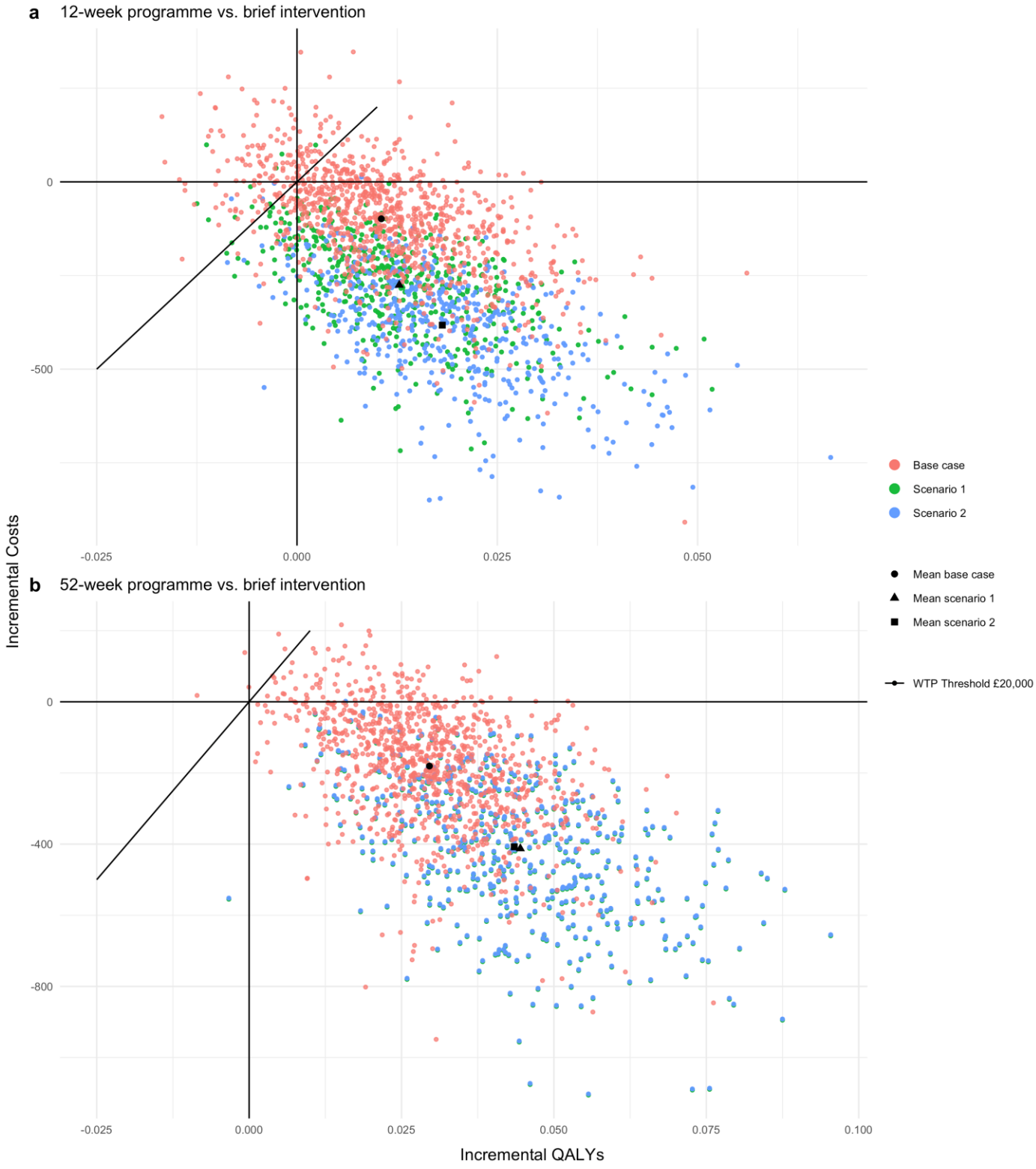

Figure 4.6 Incremental costs and QALYs of the 12- and 52-week intervention compared to the brief intervention; Sensitivity analysis

4.5 Discussion

The aim of the current study was to examine the feasibility of estimating change in BMI and long-term cost-effectiveness using change in mechanisms of action, within a health economic model of obesity. After adapting an existing health economic model to include dietary restraint, habit strength and autonomous diet self-regulation, the first part of the analysis was to compare a model specification in which BMI was predicted based on mechanisms of action to commonly used methods to input intervention effect. The findings suggest that BMI can be reliably predicted within health economic modelling based on changes in habit strength, dietary restraint and autonomous diet self-regulation, demographic factors and baseline BMI. None of the BMI means and distributions were significantly different from the actual data indicating that, at a population level, all models predict BMI accurately. The Demographic-adjusted and Demographic plus MoA-adjusted model specifications both resulted in lower cost savings and lower incremental QALYs than the Mean model specification. In this case, the conclusions regarding cost-effectiveness and funding decisions would likely be the same for all three model specifications, however, this is in part due to the intervention being cost saving. In evaluations in which the estimates of cost-effectiveness is closer to the cost-effective threshold, this difference could be sufficient to impact on funding decisions. The difference in estimates of cost-effectiveness is likely because, although the predictions of BMI were accurate on a population level, both the Demographic-adjusted and Demographic plus MoA-adjusted models allow variation among individuals which resulted in higher costs and lower QALYs. However, individual variation is represented in both the Demographic-adjusted and Demographic plus MoA-adjusted model specifications. This supports the use of model in which BMI is conditional on demographic and/or psychological mechanisms of action, but the cost-effectiveness results alone do not provide a strong rationale for including the psychological mechanisms of action over and above demographic factors.

This finding that cost-effectiveness estimates of the Demographic-adjusted, and Demographic plus MoA-adjusted model specification were similar suggests that Demographic plus MoA-adjusted model specification offer little or no predictive advantage over the Demographic-adjusted model specification. The Demographic-adjusted model is likely to be easier to implement as it does not require the complex mediation analysis needed

for the Demographic plus MoA-adjusted model specification (Chapter 3) (20). This may indicate that while the mediation analysis provided a greater understanding of how and why the intervention worked, which is useful in intervention design and implementation, it may not provide a predictive advantage over the demographic-adjusted model in health economic modelling. However, the impact of including mechanisms of action may differ depending on the content of the intervention, the mechanisms of actions targeted and the target population. Further research is needed to test whether including psychological mechanisms of action offer a predictive advantage when evaluating other interventions or comparing interventions that target different mechanisms of action.

The second part of the research was to explore the impact of additional analyses based on the psychological mechanisms of action. The outcomes for individual with high and low scores on baseline psychological mechanisms of action were compared. The results indicate that cost-effectiveness of the 12- and 52-week weight management interventions did not vary substantially between the subgroups based on baseline levels of dietary restraint, habit strength and autonomous diet self-regulation. This suggests that the interventions are cost-effective regardless of an individual's level of these variables at baseline and does not support allocation of treatment based on these factors. However, there were consistent differences in costs and QALYs across treatment groups. For example those with low habit strength had higher costs and QALYs than individuals with high habit in both the 12- and 52-week intervention and the brief intervention. In this evaluation, the two interventions were the same other than duration and therefore targeted the same mechanisms of action. Furthermore, the mediation analysis in Chapter 3 (20) indicated that all three interventions, including the brief intervention, showed a similar direction of change in mechanisms of action although with different effect sizes. Therefore, any impact that baseline psychological factors had on the effectiveness of the intervention may have been present across all groups and so would have had little impact on incremental costs and QALYs. Including mechanisms of action in health economic modelling may have a greater impact on outcomes when comparing interventions that target different mechanisms of action.

The Demographic plus MoA-adjusted model specification enabled an alternative approach to extrapolating weight which is based on psychological theory and the specific mechanisms of action targeted by the

intervention being evaluated. In this study, alternative assumptions about weight regain based on potential trajectories of the mechanisms of action were tested in sensitivity analysis. Testing alternative scenarios of weight regain is often conducted as part of sensitivity analysis because of the potential impact of duration of intervention effect on cost-effectiveness outcomes (12) (Chapter 2). However, in previous analyses, the duration of effect has been chosen arbitrarily or based on previous studies of weight management interventions. The sensitivity analysis in the current evaluation was based on the theorised impact of the intervention on mechanisms of action which enables intervention-specific assumptions to be used in the absence of long-term data. This sensitivity analysis supported findings in a recent systematic review (Chapter 2) (12), that the duration of intervention effect has the potential to impact on cost-effectiveness estimates. Furthermore, the finding that an assumption of maintenance of the changes in mechanisms of action change resulted in the same simulated duration of effect as the base-case supports the base-case assumption used in this model (weight regain by 5 years). Although in this study, the funding decision would likely be the same in all scenarios, alternative hypothesised trajectories of mechanisms of action may have an impact on evaluations in which the intervention isn't so cost-saving.

Together the findings suggest that inputting observed or predicted change in dietary restraint, habit strength and autonomous diet self-regulation may be a reliable proxy for entering treatment effect as a change in BMI when estimating cost-effectiveness. The Demographic plus MoA-adjusted model specification simulated the mean and variation in BMI observed in the original study and there is also no evidence that bias was introduced. The finding that BMI and cost-effectiveness can be reliably estimated based on change in mechanisms of action provides evidence that conducting pre-trial modelling based on expected change in mechanisms of action is feasible and will complement the increasing focus on describing a planned intervention in terms of the behaviour change techniques utilised and mechanisms of action targeted (7, 8). An intervention will comprise a selection of behaviour change techniques, each of which will impact on one or more mechanisms of action to get an aggregate change in mechanisms of actions. The mediation analysis integrated into the health economic model translates the overall change in mechanisms of action into a change in BMI and cost-effectiveness. This allows a more theory-based and intervention-specific estimation of expected effect and cost-effectiveness rather than using weight change observed in previous trials which may be based on

interventions that differ in content. This can be used to conduct pre-trial modelling such as justifiable cost and value of information analyses; important methods which can be used to inform the design of interventions and progression of trials.

The analysis presented has some limitations and challenges. First, because the HSE survey (28), which is representative of the English population, did not have measures of the mechanisms of action in the study (dietary restraint, habit strength and autonomous diet self-regulation) or similar variables, the sample population from the original analysis was used as the baseline population. Although the trial sample was broadly generalisable to the English population that would be eligible for a weight management intervention based on socioeconomic factors, ethnicity and BMI (19), only 32% were males and the smaller sample size compared to the HSE would have limited the variability of the sample and thus, the generalisability of the results. Second, although this study demonstrates how mechanisms of action can be added to a health economic model, only three variables were included as these were the mechanisms of action relevant for this study and intervention. It is likely that there are other mechanisms of action that would be important to include for this model to be relevant to a wider range of weight management interventions. For example, in a review of mediation analyses of weight management interventions, there were was strong evidence that self-efficacy and self-regulation skills such as self-monitoring were important mediators (15). Supporting this is the findings from the original mediation analysis in which the direct effect of the intervention on BMI became positive (increased BMI) when the mechanisms of action were included as mediators, suggesting that there are other factors that weren't measured in this study, that have an opposing impact on BMI by increasing weight, weight regain or limiting weight loss. While the intervention had an impact on dietary restraint, habit strength and autonomous diet self-regulation which resulted in a reduction in BMI, the intervention may have had a negative impact on another determinant of behaviour change which had the opposing effect on BMI; for example, in a previous group-based weight loss intervention, seeing others lose weight increased perception of own progress which was then associated with reduced weight loss (32). In addition, while the three mechanisms impacted on BMI via dietary behaviours, there is evidence that compensatory physiological adaptations that occur following diet-induced weight loss can promote weight regain (33). A greater understanding of the mechanisms of action of behaviour change techniques used in interventions, the wider determinants of weight change and

how these interact will likely enable better estimation of long-term weight change. Existing theories of behaviour change and behaviour change maintenance may inform development of the model to include additional factors (13). Collating data from existing studies and conducting analyses and meta-analyses could help to establish associations between interventions, their mechanisms of action and BMI as well as interactions between different interventions and mechanisms of action. To include all factors relevant to weight management in the health economic model would likely require data from multiple studies and data sets but would enable the models to represent the broader framework of factors that impact on weight management and would make the model applicable to a wider range of behavioural interventions.

To the best of our knowledge, this is the first time that psychological mechanisms of action have been used in estimating BMI trajectories in health economic modelling of a behavioural weight management intervention. Although limited to one study and three variables, this demonstrates how mechanisms of action identified in mediation analysis of behavioural weight management interventions can be used to reliably estimate BMI within health economic modelling. While the findings do not suggest that including psychological mechanisms of action in a health economic model of obesity, provides a predictive advantage compared to a model that adjusts for demographic variables only when predicting cost-effectiveness, it does enables subgroup and sensitivity analysis based on psychological mechanism of action. Although including mechanisms of action did not impact on the likely funding decision in this study, there is the potential for this to have an impact in other evaluations. The findings also indicate the potential to conduct pre-trial modelling of behavioural interventions based on expected impact on the mechanisms of action. Future research should investigate whether the impact of including psychological mechanisms of action in a health economic model varies depending on the intervention, the mechanisms of action targeted, and the mechanisms of action targeted in the comparison group.

4.6 Contribution to thesis

In Chapter 3, three mechanism of action were identified in mediation analysis. In this chapter, I used the outcomes of the mediation analysis to adapt an existing health economic model. Based on the findings of the review in Chapter 2, this is reportedly the first health economic model of obesity to incorporate psychological factors and so this represents a novel methodological advance in health economic modelling of weight management intervention.

Including the psychological factors provided no predictive advantage compared to inputting BMI conditional on demographic factors when estimating cost-effectiveness which raises doubt about the benefit of including psychological factors especially given the complex mediation analysis (Chapter 3) that was required to make the adaptation detailed in this chapter. However, this is likely, in part, because the intervention that was tested which was associated with high cost-savings and so a large difference in outcomes would be needed to impact funding decisions. Furthermore, including the mechanisms of action allowed additional analyses which may be useful in making decisions about allocation of resources. These additional analysis can be specific to the behaviour change techniques used in an intervention and the mechanisms of action targeted. Although, I adapted the model based on a single study and the subgroup and sensitivity analyses conducted would not have impacted on funding decisions in this case, the study demonstrated a method of including psychological variables in health economic modelling of weight management and the potential benefits of doing so.

The findings have implications for pre-trial modelling methods. Pre-trial health economic modelling of a planned intervention can be conducted based on the effectiveness of previous interventions which will be explored in Chapter 5, but the adapted model, described in the current chapter, would enable pre-trial modelling based on expected changes in mechanisms of action which will be explored in Chapter 6.

4.7 References

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4.8 Supplementary Material

4.8.1 Equations used in latent growth curves

The full equations for the latent growth curves fitted to each of the mechanisms of action and to BMI are detailed below. The results from the mediation analysis were used to predict BMI at year 1 and 2 in the MoA specification. In the direct specification, coefficients from a model in which the mechanisms of action weren't included as mediators was used.

The habit score for participant j at time t can be specified as

$$Habit_{jt} = \theta_{0j} + \theta_{1j}t + \theta_{2j}t^2 + a_{jt} \quad \textit{Equation 9}$$

Where $\theta_{0j,}$ θ_{1j} and θ_{2j} represent the intercept, linear slope component and quadratic component growth factors of the habit trajectory and a_{jt} is the random error.

$$\theta_{0j} = \beta_0 + \gamma_0 Age + \nu_0 Gender + h_{0j} \quad \textit{Equation 10}$$

$$\theta_{1j} = \beta_1 + \gamma_1 Age + \nu_1 Gender + H_{11} Tx12 + H_{12} Tx52 + h_{1j} \quad \textit{Equation 11}$$

$$\theta_{2j} = \beta_2 + \gamma_2 Age + \nu_2 Gender + H_{21} Tx12 + H_{22} Tx52 + h_{2j} \quad \textit{Equation 12}$$

Where $\beta_{0,}$ β_1, and β_2 are the intercepts for each growth factor (intercept, slope and quadratic). $\gamma_{0,}$ γ_{1} , γ_2 represent the magnitude of the coefficient linking Age to the intercept, slope and quadratic respectively. $\nu_{0,}$ ν_{1} , ν_2 represent the magnitude of the coefficient linking gender to the intercept, slope and quadratic respectively and $h_{0j,}$ h_{1j} , h_{2j} represent the random error for the intercept, slope and quadratic respectively. H_{11} and H_{12} represent the magnitude of the coefficient linking the intervention (12-week intervention and 52-week intervention respectively) to the slope and H_{21} and H_{22} represent the magnitude of the coefficient linking the intervention (12-week intervention and 52-week intervention respectively)) to the quadratic component.

The restraint score for participant j at time t can be specified as

$$Restraint_{jt} = \Psi_{0j} + \Psi_{1j}t + \Psi_{2j}t^2 + b_{jt} \quad \textit{Equation 13}$$

Where $\Psi_{0j,}$ Ψ_{1j} and Ψ_{2j} represent the intercept, linear slope component and quadratic component growth factors of the dietary restraint trajectory and b_{jt} is the random error.

$$\Psi_{0j} = \chi_0 + \varphi_0 Age + \kappa_0 Gender + r_{0j} \quad \textit{Equation 14}$$

$$\Psi_{1j} = \chi_1 + \varphi_1 Age + \kappa_1 Gender + \Gamma_{11} Tx12 + \Gamma_{12} Tx52 + r_{1j} \quad \textit{Equation 15}$$

$$\Psi_{2j} = \chi_2 + \varphi_2 Age + \kappa_2 Gender + \Gamma_{21} Tx12 + \Gamma_{22} Tx52 + r_{2j} \quad \textit{Equation 16}$$

Where χ_0, χ_1, and χ_2 are the intercepts for each growth factor (intercept, slope and quadratic). φ_0, φ_1 , φ_2 represent the magnitude of the coefficient linking Age to the intercept, slope and quadratic respectively. κ_0, κ_1 , κ_2 represent the magnitude of the coefficient linking gender to the intercept, slope and quadratic respectively. Γ_{11} and Γ_{12} represent the magnitude of the coefficient linking the intervention (12-week intervention and 52-week intervention respectively) to the slope and Γ_{21} and Γ_{22} represent the magnitude of the coefficient linking the intervention (12-week intervention and 52-week intervention respectively) to the quadratic component. r_{0j}, r_{1j} , r_{2j} represent the random error for the intercept, slope and quadratic respectively.

The autonomous diet restraint score for participant j at time t can be specified as

$$ADSR_{jt} = \Sigma_{0j} + \Sigma_{1j} t + \Sigma_{2j} t^2 + c_{jt} \quad \textit{Equation 17}$$

Where Σ_{0j}, Σ_{1j} and Σ_{2j} represent the intercept, linear slope component and quadratic component growth factors of the autonomous diet self-regulation trajectory and c_{jt} is the random error.

$$\Sigma_{0j} = \iota_0 + \delta_0 Age + \omega_0 Gender + s_{0j} \quad \textit{Equation 18}$$

$$\Sigma_{1j} = \iota_1 + \delta_1 Age + \omega_1 Gender + \Phi_{11} Tx12 + \Phi_{12} Tx52 + s_{1j} \quad \textit{Equation 19}$$

$$\Sigma_{2j} = \iota_2 + \delta_2 Age + \omega_2 Gender + \Phi_{21} Tx12 + \Phi_{22} Tx52 + s_{2j} \quad \textit{Equation 20}$$

Where ι_0, ι_1, and ι_2 are the intercepts for each growth factor (intercept, slope and quadratic). δ_0, δ_1 , δ_2 represent the magnitude of the coefficient linking Age to the intercept, slope and quadratic respectively. ω_0, ω_1 , ω_2 represent the magnitude of the coefficient linking gender to the intercept, slope and quadratic respectively. Φ_{11} and Φ_{12} represent the magnitude of the coefficient linking the intervention (12-week intervention and 52-week intervention respectively) to the slope and Φ_{21} and Φ_{22} represent the magnitude of the coefficient linking the intervention (12-week intervention and 52-week intervention respectively) to the quadratic component. s_{0j}, s_{1j} , s_{2j} represent the random error for the intercept, slope and quadratic respectively.

The coefficients for age, gender and treatment group on the intercept, slope and quadratic for each of the mechanisms of action are listed in Table 4.5.

Table 4.5. Coefficients for age, gender and treatment group for growth factors of mechanisms of action

	Habit strength			Dietary restraint			Autonomous diet self-regulation		
	Intercept	Slope	Quadratic	Intercept	Slope	Quadratic	Intercept	Slope	Quadratic
Age	0.022	-0.003	0.001	0.023	0.006	-0.002	0.001	0.012	-0.005
Gender	0.237	0.047	-0.023	1.568	-0.877	0.284	0.269	-0.255	0.093
Intervention (reference group: Brief intervention)									
12-week intervention	0.305	-0.128		0.926	-0.361		0.265	-0.061	
52-week intervention	0.482	-0.186		1.494	-0.507		0.418	-0.143	

The quadratic model for the BMI can be specified as

$$BMI_{jt} = \pi_{0j} + \pi_{1j}t + \pi_{2j}t^2 + d_{jt} \quad \textit{Equation 21}$$

Where BMI_{jt} represent the BMI for participant *j* at time t. The intercept (π_{0j}), slope (π_{1j}), and quadratic (π_{2j}) components on the BMI trajectory can be represented as

$$\pi_{0j} = \Omega_0 + \gamma_0 Age + \eta_0 Gender + \alpha_0 Income + \mu_0 Education + \varepsilon_{0j} \quad \textit{Equation 22}$$

$$\pi_{1j} = \Omega_1 + \gamma_1 Age + \eta_1 Gender + \alpha_0 Income + \mu_0 Education + \rho(\theta_{1j}) + \sigma(\Psi_{1j}) + \nu(\Sigma_{1j}) + \tau_{01} Tx12 + \tau_{02} Tx52 + \varepsilon_{1j} \quad \textit{Equation 23}$$

$$\pi_{2j} = \Omega_2 + \gamma_2 Age + \eta_2 Gender + \alpha_0 Income + \mu_0 Education + \tau_{11} Tx12 + \tau_{12} Tx52 + \varepsilon_{2j} \quad \textit{Equation 24}$$

Where Ω_0, Ω_1, and Ω_2 are the intercepts for each growth factor (intercept, slope and quadratic). γ_0, η_0, α_0, μ_0 represent the magnitude of the coefficients linking age, gender, income and education respectively to the intercept of BMI. γ_1, η_1, α_1, μ_1 represent the magnitude of the coefficients linking age, gender, income and education respectively to the slope component of the BMI trajectory. γ_2, η_2, α_2, μ_2 represent the magnitude of the coefficients linking age, gender, income and education respectively to the quadratic component of the BMI trajectory. ρ, σ and ν represents the magnitude of the coefficients linking the slope of habit (θ_{1j}), dietary

restraint (Ψ_{1j}) and autonomous diet self-regulation (Σ_{1j}) to the slope of BMI. τ_{01} and τ_{02} represent the magnitude of the coefficient linking the intervention (12-week intervention and 52-week intervention respectively) to the slope component of the trajectory. This represents the remaining non-significant direct effect of the treatment group on BMI when the mechanisms of action were included as mediators. τ_{11} and τ_{12} represent the magnitude of the coefficient linking the intervention (12-week intervention and 52-week intervention respectively) to the quadratic component of the BMI trajectory. $\varepsilon_{0,}\, \varepsilon_{1\,,}\, \varepsilon_{2}$ represent the random error for the intercept, slope and quadratic respectively.

BMI at years 1 and 2 was calculated using the baseline line BMI as follows:

$$BMI_{jt} = \text{Baseline BMI}_j + \pi_{1j}t + \pi_{2j}t^2 \qquad \textit{Equation 25}$$

The coefficients for demographic variables and treatment group on the slope and quadratic for BMI is listed in Table 4.6.

Table 4.6. Coefficients for demographic variables and treatment group on the slope and quadratic growth factors of BMI used in Demographic plus MoA-adjusted specification

	Slope	Quadratic
Age	-0.028	0.008
Gender	-1.178	0.124
Education (reference group: below GCSE)		
GCSE – A-level	0.312	-0.154
Degree and above	0.256	-0.150
Income reference group (under £20 000)		
£20 000 - £50 000	-0.119	0.061
£50 000 and above	-0.144	0.043
Not disclosed	-0.312	-0.269
Dietary restraint slope	-0.656	
Habit strength slope	-1.851	
Autonomous diet self-regulation	-0.656	
Baseline BMI	-0.014	
12-week intervention*	0.640	0.319
52-week intervention*	0.415	0.636

*This represent the remaining non-significant impact of the treatment group on BMI.

Conditional model

The intercept and quadradic of the BMI were represented by the same equations (equations 14 and 16 respectively) in the MoA specification but the slope is as follows

$$\pi_{1j} = \beta_1 + \gamma_1 Age + \eta_1 Gender + \alpha_0 Income + \mu_0 Education + \tau_{01} Tx12 + \tau_{02} Tx52 + \varepsilon_{1j} \quad \textit{Equation 26}$$

Where β_1, is the intercepts, γ_1, η_1, α_1, μ_1 represent the magnitude of the coefficients linking age, gender, income and education respectively to the slope component and τ_{01} and τ_{02} represent the magnitude of the coefficient

linking the intervention (Tx12 and Tx52 respectively) to the slope component of the trajectory. ε_1 represent the random error for the intercept, slope and quadratic respectively.

BMI at years 1 and 2 was then calculated as specified in equation 17.

Table 4.7. Coefficients for demographic variables and treatment group on the slope and quadratic growth factors of BMI used in the demographic-adjusted model specification

	Slope	Quadratic
Age	-0.033	0.008
Gender	-0.525	0.126
Education (reference group: below GCSE)		
GCSE – A-level	0.251	-0.149
Degree and above	0.181	-0.142
Income reference group (under £20 000)		
£20 000 - £50 000	-0.183	0.068
£50 000 and above	-0.230	0.055
Not disclosed	-0.421	0.128
Baseline BMI	-0.014	
12-week intervention	-0.658	0.308
52-week intervention	-1.716	0.639

4.8.2 Baseline Population Characteristics SPHR model

The model required demographic, anthropometric and metabolic characteristics that would be representative of the UK general population. In the original health economic model, the Heath Survey for England (HSE) was suggested by the stakeholder group because it collects up-to-date cross-sectional data on the characteristics of all ages of the English population. It also benefits from being a reasonably good representation of the socioeconomic profile of England. However for this study, levels of dietary restraint, habit strength and autonomous diet self-regulation were required, and these were not available in the HSE. Thus, the study sample from the weight loss referrals for adults in primary care (WRAP) trial were used. Summary statistics for the WRAP data extracted from the dataset are reported in Table 4.8.

Table 4.8. Characteristics of WRAP trial sample (N=1267)

Variable name (description)	Mean	Median	SD	Missing (N)
Age	53.19	54.00	13.71	3
Weight	95.16	93.90	17.05	0
Height	166.70	165.80	9.05	0
BMI	34.54	33.32	5.17	0
Total Cholesterol	5.33	5.26	1.12	425
HDL Cholesterol	1.67	1.54	0.61	425
HbA1c	5.71	5.28	1.73	462
SBP	132.93	131	17.37	4
DBP	80.21	80	9.77	4
EQ-5D	0.80	0.85	0.25	347
Habit strength	3.20	3	1.49	38
Dietary restraint	5.16	4.67	3.09	33
Autonomous diet self-regulation	6.00	6.17	0.97	37

Table 4.9. Summary data for categorical variables (N=1267)

Variable name (description)	Category	N	%
Sex	Male	405	32.2%
	Female	859	67.8%
	Missing	0	0%
Income	£0-£19,999	328	25.9%
	£20,000-£49,999	415	32.8%
	£50,000 and over	216	17.1%
	Not disclosed	165	13.1%
	Missing	140	11.1%
Origin	Asian or Asian British	35	2.7%
	Black or Black British	23	1.8%
	Mixed or multiple ethnic group	15	1.2%
	White or white British	1136	89.7%
	Other	15	1.2%
	Missing	43	3.4%
Smoking group	Current	27	2.1%
	Ex-smoker	33	2.6%
	Never smoke	407	32.1%
	Missing	800	63.1%
Hypertensive treatment	Yes	628	49.6%
	No	631	50.4%
	Missing	1	0.001%
Diabetes	Yes	204	16.1%
	No	1016	80.1%
	Missing	47	3.7%

A complete dataset was required for all individuals at baseline. However, no measurements for Fasting Plasma Glucose (FPG) or 2-hour glucose were obtained. In addition, the questionnaire did not collect information about individual family history of diabetes or family history of CVD. These variables were imputed from the Whitehall II dataset (see below) (5;6).

4.8.3 Missing data for WRAP sample population

The majority of missing data methods are documents in Appendix 3 and match those used in the original model. Those detailed below are the methods specific to the baseline population from the WRAP study.

Anxiety/Depression

We did not have information on whether participants had depression or anxiety. We therefore made the assumption that individuals in this sample did not have severe anxiety/depression.

Rheumatoid Arthritis, Atrial Fibrillation, History of Cardiovascular disease

We did not have information on whether participants had arthritis, or any cardiovascular disease and we therefore made the assumption that the baseline prevalence of these conditions was zero.

Habit strength, dietary restraint and autonomous diet self-regulation

Dietary restraint, habit strength and autonomous diet self-regulation variables weren't in the original model and so for these, multiple imputation was used with a single imputation generated for each PSA run. A subset of the relevant variables was taken including the variables used in the multiple imputation described (sex, age, BMI, education and income) and the mediators (dietary restraint, habit strength and autonomous diet self-regulation). The method chosen for the continuous variable was predictive mean matching which is a semi-parametric method which restricts the imputed values to the observed values and preserves non-linear relationships between the variables used to impute the missing data. It was assumed that gender and age predicted the missing data of habit strength, dietary restraint and autonomous diet self-regulation. Any variables that were correlated (with a correlation of at least .30) and had enough usable cases to predict missing values in the other variable were also retained as predictors. During probabilistic sensitivity analysis (PSA), a single imputation was conducted on each model run, and the values were imputed. As a result, the total number of imputations reflected the number of PSA runs. A description of the adaptions made for the WRAP sample population to be used in the model is described in Supplementary Material, Section 4.8.2.

4.8.2 Additional Results

Incremental costs of health conditions

All model specifications estimated similar reduction in the costs associated with cardiovascular disease and type 2 diabetes and diabetes-related complications (including blindness, ulcer, amputation and renal) when compared to the brief intervention (Figure 4.6). In all model specifications, there was small increases in costs related to cancer and depression. This is likely a result of living longer (and therefore being at higher risk of cancer) and living longer with health conditions associated with depression.

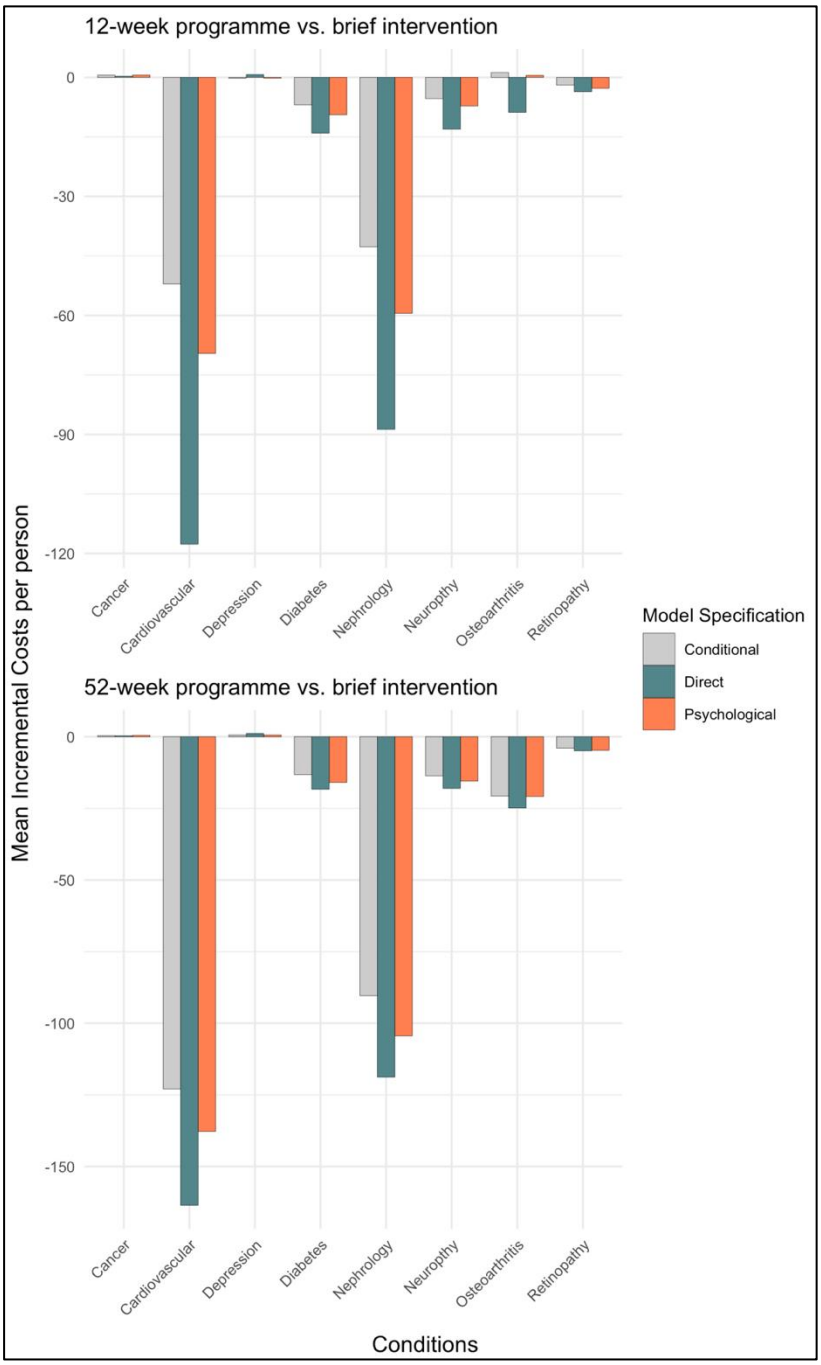

Figure 4.6. Incremental costs estimated in each model specification

Subgroup analysis

Table 4.10. Number of eligible participants in the baseline population (from the WRAP study) out of the full sample (N=1267) that met the criteria of each group

Subgroup	Number of eligible participants in the baseline population
High habit strength	335
Low habit strength	333
High dietary restraint	320
Low dietary restraint	318
High autonomous diet-self regulation	354
Low autonomous diet-self regulation	362
High all mechanisms of action	76
Low all mechanisms of action	55

Cost-effectiveness planes

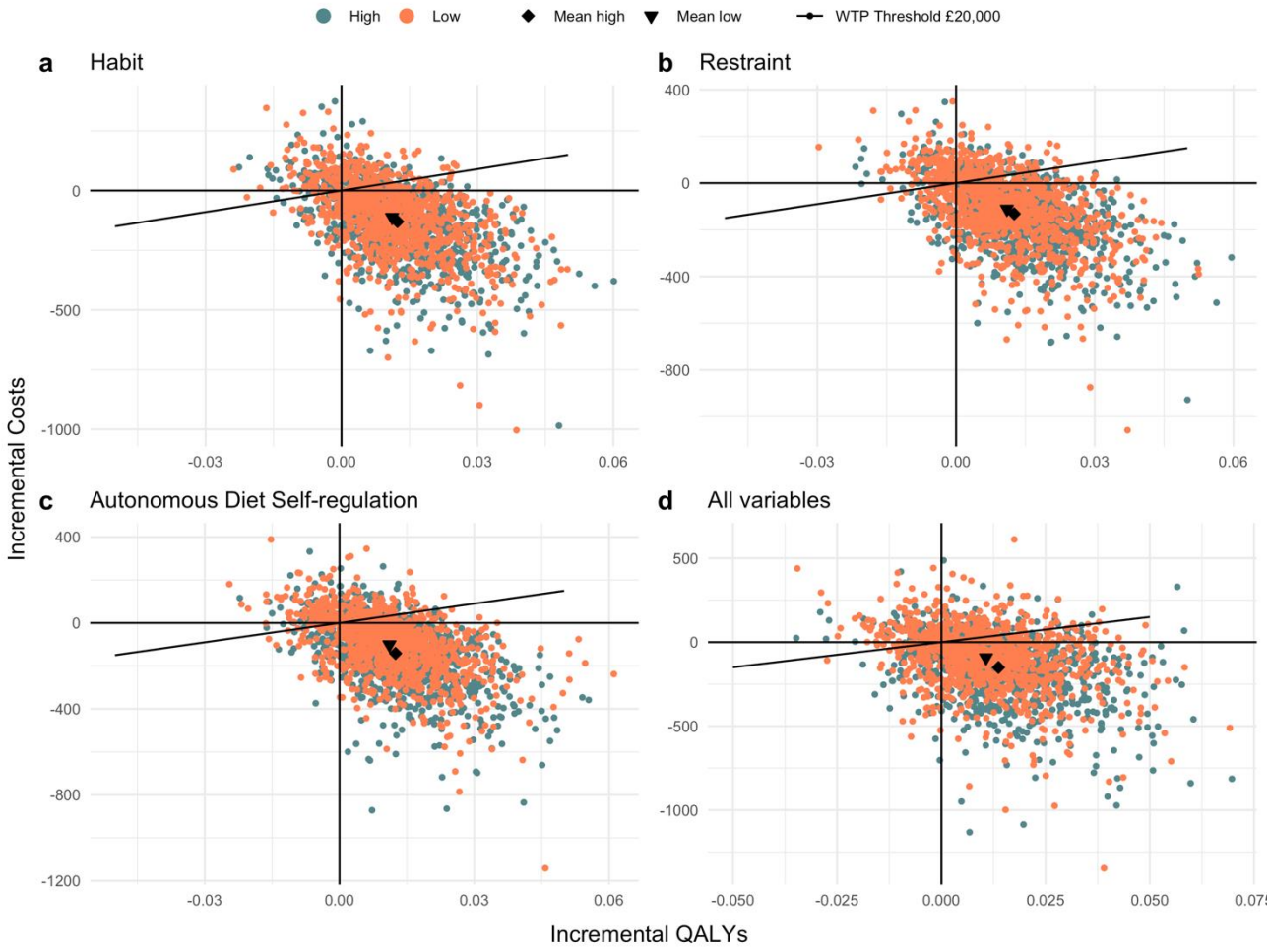

Figure 4.7. Cost-effectiveness of the 12-week intervention compared to the brief intervention in each subgroup

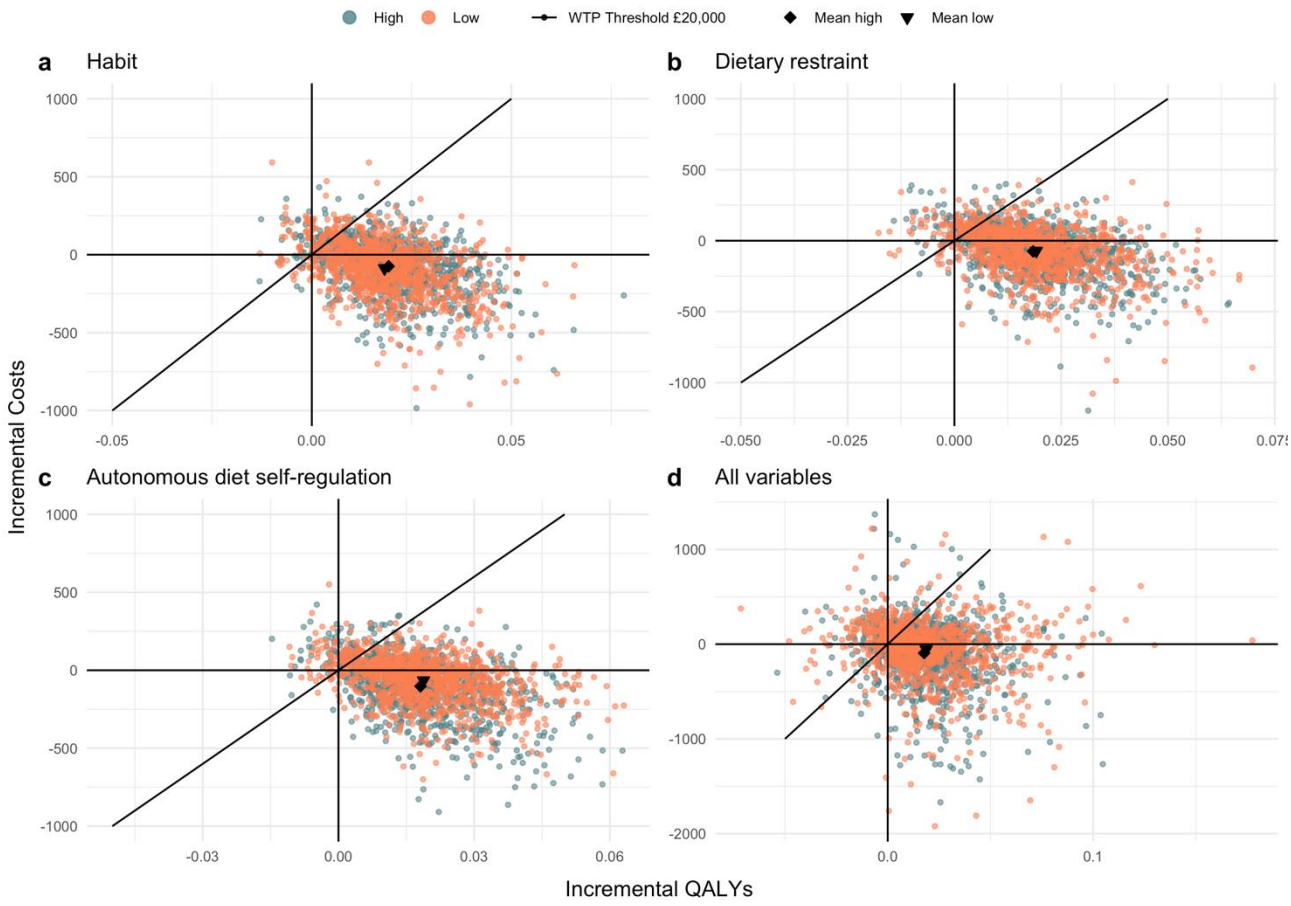

Figure 4.8. Cost-effectiveness of the 52-week intervention compared to the brief intervention in each subgroup

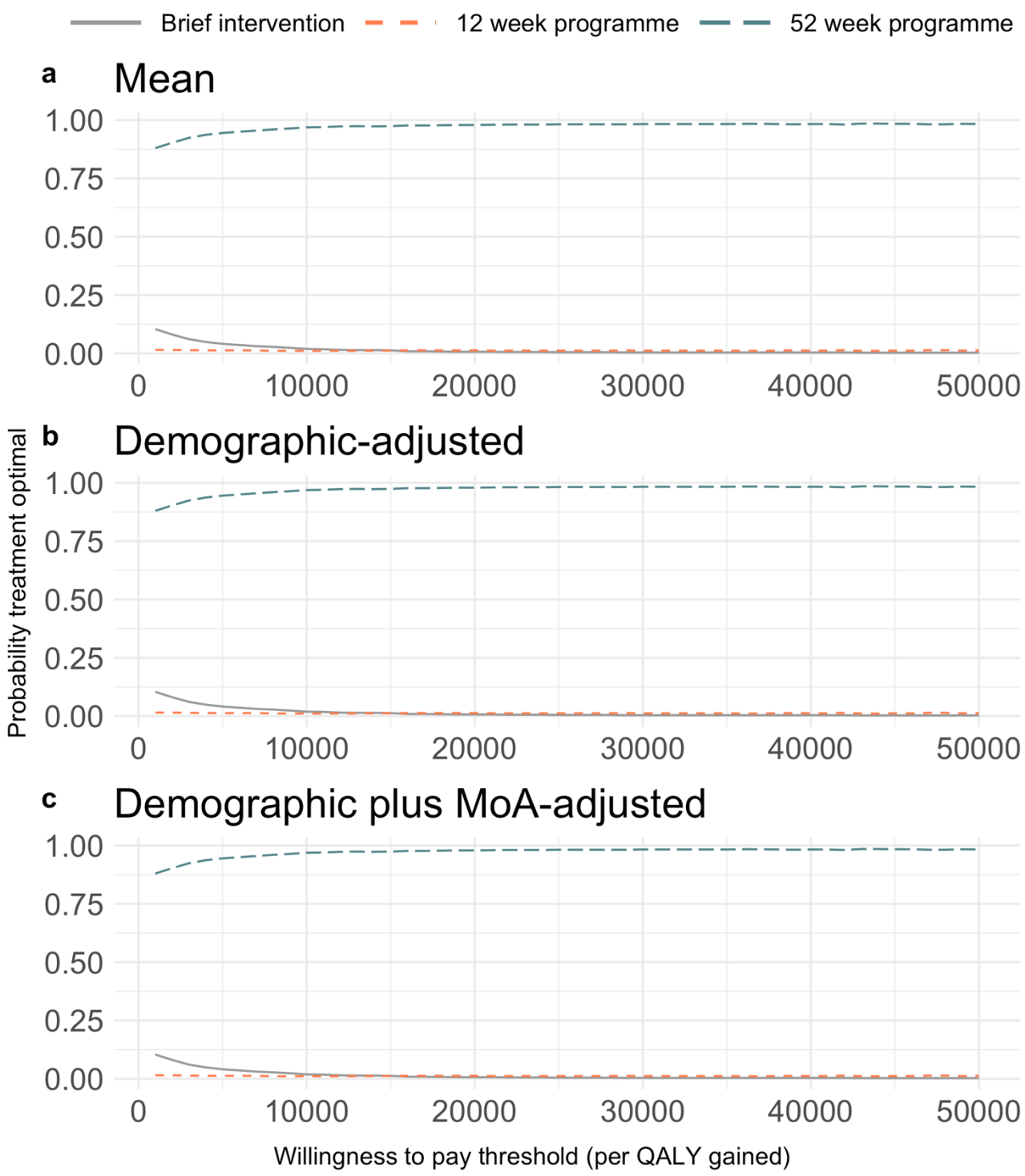

Figure 4.9. Cost Effectiveness Acceptability curves for each model specification

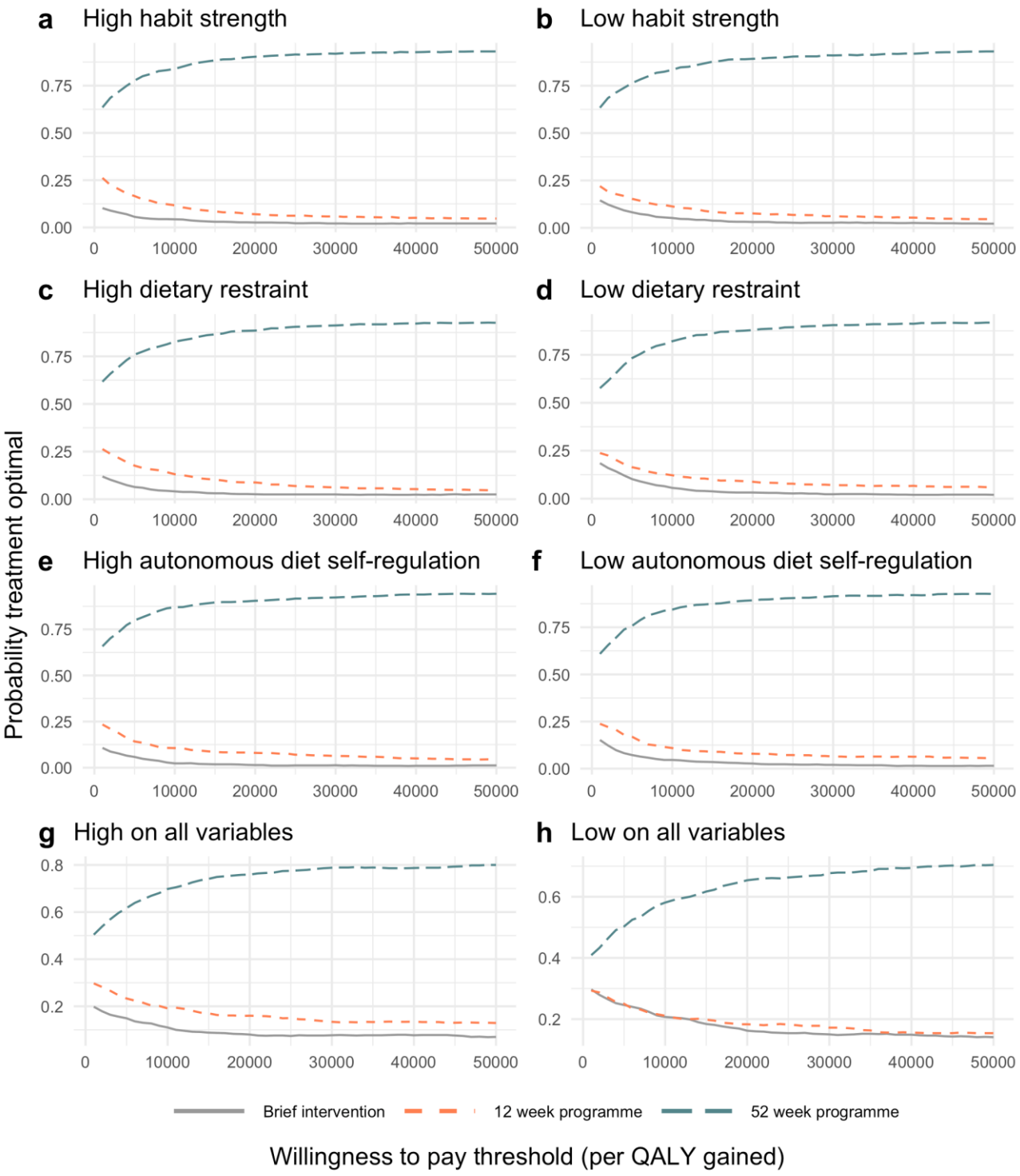

Figure 4.10. Cost Effectiveness Acceptability curves for each subgroup

CHAPTER 5: CALCULATING THE MAXIMUM JUSTIFIABLE COST OF A WEIGHT LOSS MAINTENANCE INTERVENTION

This chapter describes an example of pre-trial health economic modelling. Pre-trial health economic modelling enables researchers to estimate the cost-effectiveness of a planned intervention but requires an estimate of treatment effect. The aim of this analysis was to conduct health economic model of a behavioural weight loss maintenance intervention for two populations; individuals with a high Body Mass Index (BMI) and individuals with type 2 diabetes. This could then be used to inform the design of a weight maintenance intervention.

Pre-trial modelling based on mechanisms of action was identified as a benefit of the model adaptation made and tested in Chapter 4. This chapter is an example of pre-trial modelling that can be conducted in the version of the model without mechanisms of action. This can be compared to pre-trial health economic modelling with the newly developed model with change in mechanisms of action (Chapter 6) to further understand the benefits that could be gained from the inclusion of the mechanisms of action in health economic modelling of weight management interventions.

This chapter was submitted to *BMC Public Health* in March 2021.

Bates, S., Thomas, C., Islam, N., Ahern, A., Breeze, P. , Griffin, S. & Brennan, A. Using Health economic modelling to inform the design and development of an intervention: estimating the justifiable cost of weight loss maintenance in the UK. *Submitted to BMC Public Health.*

The paper was written with 6 co-authors; Amy Ahern, Penny Breeze, Alan Brennan, Simon Griffin, Nazrul Islam and Chloe Thomas. This work was completed as part of a larger project; Scalable behavioural weight management programmes for the prevention and treatment of type 2 diabetes (NIHR PGfAR: RP PG 0216 20010).

Amy Ahern proposed the idea of including pre-trial modelling for the project. Sarah Bates, Penny Breeze, Alan Brennan and Chloe Thomas planned the pre-trial health economic modelling methods. Amy Ahern, Nazrul Islam and Simon Griffin conducted the meta-analysis that informed the estimation of intervention effect in section 5.3.3. Sarah Bates conducted the health economic modelling and wrote the original draft of the manuscript. All authors provided feedback on the manuscript.

As stated in the author statement, the meta-analysis reported in section 5.3.3. was completed by co-authors Amy Ahern, Nazrul Islam and Simon Griffin. It is included in this thesis as it inform the pre-trial modelling that is conducted as part of the Chapter.

USING HEALTH ECONOMIC MODELLING TO INFORM THE DESIGN AND DEVELOPMENT OF AN INTERVENTION: ESTIMATING THE JUSTIFIABLE COST OF WEIGHT LOSS MAINTENANCE IN THE UK

5.1 Abstract

Background. There is a need to develop cost-effective weight loss maintenance interventions to prolong the positive impact of weight loss on health outcomes. Conducting pre-trial health economic modelling is recommended to inform the design and development of behavioural interventions. We aimed to use health economic modelling to estimate the maximum cost per-person (justifiable cost) of a cost-effective behavioural weight loss maintenance intervention, given an estimated intervention effect for individuals with: i) a Body Mass Index (BMI) of 28 kg/m^2 or above without diabetes and ii) a diagnosis of type 2 diabetes prescribed a single non-insulin diabetes medication.

Methods. The School for Public Health Research Diabetes prevention model was used to estimate the lifetime Quality-adjusted life year (QALY) gains, healthcare costs, and maximum justifiable cost associated with a weight loss maintenance intervention. Based on a meta-analysis, the estimated effect of a weight loss maintenance intervention following a 9kg weight loss, was a regain of 1.33kg and 4.38kg in years one and two respectively compared to greater regain of 2.84kg and 5.6kg in the control group. Sensitivity analysis was conducted around the rate of regain, duration of effect and initial weight loss.

Results. The justifiable cost for a weight loss maintenance intervention at an ICER of £20,000 per QALY was £104.64 for an individual with a BMI of 28 or over and £88.14 for an individual with type 2 diabetes. Within sensitivity analysis, this varied from £36.42 to £203.77 for the former, and between £29.98 and £173.05 for the latter.

Conclusions. Researchers developing a weight loss maintenance intervention should consider these maximum justifiable cost estimates and the potential impact of the duration of effect and initial weight loss when designing intervention content and deciding target populations. Future research should consider using the methods demonstrated in this study to use health economic modelling to inform the design and budgetary decisions in the development of a behavioural interventions.

Keywords: Health economic modelling, weight loss maintenance, Behavioural intervention

5.2 Introduction

Overweight and obesity is a risk factor for several negative health outcomes including cardiovascular disease (CVD), diabetes and cancer (1). Behavioural weight management programmes have been associated with significant weight loss (2) and can even result in remission from type 2 diabetes (3) but there is evidence that, on average, individuals regain weight loss by 5 years post-treatment (4). Furthermore based on a large observational study, only 21% of individuals are successful at maintaining weight loss, defined as losing at least 10% of their body weight and maintaining this weight loss for at least one year (5). While moderate reductions in weight have positive benefits for individuals who are overweight or obese and for those who have type 2 diabetes even if weight loss is regained (6-8), weight loss maintenance is required to maintain full improvements in risk reduction. For example, individuals who lost 8-20% of their initial body weight and maintained this for 4 years (regained less than 3% of initial body weight) in a randomised control trial of a behavioural intervention achieved sustained improvements in blood glucose (HbA_{1c}), systolic blood pressure (SBP) and cholesterol, all biomarkers linked with health outcomes (9). Thus, there is a need to develop cost-effective weight loss maintenance interventions in order to prolong the positive impact of weight loss on health outcomes (10).

Conducting pre-trial health economic modelling is recommended to estimate the likelihood of cost-effectiveness, inform decision about whether a trial is justified, and identify potential improvements to the intervention (9). Using an estimated intervention effect based on previous research, a maximum cost-per-person (justifiable cost) can be estimated at which the intervention would remain cost-effective given a certain incremental cost-effectiveness ratio (ICER). This can be compared to expected costs to ensure that an intervention is not predicted to incur a cost at which it is unlikely to be cost-effective. Pre-trial modelling has been conducted previously; for example Asaria et al. (2016) used a health economic model to estimate the annual costs at which interventions with varying impacts on cardiovascular risk would be cost-effective for individuals with different risk profiles (11) and pre-trial modelling was used to inform the design of a fall-prevention intervention and trial (12). However, these studies were either based on hypothetical, rather than intervention-specific, risk changes (10) or based on the results from a pilot trial (11) and so is not a method

that can be use before a pilot trial had taken place. The aim of this analysis was to use a health economic model to determine the justifiable cost of a behavioural weight loss maintenance intervention compared to no intervention in two populations; i) individuals with a Body Mass Index (BMI) of 28 kg/m^2 or above without diabetes and ii) individuals with a diagnosis of type 2 diabetes prescribed a single non-insulin diabetes medication.

5.3 Methods

The reporting of this study followed the 2013 Consolidated Health Economic Evaluation Reporting Standards guidelines (13).

5.3.1 SPHR Diabetes Prevention Model

The School for Public Health Research (SPHR) Diabetes prevention model has been used to assess the cost-effectiveness of diabetes prevention interventions (14-16). For this study we use version 3.3 of the model and full detail of the model background, methods, assumptions and parameters is in Appendix 3and 4.

The SPHR models is an individual patient level model in which the baseline characteristics of an individual are used to estimate annual changes in metabolic risk factors and the risk of related diseases. This model was used because it enables change in BMI to be modelled, trajectories of BMI and other metabolic factors to vary among individuals and estimates of the impact of weight loss and weight loss maintenance on a range of health conditions including CVD, type 2 diabetes, osteoarthritis and depression. The model structure is shown in Appendix 3, Figure 1. Each year changes in metabolic factors, namely BMI, HbA1c, SBP and total cholesterol, occur depending on the individual baseline characteristics including age, sex, ethnicity, smoking, family history of CVD, and family history of type 2 diabetes. Associations between the trajectories of the metabolic risk factors were based on latent growth curve modelling analysis conducted on the Whitehall II prospective cohort study (17). Change in glycaemia, SBP and total cholesterol are all conditional on change in BMI.

These metabolic factors then contribute to the risk of an individual patient experiencing a disease or related complications. At GP visits, an individual in the model may be diagnosed with diabetes, hypertension and dyslipidaemia. GP attendance is conditional on age, sex, BMI, ethnicity and health outcomes (heart disease, depression, osteoarthritis, diabetes, stroke, cancer) based on the South Yorkshire Cohort study (18). Individuals can also experience cancer (breast or colon), osteoarthritis and depression, CVD events (angina, myocardial infarction (MI), stroke, or transient ischemic attack (TIA) and diabetes related complications (renal failure, amputation, foot ulcer, and blindness) based on risk equations described in section 7 of Appendix 3. Many of the diagnoses and events in the model are conditional on BMI. It contributes to the risk of the first cardiovascular events as part of the QRISK2 prediction model (19). This is a validated algorithm to identify individuals at high risk of cardiovascular disease. Subsequent cardiovascular events are conditional on the nature of the first event. Incidence of breast and colorectal cancer were estimated from the European prospective investigation of cancer (EPIC) cohort (20) and based on a large meta-analysis including 221 prospective observational studies (21), a risk adjustment was included such that individuals with a high BMI have a higher probability of the cancer diagnosis. Osteoarthritis was also conditional on BMI; this was based a stakeholder discussion and a longitudinal analysis based in Italy as there were no appropriate UK studies available (22). A diagnosis of diabetes was dependent on blood glucose (HbA_{1c}), the trajectory of which is associated with BMI and, of the diabetes-related complications, neuropathy (ulcer and amputation) was conditional on BMI based on the UKPDS outcomes model v2 (23). Depression was not conditional on BMI however it was assumed that a diagnosis of diabetes and/or cardiovascular disease increased the incidence of depression for individuals who did not have depression at baseline based on two US cohort studies (24, 25). Depression was not a casual factor for any health outcomes in the model.

The consequences of interventions are measured in Quality Adjusted Life Years (QALYs), as recommend by the National Institute for Health and Care Excellence (NICE) (26), based on the EQ-5D-3L, and costs/savings in pounds sterling. The model has an annual cycle length and a lifetime horizon as weight loss and maintenance have the potential to impact long-term health outcomes. The setting is primary care in England, UK and a we used a healthcare perspective (National Health Service (NHS) in England). This includes cost healthcare costs incurred by the NHS and excludes any costs incurred by the patient such as travel and time costs association

with the intervention. Both costs and QALYs were discounted at an annual rate of 3.5% as recommended by NICE (26).

5.3.2 Populations

The analyses were conducted for two separate populations; i) individuals with a BMI of 28 kg/m^2 or above without diabetes and ii) individuals with a diagnosis of type 2 diabetes prescribed one non-insulin diabetes medication. These populations were chosen as they are at high risk of negative health impacts, have the potential to respond to early intervention (i.e. before developing diabetes, or diabetes dependent on insulin or several medications) and were likely target populations for this type of intervention (27). The baseline characteristics of both populations can be found in Supplementary Material, Table 5.4.

For population (i), the baseline data on individuals was obtained from Health survey for England (HSE) 2014 (28), which is representative of the population of England (29) and includes clinical risk factors including HbA1c, SBP, BMI and cholesterol and health outcomes. The population of interest was defined as adults with a BMI of 28 kg/m^2 and over (prior to initial weight-loss), based on previous studies in which this was a criteria for referral to a weight management programme by a GP (30), and with a HbA_{1c} below 6.5% (the criteria used for a diabetes diagnosis). Children aged under 18 and adults with a diagnosis of diabetes were excluded. Within the final sample (n = 2738), a subgroup of individuals with an HbA_{1c} of 6-6.49% were examined separately (n = 322) as this criteria is used to identify individuals at higher risk of diabetes (31).

For population (ii), HSE only included a small number (approximately 400) of individuals with diabetes and thus would be unlikely to represent the diabetic population well and has little information about the diabetes diagnosis such as time of diagnosis and treatment. For this population, people with type 2 diabetes were selected from the THIN (The Health Improvement Network) 2014 dataset (32) as this had a large number of individuals with diabetes. Of the 3.7 million individuals from 427 GP practices, 131,000 had type 2 diabetes. The time since diagnosis and treatment prescribed was also available for this dataset alongside BMI, HbA1c, cholesterol, and SBP and demographic factors such as age, gender and ethnicity. A baseline population was

created by sampling from the summary statistics of this data taking into account correlation between variables, rather than individual patient data. The sample was not restricted by time spent on this medication but those on more than one anti-diabetic mediation or on insulin were excluded. A subgroup analysis for those with a BMI of 28 or above was also included based on previous studies in which this was a criteria for GP referral to a weight management programme (30).

5.3.3 Intervention Effect

The estimated effect of the intervention on weight has been obtained by examination of the literature. We conducted a random-effects meta-analysis of behavioural weight loss maintenance studies to estimate the expected effect of a weight loss maintenance intervention compared to no intervention (current standard care in the UK) after weight loss resulting from a behavioural intervention. Following the PRISMA process, relevant studies were screened from two previous systematic review and meta-analysis studies of weight loss maintenance interventions (33, 34) to identify those studies that met our pre-specified inclusion criteria. The inclusion criteria were chosen to reflect likely commissioning of services in the UK NHS and were informed by current practice and discussions with our stakeholder group comprising health economists, clinicians and researchers and lay members. Studies had to include adult participants with a BMI $\geq$ 25kg/m^2, who had lost $\geq$5% of their weight before starting the weight loss maintenance programme. Studies that required $\geq$10% initial weight loss to join the study or which solely recruited participants with a specific health condition were excluded as this population was deemed highly selective and not representative of the intended population. The intervention had to be a behavioural intervention including advice on diet and physical activity for the primary purpose of weight management. Interventions that used meal replacements and financial incentives were excluded as these interventions are unlikely to be widely commissioned in the UK NHS. Studies had to report weight outcomes $\geq$ 12 months from the start of the weight maintenance intervention. Only randomised controlled trials were included. We applied these inclusion and exclusion criteria to the two systematic reviews, which reported data from a total of 32 behavioural intervention arms from 20 studies (35-54). Nine studies were excluded from our analyses for the following reasons: (a) inclusion criteria did not reflect the target population, (36, 43, 50, 54) (b) intervention included meal replacement or financial incentives (39, 47, 53) (c)

primary purpose of the intervention was not weight management (52) or (d) did not report weight outcomes ≥12 months from the start of the weight maintenance intervention (38, 42).

Three analyses of the studies were undertaken. Firstly, fourteen intervention arms from nine studies (35, 40, 41, 44-46, 48, 49, 51) were included in a meta-analysis to estimate initial weight loss of participants that were eligible for a weight loss maintenance intervention. Second, fifteen intervention arms from ten studies (35, 37, 40, 41, 44-46, 48, 49, 51) contributed to the meta-analysis to estimate weight loss maintenance intervention effects at 12-month post-weight loss. Third, two intervention arms from one study contributed to the estimates at 2-year post-weight loss (51) as this was the only eligible study that included a 2 year follow-up.

Table 5.1 shows the results of the random-effects meta-analysis; the initial weight loss before the weight maintenance intervention is estimated at 8.93kg, and individuals partaking in a weight loss maintenance intervention had an average regain of 1.33kg by year 1 and 4.38kg by year 2 compared to a regain of 2.84kg by year 1 and 5.6kg by year 2 in a control group. Forest plots comparing the active intervention with control group at 12- and 24-month follow-up are shown Supplementary Material (Figure 5.4 and 5.5). There was no evidence of an influence of individual studies on the overall estimates at 12 months (Figure 5.6, Supplementary Material). Influence plots were not generated for 24 months follow-up as only one study provided data at this time point. The revised Cochrane risk of bias tool for randomised trials (55) was used to assess the studies; four were low risk of bias (40, 41, 48, 51), 3 were high risk (35, 46, 49) and there were some concerns regarding the remaining three studies (37, 44, 45). A sensitivity analysis in which the meta-analysis excluded the studies with a high risk of bias did not significantly impact the outcomes (Table 5.5, Supplementary Material) There was moderate heterogeneity across studies in weight maintenance at 12 months (I^2=59%, P = 0.002).

In the absence of data on the longer-term weight trajectories, we made the conservative assumption that participants would return to baseline weight trajectory at some point. To determine when this point would be, the regain between years 1 and 2 was extrapolated linearly (assuming the same regain as between years 1 and 2 for each subsequent year), until the trajectory reached that of the simulated individual's weight if they had never had the initial weight-loss intervention (based on the simulated trajectories from the SPHR health

economic model). Both the control and treatment group returned to this original trajectory by 5 years (to the nearest full year) after the initial weight loss (Figure 5.1). The initial weight-loss was simulated in year 0, at the start of the model, and the regain in subsequent years.

Table 5.1. Weight regain per annum: estimates from random-effects meta-analysis

	Weight maintenance intervention (n = 661)			Control (no intervention) (n= 383)			Difference between groups		
Year	N	Mean	95% CI*	N	Mean	95% CI*	N	Mean	95% CI
0	14	-8.93	(-9.49, -8.36)	14	-8.93	(-9.49, -8.36)			
1	15	1.33	(0.67, 1.99)	15	2.84	(2.01, 3.67)	15	-1.38	(-2.2, -0.55)
2	2	4.38	(3.64, 5.11)	2	5.6	(5.19, 6.02)	2	-1.23	(-1.96, -0.49)

N indicates total number of intervention arms; CI: Confidence intervals; estimates are in kg; *95% CI of mean weight change. The weight for year 0 is the weight loss before weight maintenance intervention begins and the weight in year 1 and 2 is the weight regain per annum during weight maintenance intervention.

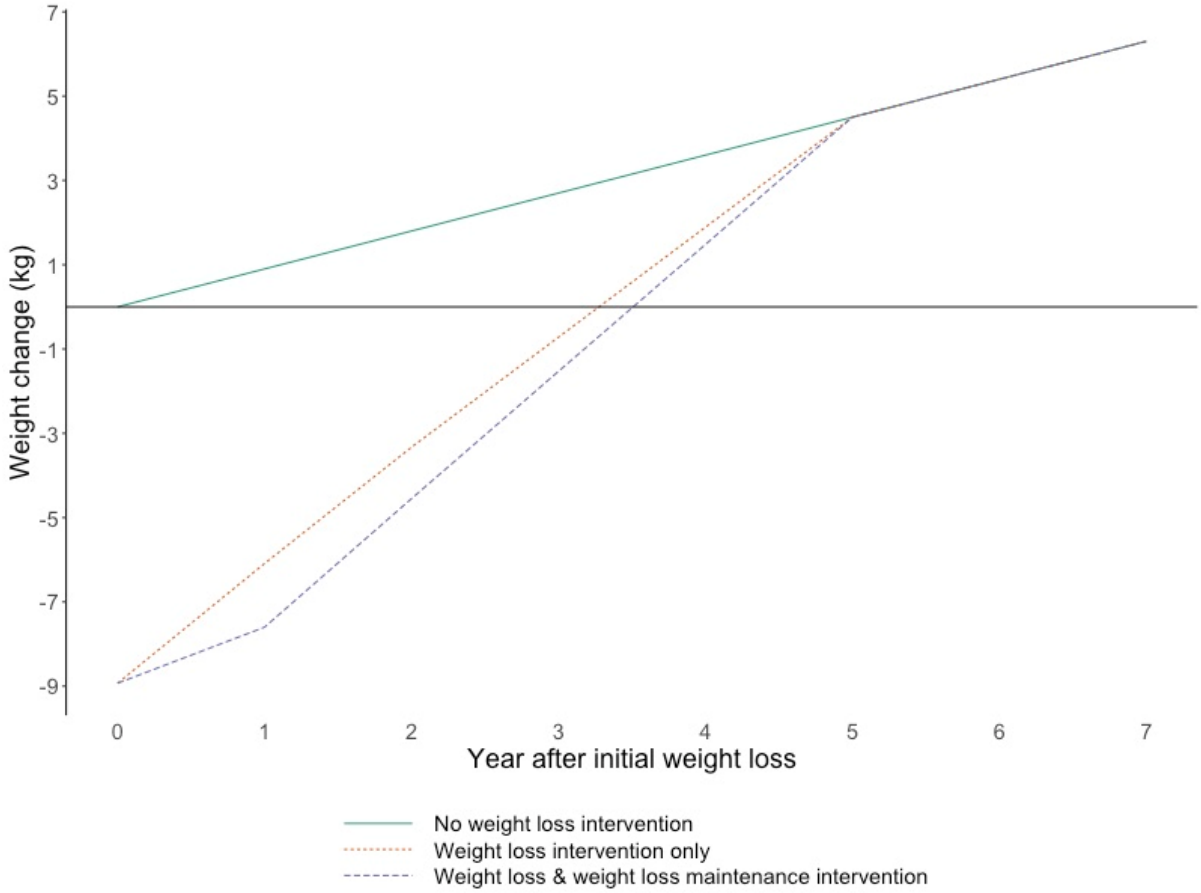

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Figure 5.1. Simulated trajectories of weight change post initial weight loss

In the absence of any data about the direct effects of the weight loss and weight regain on other metabolic factors, an indirect effect of the change in BMI on HbA_{1c}, SBP and cholesterol was modelled. Specifically, covariates from the analysis conducted on the Whitehall dataset were used to predict the change in the metabolic factors from changes in BMI in the population simulated (17) (Appendix 3).

5.3.4 Intervention Costs

This analysis was conducted with the assumption that the proposed intervention would be funded for patient through primary care i.e. the payer would be the NHS. This is already the case for some commercial weight loss and diabetes prevention programmes in the UK (56). There is no fee charged to the individual receiving the interventions and patient borne costs e.g. travel etc. are not included. Justifiable costs will be calculated for each person who has the intervention based on the assumption that all eligible individuals will participate in the intervention.

5.3.5 Health economic modelling

For each run of the model, 20,000 eligible individuals were randomly sampled from the two baseline populations with replacement. As the aim of this analysis was to estimate a justifiable cost for a proposed intervention, the cost of the weight loss maintenance intervention was set to £0 within the model and the amount that could be spent on this intervention while remaining cost-effective was calculated using increasing maximum ICERs. For NICE, this is estimated to be between £20,000 and £30,000 per QALY (57) and therefore the cost per person at these ICER values were the targets for the analysis. Public health interventions often have a lower threshold because the benefits are further in the future, therefore the maximum cost of the intervention while being cost-saving was also calculated. At this cost or lower, the cost savings as a result of the intervention is greater than the cost of the intervention.

5.3.6 Sensitivity Analysis

Sensitivity analysis was conducted on the duration of effect, the initial weight-loss and the rate of regain (Table 5.2). By duration of effect, we are referring to the amount of time between year 0 and the point at which the

weight trajectories reaches the trajectory they would have followed without any weight loss. Because the duration was estimated by extrapolating the regain from the first two years, in sensitivity analysis the impact of different durations (4-6 years) were examined (scenarios 1-3). The rate of regain, the amount regained at year 1 and year 2, was varied using the 95% confidence intervals (CIs; scenarios 4 and 5). The weight loss that both groups achieved before entering either a weight loss maintenance intervention or control condition (no intervention) was also examined. The figure of 8.93kg obtained from the meta-analysis conducted for this analysis is based on a target population of people who have lost ≥5% weight, which reflects the likely implementation of a weight loss maintenance programme in practice. We also examined a scenario in which there was not a minimum weight loss required to take part in the weight loss maintenance programme and examined the impact of a lower initial weight loss of 2.84kg (scenario 6), based on average weight loss from a previous meta-analysis (2) of weight loss interventions that were applicable to UK primary care. An initial weight loss of 6.12kg (scenario 7), which was the midpoint between the lower value of 2.84kg and the base case value of 8.93kg, was also tested. The regain was adjusted proportionally. These are represented graphically in the Supplementary Material (Figure 5.7). Probabilistic sensitivity analyses was conducted to assess uncertainty within the model inputs using probabilistic sensitivity analysis with 5000 Monte Carlo simulations. The model parameters and uncertainty distributions are shown in Appendix 4.

Table 5.2. Scenarios modelled in sensitivity analysis

Scenario	Initial weight loss (*kg*)	Regain (*year 1, year 2)*	Duration of effect (*years*)	
			Control	Intervention
Base case	**8.96**	**1.33, 4.38**	**5**	**5**
1 [Duration]	8.96	1.33, 4.38	4	6
2 [Duration]	8.96	1.33, 4.38	5	6
3 [Duration]	8.96	1.33, 4.38	4	4
4 [Regain rate]	8.96	0.67, 3.64	5	5
5 [Regain rate]	8.96	1.99, 5.11	5	5
6 [Initial weight loss]	2.84	0.42,1.39	5	5
7 [Initial weight loss]	6.12	0.91, 2.99	5	5

5.4 Results

5.4.1 High BMI (≥ 28kg/m2)

The estimated maximum amount that can be spent on an intervention while remaining cost-effective at increasing ICER values, with the assumption of the effect is detailed in Table 5.1 and shown in Figure 5.2. For ICERs of £20,000 and £30,000 per QALY, the maximum justifiable cost-per-person was £104.64 and £137.78 respectively assuming duration of effect of 5 years and health benefits accrued over the lifetime. For the subgroup that had a BMI ≥28 and an HbA_{1c} between 6 and 6.5%, the maximum justifiable cost-per-person was £158.88 and £209.81 respectively.

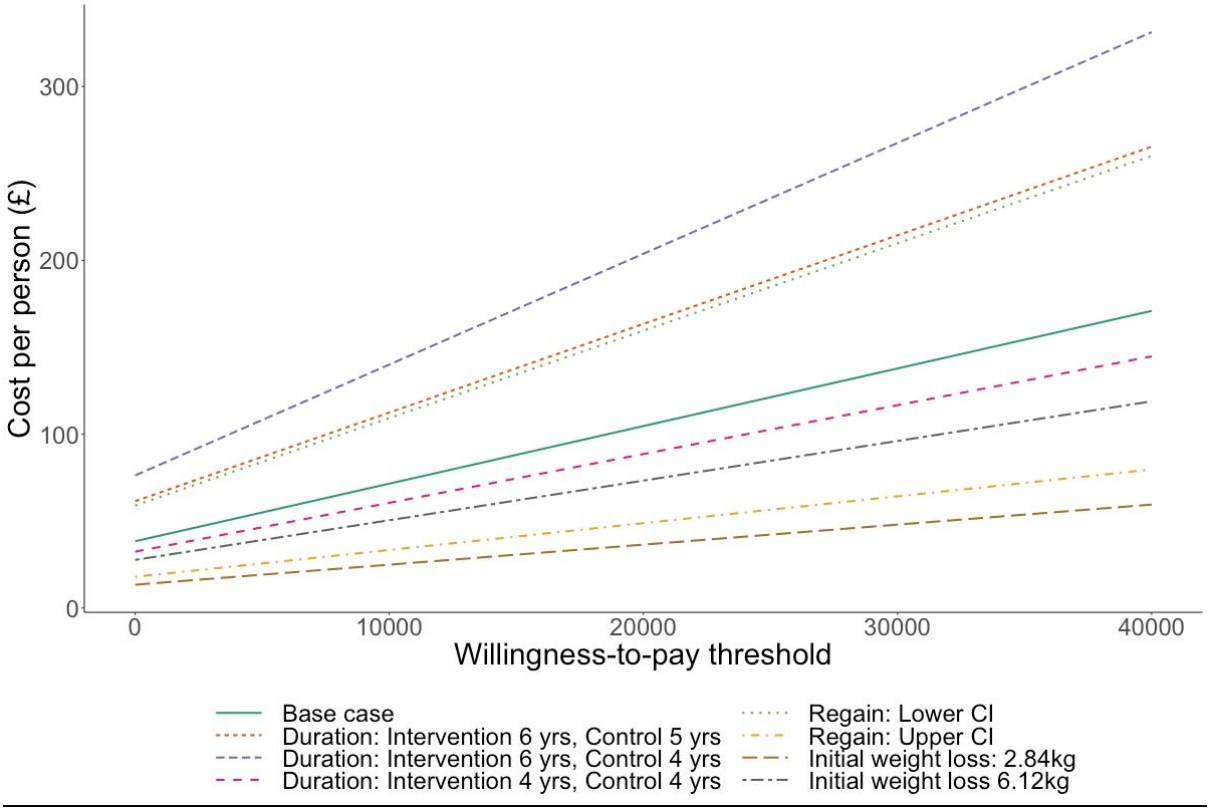

Figure 5.2. Justifiable cost per person for a cost-effective intervention: Base case and sensitivity analyses (BMI ≥28)

The average incremental QALYs per individual was 0.003 and the cost saving was £38.37. The detail of cost and QALY savings for sensitivity analysis is in the Supplementary Material, Tables 5.6 and 5.7. Per 100,000 individuals, there were 8 cases of diabetes and 23 cases of cardiovascular disease averted. For those at higher

risk of diabetes (with and HbA_{1c} of between 6 and 6.5%) this increased to 49 cases of diabetes and 33 cases of CVD averted. In order to be cost saving, the maximum justifiable cost was £38 per-person for an intervention targeted at individuals with a high BMI and £57 per-person for those who also have an HbA_{1c} between 6 and 6.5%.

Sensitivity analysis was conducted around the duration of intervention effect, the initial weight-loss and the rate of regain. The maximum justifiable cost per person for a cost-effective intervention for the ICERs of £20,000 and £30,000 for each scenario are shown in Table 5.3. The largest maximum justifiable cost obtained from the sensitivity analysis was when the duration of effect was six and four years for the intervention and control group respectively and the lowest was for the lowest initial weight loss.

Table 5.3. Cost per person at incremental cost-effectiveness ratios of £20,000 and £30,000

Scenario		High BMI (≥ 28kg/m^2)		Type 2 Diabetes[a]	
		£20,000	£30,000	£20,000	£30,000
	Base case	£104.64	£137.78	£88.14	£112.64
1	Duration (years): intervention 6, control 4	£203.77	£267.52	£173.05	£219.75
2	Duration (years): intervention 6, control 5	£163.40	£214.39	£135.98	£171.97
3	Duration (years): intervention 4, control 4	£88.56	£116.65	£74.80	£96.08
4	Regain: Lower confidence interval	£159.52	£209.80	£134.91	£172.57
5	Regain: Upper confidence interval	£48.79	£64.22	£41.62	£53.22
6	Initial weight loss: 2.84kg	£36.42	£47.94	£29.98	£38.09
7	Initial weight loss: 6.12kg	£73.27	£96.07	£45.14	£55.01
	BMI of 28 or above			£96.61	£122.34

[a] Diagnosis of type 2 diabetes and prescribed single, non-insulin diabetes medication

5.4.2 Type 2 Diabetes

The maximum amount that could be spent on an intervention while remaining cost-effective, with the assumption of the effect detailed in Table 5.1, at increasing ICER values is shown in Figure 5.3. For ICERs of £20,000 and £30,000 per QALY, the maximum justifiable cost per person was £88.14 and £112.64 respectively assuming duration of effect of 5 years and health benefits accrued over the lifetime. This increased to £96.61

and £122.34 when the population was limited to individuals with a BMI of 28 or above. The average incremental QALYs per individual was 0.002 and the cost saving was £39.14 (full details of incremental costs and QALYs for sensitivity analyses are in Supplementary Material, Tables 5.6 and 5.7). There were an estimated 53 cases of CVD averted per 100,000 individuals. To be cost saving this intervention would have to cost less than £39 per-person.

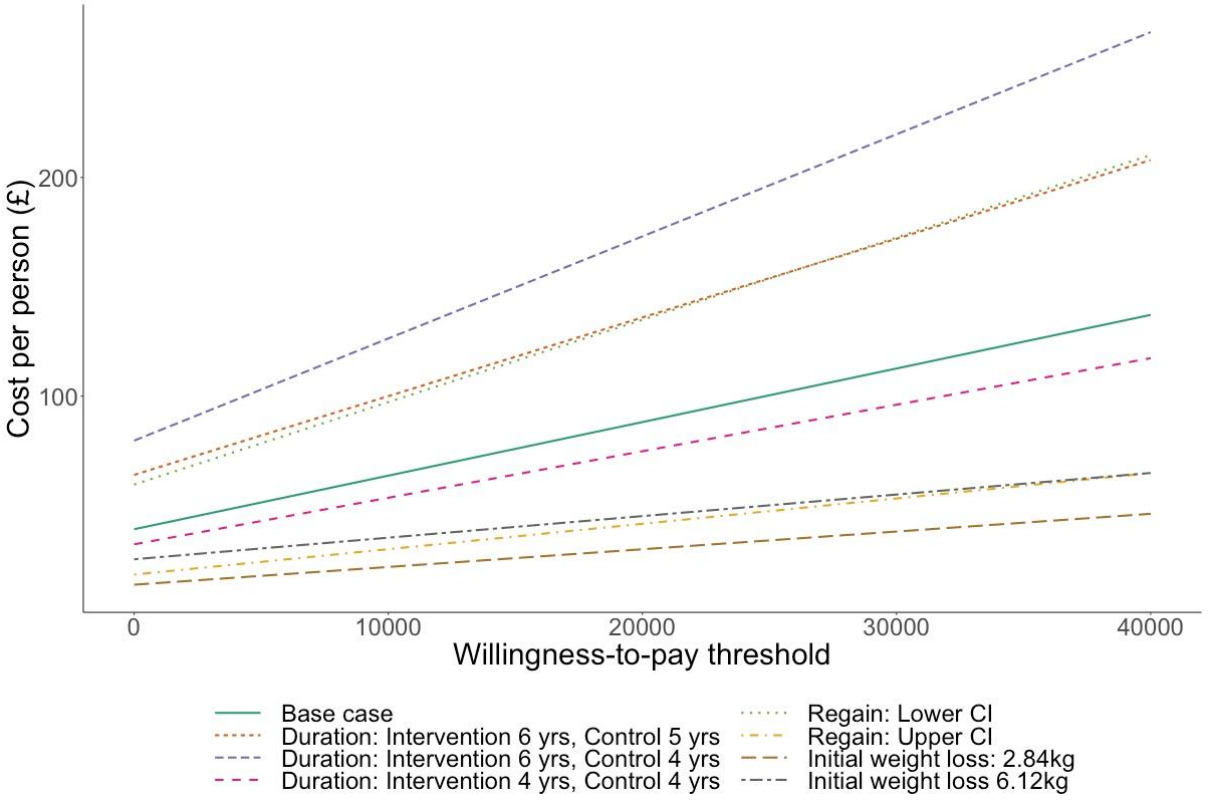

Figure 5.3. Justifiable cost per person for a cost-effective intervention: Base case and sensitivity analysis (Diagnosis of type 2 diabetes on single non-insulin medication)

Sensitivity analysis was conducted around the duration of intervention effect, the initial weight-loss and the rate of regain and the results of this are shown for ICERS of £20,000 and £30,000 in Table 5.4. As found with the high BMI population, when the duration of effect was 6 years for the intervention for 4 years for the control, the maximum justifiable cost was highest, and it was lowest when the initial weight loss was 2.84kg.

5.4.3 Probability Sensitivity Analysis (PSA)

PSA was conducted to examine the uncertainty of the justifiable cost estimate for both groups. Figure 5.8 and 5.9 in the Supplementary Material shows the incremental cost if the justifiable cost (generated from the base case analysis) was applied to each simulation, and incremental QALYs. For both groups, over 98% of the PSA runs resulted in positive incremental QALYs. There was greater variation in incremental costs in the diabetes population; for 8.5% of PSA runs, the intervention resulted in lower costs than the control group when the mean justifiable cost is applied. For the high BMI group, when the justifiable cost is applied, over 99% of PSA runs resulted in a higher cost for the weight loss maintenance intervention compared to no intervention.

5.5 Discussion

At an ICER of £20,000, the maximum justifiable cost was estimated to be £105 for individuals with a high BMI, £159 for individuals with a high BMI and a high HbA_{1c} (high risk of diabetes) and £88 for individuals with a diagnosis of type 2 diabetes on a single non-insulin medication. In sensitivity analysis, duration of effect and the initial weight loss had the greatest impact on justifiable cost. The time it takes for participants to return to their original trajectory, if they do at all, is hard to determine due to short-term follow-up within trials (4) and therefore a range of values should be considered when calculating a justifiable cost. The outcomes of sensitivity analysis also indicates that a weight maintenance intervention is more likely to be cost-effective for individuals with a larger initial weight loss. Previous evidence does suggest that greater initial weight-loss is associated with weight maintenance (58) supporting these findings.

The finding that the maximum justifiable cost is lower on average for those with a diagnosis of diabetes than for those with a high BMI may seem counterintuitive given that those with a high BMI and at high risk of diabetes had the highest maximum justifiable cost. This is likely to be because, for individuals without type 2 diabetes, this intervention may be able to avert or delay a diagnosis of diabetes, which is associated with a reduction in the immediate costs associated with this diagnosis. This is particularly important for those with a high HbA_{1c} as the intervention averts or delays a potentially imminent diagnosis. Conversely, simulated individuals that have diabetes already have a higher associated cost than those without and less potential

incremental gains; they cannot be 'undiagnosed' in the model. Although, there is some evidence that remission from diabetes can be achieved (3), which contradicts the model assumption that type 2 diabetes is irreversible, it is not yet clear that this remission is maintained. Overall, this indicates that the benefits of intervening in high-risk individuals (and therefore preventing or delaying diabetes) are higher than the benefits of intervening in people who already have diabetes.

Weight maintenance interventions that cost more than the maximum justifiable cost estimated are unlikely to be cost-effective based on the estimated intervention effect. While there is evidence that weight maintenance interventions are able to result in an additional 3.2kg maintenance of weight loss over 18 months (10), there is less evidence regarding the cost. In a weight loss maintenance trial for participants that had lost at least 5% of their body weight, interventions costs were between £16 and £49 depending on the amount of face-to-face contact but it was concluded that neither intervention was likely to be cost-effective in routine practice (59). Further evidence is required to determine the feasibility of developing an effective intervention within the justifiable costs estimated.

The method used in this analysis highlights the role that health economic modelling can have in the design and development of a new weight loss maintenance intervention. Although type of modelling is recommended in intervention design guidance, there is little published research detailing the methods used to do this. While previous studies have used the results from a pilot trial (12), the method presented here provides an estimate of justifiable cost without a pilot trial based on a range of previous studies; this can inform the design of the trial before a pilot trial. In addition, while pre-trial modelling has been used to identify the cost of an intervention that achieves a certain risk reduction (11), these estimated impacts are not specific to a planned intervention which may limit application to certain interventions. The maximum justifiable cost provides an estimated upper bound over which the intervention would not be cost-effective, which can be compared to the predicted cost of the planned interventions. This could help to avoid an intervention which is unlikely to be cost-effective proceeding to the trial stage. Subgroup and sensitivity analysis can also inform decisions about whom the intervention should be targeted at and what factors are most likely to impact on cost-effectiveness. Although the current study is specific to a weight management intervention in the UK the methods can be

applied to behavioural interventions in other health areas and countries. The increased number of public health economic models being developed (60) will facilitate this type of modelling. However, as with many public health interventions, there is likely to be a large amount of heterogeneity in effect within the patient groups and therefore there may be limited application when using the mean effect only. Additional research into the different factors that impact on the intervention effect would be informative in this type of pre-trial modelling.

There were some limitations of this analysis. Firstly, due to limited research in this area the same weight loss and regain was applied for each person and in both populations, despite some evidence of heterogeneity in weight trajectories (4, 58) and the estimate of weight regain at 24 months was based on only two intervention arms and so caution should be exercised in interpreting this result. Given the potential impact of differing weight trajectories, we conducted a range of sensitivity analysis to estimate the impact of alternate trajectories (61). Secondly, remission from diabetes is currently not a scenario in the model. There is some evidence that remission from diabetes (an HbA1c of below 6% and no requirement for antidiabetic medication) can be achieved by following a low-calorie diet for 3-5 months, with stepped re-introduction to food and ongoing weight loss maintenance support (3). Given that those eligible for a weight loss maintenance intervention have already been successful in weight loss, in this study approximately 9kg, there is a possibility that some individuals would go into remission. This means that the model may underestimate the positive impact of the intervention for those with diabetes as the cost-reduction associated with potential diabetes remission wasn't captured. However, it is not yet clear that this remission is maintained and it's likely that these patients will be required to attend regular screenings due to their previous diagnosis and so associated costs will still apply. Ongoing research will provide more information about the long-term impact of diabetes remission on costs and QALYs (62). Finally, as the healthcare perspective was used, the costs incurred by patients as a result of a change in lifestyle are not considered. These costs may differentially impact subgroups, and this is not accounted for in the analysis.

5.5.1 Conclusions

In conclusion, given the expected weight loss and regain estimated in the current analyses, intervention designs associated with a cost of above £105 per-person for those with a BMI of 28 or above or £88 per-person for those on first-line diabetes treatment (one medication only) should be carefully considered as these are less likely to be cost-effective. This method demonstrated, that uses results from previous relevant studies to conduct pre-trial modelling prior to a pilot study to inform the design and budgetary decisions of a weight loss maintenance intervention, can be applied to a wider range of behavioural interventions and contexts.

5.6 Contribution to thesis

In this chapter, I conducted pre-trial modelling of a planned weight loss maintenance intervention for two populations. This was part of a larger project and this analysis directly informed the design of an intervention; for example, given the relatively low justifiable cost, a decision was made to deliver the intervention in an online format to reduce costs. While this pre-trial health economic modelling was used to inform the design of an intervention, the findings were based on the effectiveness of previous interventions. Although efforts were made to ensure that the previous intervention reflected the planned intervention, it is likely that these previous interventions contained different behaviour change techniques compared to the planned intervention. Estimating impact of a planned weight management intervention on BMI was therefore challenging.

In Chapter 4, a health economic model was adapted to include mechanisms of action. This introduces the ability to input intervention effect as a change in a psychological determinant of change in BMI. Estimating change in BMI, as was done in the current chapter, is limited by a reliance on the results of previous interventions that may have a different content. However, estimating the impact of a treatment on a mechanisms of action would enable use of existing theoretical and empirical research linking behaviour change techniques to mechanisms of action and therefore pre-trial modelling could be both theory-based and specific to the planned intervention. This will be investigated in the next chapter.

Ideally, I would have like to have conducted pre-trial health economic modelling of the same intervention as evaluated in this Chapter, but by estimating the impact of the intervention on the determinants of change in BMI in the health economic model. This would enable a comparison of the two methods of pre-trial health economic modelling (based on estimated change in BMI, based on estimated impact on dietary restraint, habit strength and/or autonomous diet self-regulation). However, due to unanticipated delays, the full description of the planned weight loss maintenance intervention was not available at the time of writing which limited my ability to do this. Chapter 6 is, however, an exploration of an alternative method of the pre-trial health economic modelling demonstrated here, using the model developed in Chapter 4.

5.7 References

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5.8 Supplementary Material

Of the additional material contained in this section, Table 5.5. and Figure 5.4 – 5.6 was the outcomes of the meta-analysis and were conducted by co-author Nazrul Islam.

Table 5.4. Population characteristics

Characteristic	Population	
	High BMI (≥ 28kg/m2) (N=2738)[a]	Type 2 Diabetes (N=90,219)[b]
Age: mean (SD)	53.84	59.8 (18.9)
BMI: mean (SD)	32.78	31.85 (6.02)
HbA_{1c} : mean (SD)	5.77 (0.93)	8.2% (2.0)
Gender: % male	45.72	57.1
Ethnicity: % White	90.12	94.6
BMI category: %		
<28	0	11.33
28-34.99	74.99	60.95
35-44.99	20.29	25.17
≥45	2.35	2.55
IMD[c] quintile		
1	21.20	21.54
2	18.76	18.92
3	20.30	19.22
4	19.69	19.10
5	20.16	21.22

[a] Population sampled from individual patient data; [b] Population derived from summary statistics of data set;

[c] Diagnoses of type 2 diabetes and prescribed single, non-insulin diabetes medication;

Table 5.5. Weight loss and regain after the intervention: estimates from random-effects meta-analysis excluding those with high risk of bias)

	Treatment			Control			Difference		
Year	**N**	**Mean**	**95% CI**	**N**	**Mean**	**95% CI**	**N**	**Mean**	**95% CI**
0	14	-8.93	(-9.49, -8.36)	14	-8.93	(-9.49, -8.36)			
1	12	1.41	(0.68, 2.14)	12	2.74	(1.73, 3.76)	12	-1.14	(-2.07, -0.22)
2	2	4.38	(3.64, 5.11)	2	5.6	(5.19, 6.02)	2	-1.23	(-1.96, -0.49)

N indicates total number of intervention arms; CI: Confidence intervals; estimates are in kg

Table 5.6. QALYs gained per person

Scenario		At high risk of diabetes			Newly diagnosed with diabetes		
		Control	Active	Incremental	Control	Active	Incremental
Base case		11.674	11.678	0.003	11.882	11.885	0.002
1	Duration (years): intervention 6, control 4	11.673	11.679	0.006	10.881	10.886	0.005
2	Duration (years): intervention 6, control 5	11.674	11.679	0.005	10.882	10.886	0.004
3	Duration (years): intervention 4, control 4	11.673	11.676	0.003	10.881	10.883	0.002
4	Regain: Lower confidence interval	11.674	11.679	0.005	10.882	10.886	0.004
5	Regain: Upper confidence interval	11.674	11.676	0.002	10.882	10.883	0.001
6	Initial weight loss: 2.84kg	11.662	11.663	0.001	10.872	10.872	0.001
7	Initial weight loss: 6.12kg	11.669	11.671	0.002	10.877	10.878	0.001

Table 5.7. Costs saved gained per person

Scenario		At high risk of diabetes			Newly diagnosed with diabetes		
		Control	Active	Incremental	Control	Active	Incremental
Base case		29030.10	28991.72	38.37	103037.93	102998.79	39.14
1	Duration (years): intervention 6, control 4	29047.39	28971.13	76.26	103057.99	102978.34	79.65
2	Duration (years): intervention 6, control 5	29030.10	28968.67	61.43	103037.93	102973.93	64.00
3	Duration (years): intervention 4, control 4	29047.39	29015.01	32.38	103057.99	103025.74	32.24
4	Regain: Lower confidence interval	29030.10	28971.13	58.97	103037.93	102978.34	59.59
5	Regain: Upper confidence interval	29030.10	29012.18	17.91	103037.93	103019.51	18.42
6	Initial weight loss: 2.84kg	29178.22	29164.85	13.37	103216.06	103202.29	13.77
7	Initial weight loss: 6.12kg	29097.56	29069.90	27.66	103117.63	103092.22	25.41

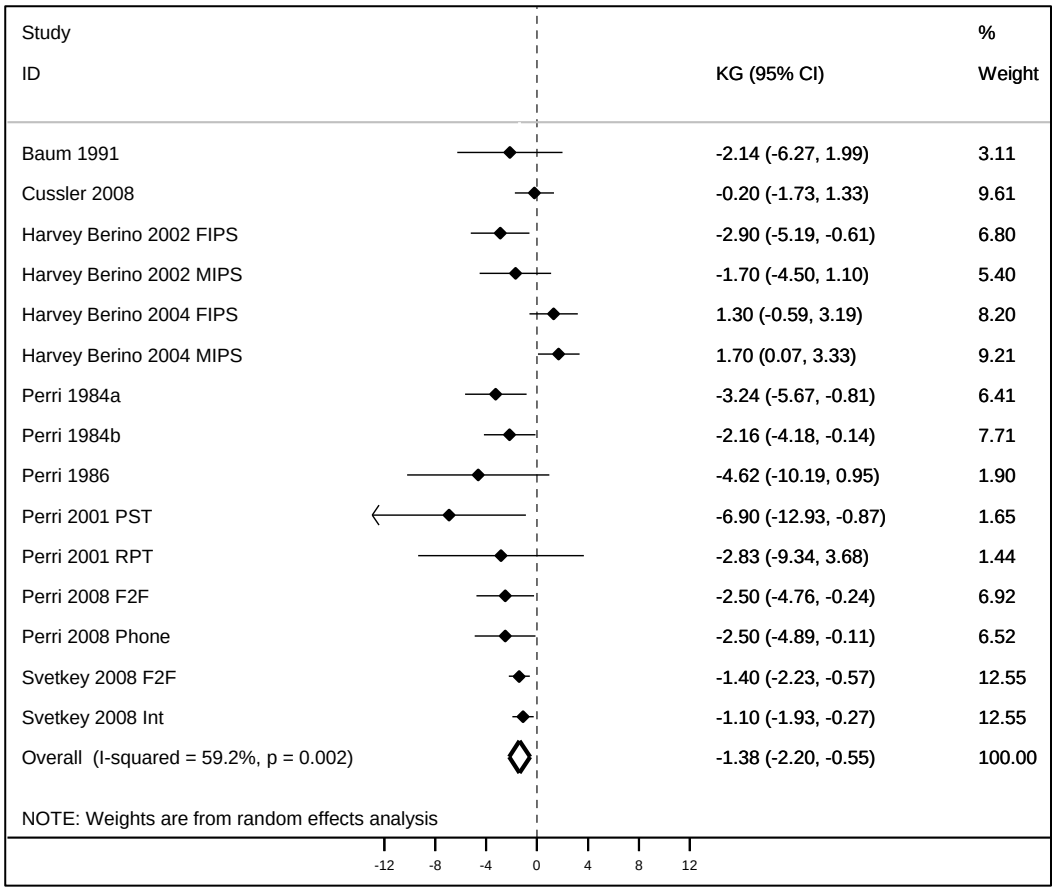

Figure 5.4. Forest plot from random-effects pairwise meta-analysis at 12-month post-intervention

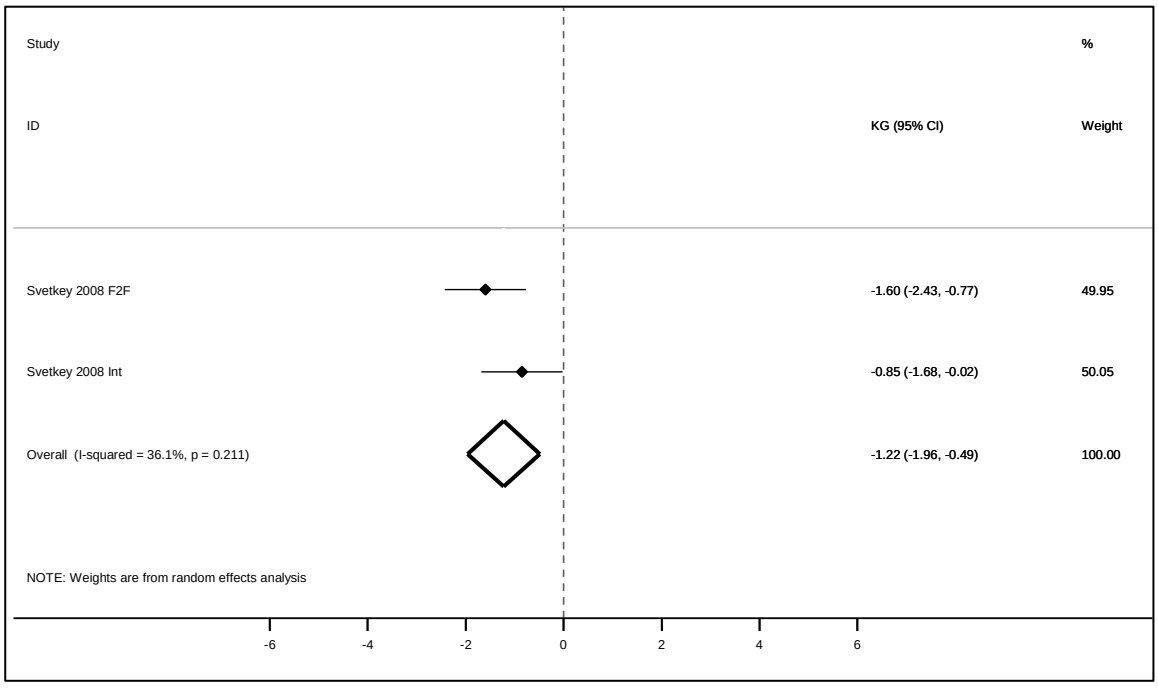

Figure 5.5. Forest plot from random-effects pairwise meta-analysis at 24-month post-intervention

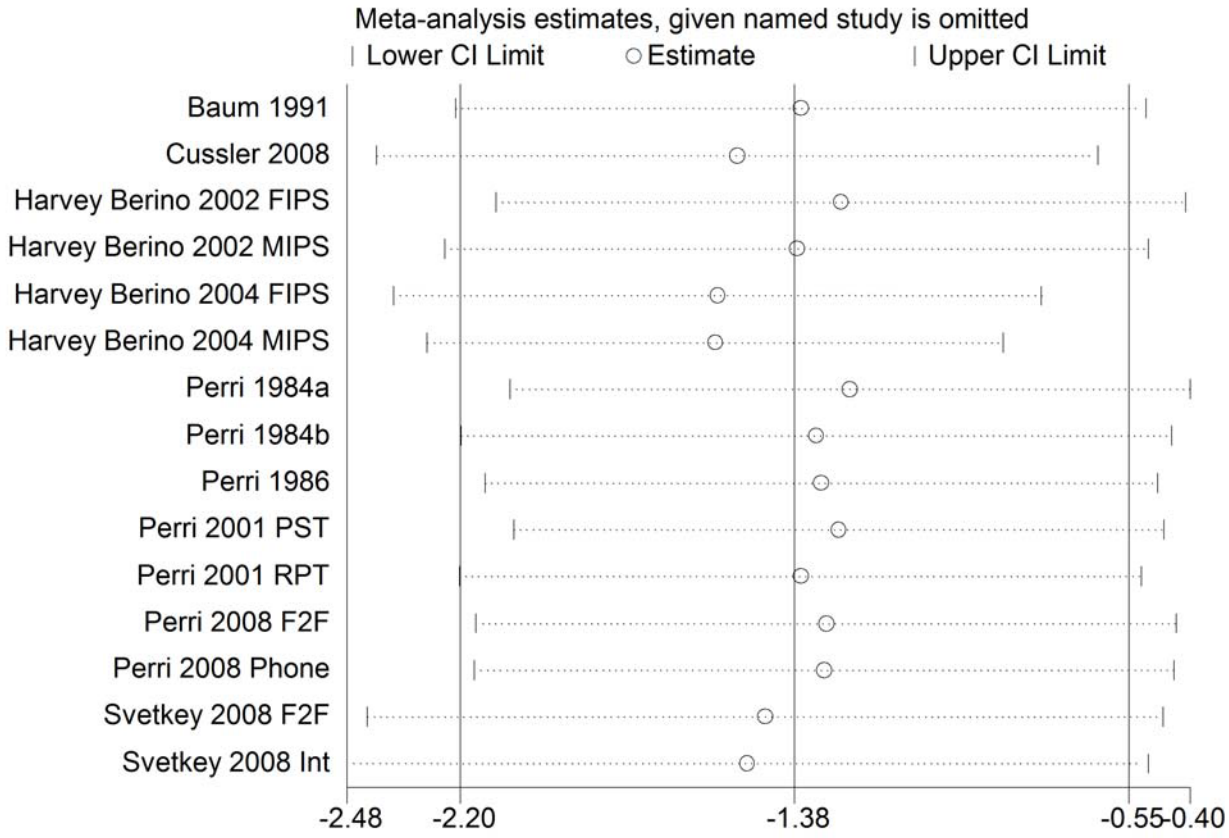

Figure 5.6. Influence plot from random-effects pairwise meta-analysis at 12-month post-intervention

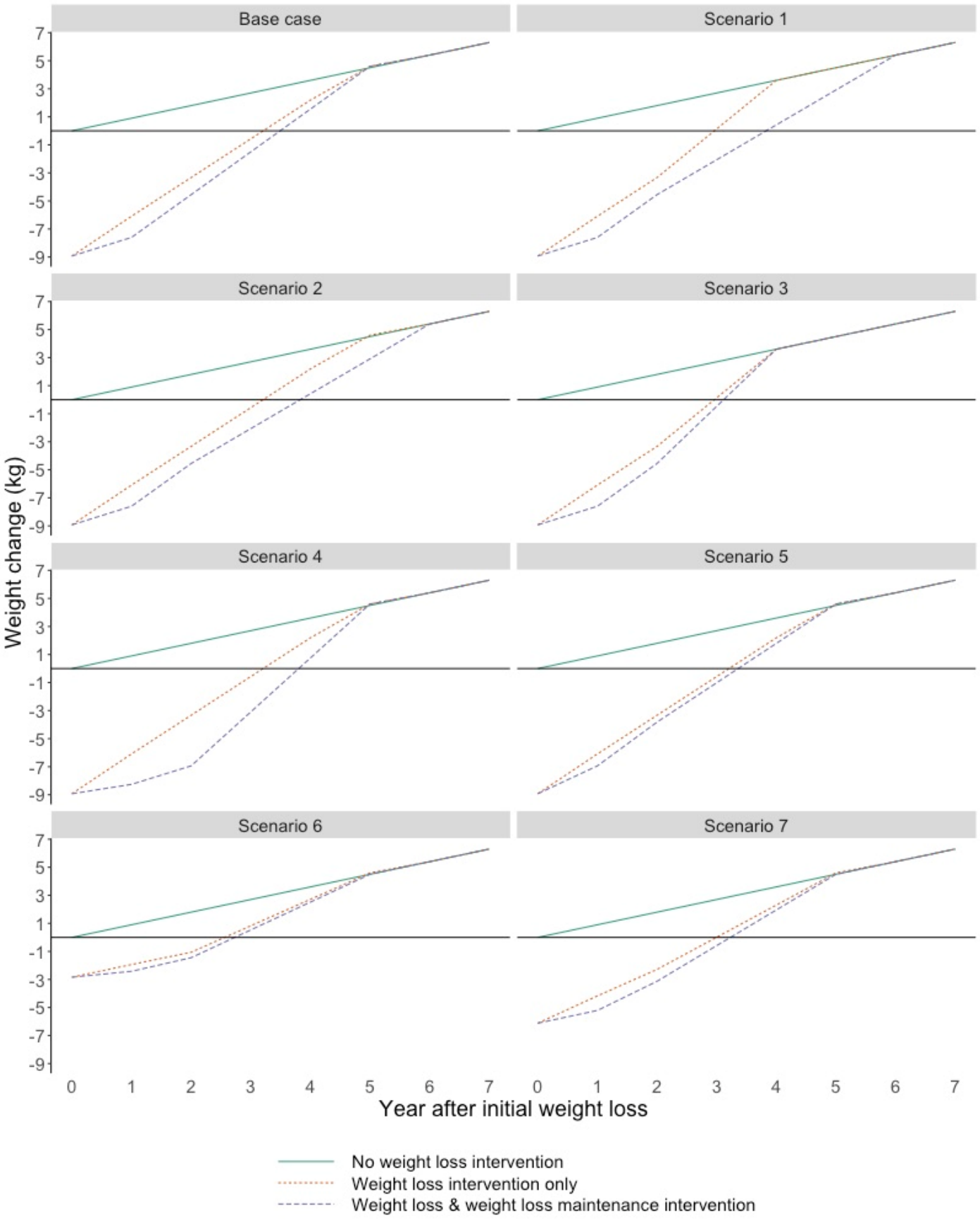

Figure 5.7. Graphical representation of sensitivity analysis

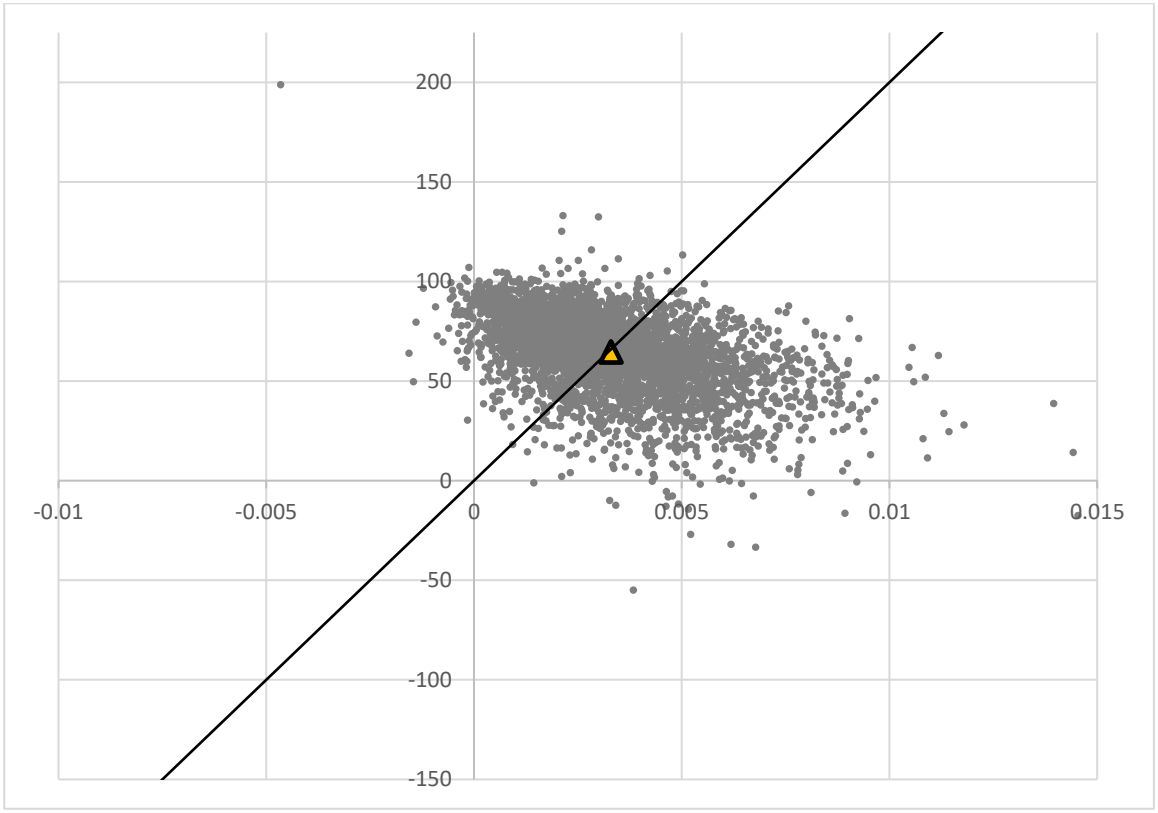

Figure 5.8. Incremental cost plus justifiable cost (£104) and incremental QALYs in high BMI population (5000 Monte Carlo simulations)

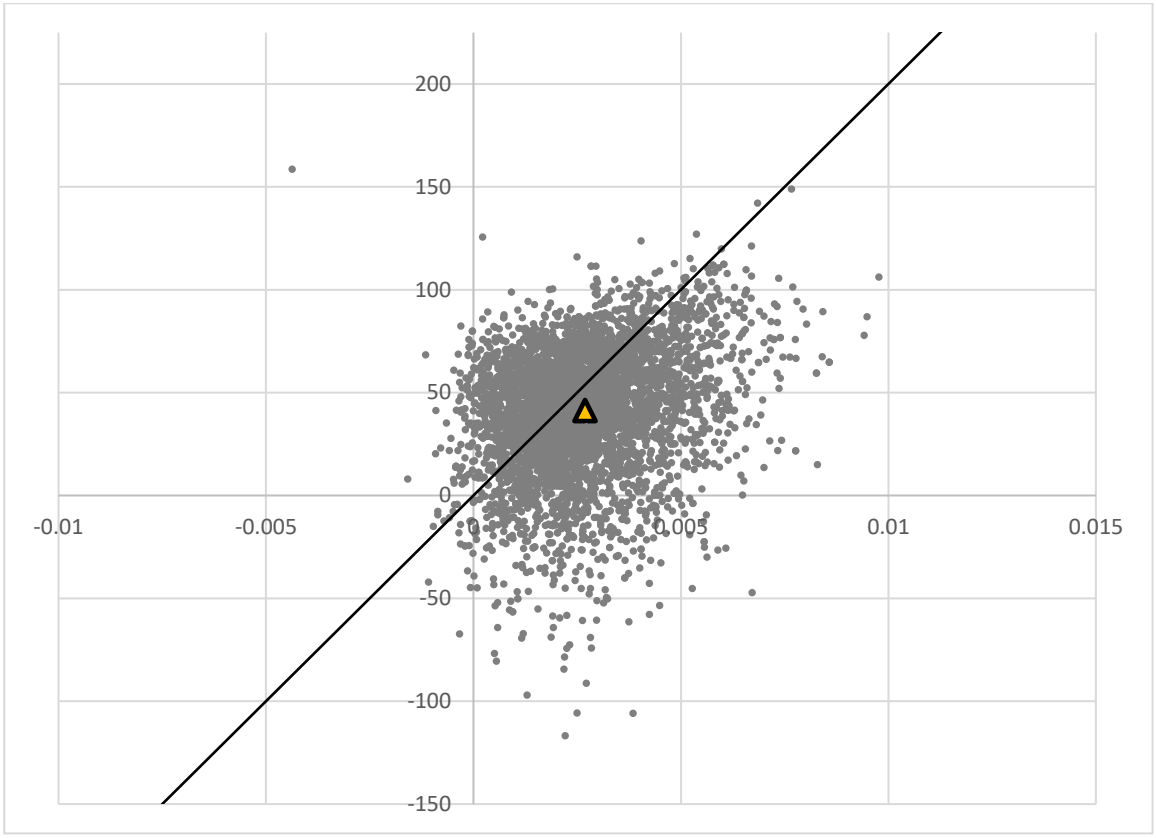

Figure 5.9. Incremental cost plus justifiable cost (£88) and incremental QALYs in diabetes population (5000 Monte Carlo simulations)

CHAPTER 6: PRE-TRIAL MODELLING BASED ON EXPECTED CHANGE IN MECHANISMS OF ACTION

This chapter explores the use of a health economic model to conduct pre-trial modelling based on changes in mechanisms of action. In Chapter 4, an existing health economic model was adapted to include dietary restraint, habit strength and autonomous diet self-regulation based on the mediation analysis conducted in Chapter 3. In this chapter, divided into three parts, the first aim was to use existing literature to estimate the effect of a behaviour change technique on a mechanisms of action to determine if it was feasible to conduct pre-trial modelling of a hypothetical planned intervention based on behaviour change techniques likely to be used. Then, pre-trial health economic modelling of intervention scenarios in which there was either a small, medium or large effect on each of the mechanisms of action was conducted. The final part of the chapter described the development of a user interface to the health economic model developed in Chapter 4, that would enable a user to investigate the impact of changes in mechanisms of action without needing to change the model code.

EXPLORING THE FEASIBILITY OF CONDUCTING PRE-TRIAL HEALTH ECONOMIC MODELLING OF BEHAVIOURAL WEIGHT-MANAGEMENT INTERVENTIONS BASED ON THE EXPECTED IMPACT ON MECHANISMS OF ACTION

6.1 Abstract

Background. When designing behavioural interventions, it is recommended that the content of the intervention and the mechanisms of action targeted are clearly described, and pre-trial health economic modelling is conducted to establish the likelihood of cost-effectiveness. The aim of this study was to explore the practical feasibility of conducting pre-trial health economic modelling based on the content of the intervention and the expected effect on mechanisms of action.

Methods. Pre-trial modelling was investigated by exploring the feasibility of estimating the effect of an intervention on a mechanisms of action based on the behaviour change techniques used (Part 1) and using intervention scenarios in which there was a small, medium or large effect size on habit strength, dietary restraint or autonomous diet self-regulation (Part 2). A user interface was then developed to enable a user to input actual or estimated changes in the mechanisms of action and examine the impact on cost-effectiveness outcomes (Part 3).

Results. In Part 1, estimating change in a mechanisms of action based on a behaviour change technique was limited by the lack of quantitative evidence linking behaviour change techniques to mechanisms of action. Pre-trial modelling of interventions in Part 2 in which there were small, medium and large effect size changes in of each of the mechanisms of action resulted in cost savings ranging from £425.89 (small effect on autonomous motivation) to £1700.27 (large effect on habit strength). In Part 3 a user interface that allows users to view the impact the intervention scenarios have on BMI and cost-effective was created and published online (https://sebates.shinyapps.io/Pre-trial-modelling/).

Conclusions. Pre-trial modelling can be conducted based on estimated or expected change in mechanisms of action. This can be used to inform the design of an intervention including the behaviour change techniques included and factors that impact budget. User interfaces can be used to make pre-trial health economic modelling an easily accessible tool for use in the design of interventions. Further research on the links between behaviour change techniques and mechanisms of action will enable more accurate estimates of intervention effect and cost-effectiveness.

6.2 Background

Behavioural weight-management interventions are the first-line treatment for individuals who are overweight or obese (1). There have been many trials of a wide range of weight-management interventions and their effectiveness in terms of weight loss and weight loss maintenance varies (2, 3). To facilitate the design of effective interventions, the Medical Research Council (MRC) guidance (4) recommends that a description of the content of the intervention or methods used, and the constructs targeted, is developed in the design stage. The content of an intervention can be described as behaviour change techniques or methods, and the process through which an intervention has an impact on the outcome is often referred to as the mechanisms of action (5). Having a clearer understanding of the hypothesized relationship between the behaviour change techniques, the mechanisms of action and the desired outcomes, can inform the development and evaluation of effective behavioural interventions (6). Previous research that has made theoretical, quantitative and qualitative links between behaviour change techniques and mechanisms of action (6-8) could potentially be used to estimate change in mechanisms of action based on behaviour change techniques. Such theory driven-intervention development may increase the chances of successful behaviour change, enables generalisation of findings and evidence synthesis across similar interventions and allows testing of hypothesized relationships between the intervention, mechanisms of action and weight change (9).

Pre-trial health economic modelling is recommended to estimate the likelihood that a planned intervention is cost-effective based on an expected effect (4). Pre-trial modelling can be used to inform decisions around proceeding to trial and to make decisions about potential adjustments, such as reducing the costs using a different mode of delivery or intensity, to the planned intervention to increase the likelihood of cost-effectiveness (4). Estimated intervention effect for the purpose of pre-trial health economic modelling can be based on the results of a pilot trial (10), using the effectiveness of previous interventions (explored in subsequent chapter) or by examining the impact of a percentage reduction of risk of a health condition (11). Pre-trial modelling based on the estimated impact on mechanisms of action which, based on MRC guidelines would be considered as part of the design process, would be specific to the content of a planned intervention and could be conducted before a pilot trial. This would also inform more specific adjustments to be made to a planned intervention, such as adding or removing certain behaviour change techniques based on expected

associated costs and effectiveness (impact on mechanisms of action and weight). Previously, this would be challenging due to the lack of consideration of psychological factors in health economic models (Chapter 2) (12).

As outlined in Chapter 4, a health economic model of obesity was adapted to include three psychological variables, or mechanisms of action; namely, habit strength, dietary restraint and autonomous diet self-regulation. This was based on a mediation analysis in which changes in habit strength, dietary restraint and autonomous diet self-regulation mediated the impact of a weight-management intervention on BMI (Chapter 3) (13). The relationships between these mechanisms of action and BMI were programmed into the School of Public Health Research (SPHR) health economic model (14) which allowed the intervention effect to be inputted in the model through change in these three mechanisms of action. Testing of this model in Chapter 4 showed that BMI trajectory, and long-term costs and effectiveness could be estimated from change in these three mechanisms of action and suggested that there may be the potential to use the model for pre-trial modelling based on expected change in mechanisms of action.

One factor that may limit the use of pre-trial modelling in intervention design is the complexity of health economic models, especially for public health-related interventions. Health economic models of obesity are often complex (12, 15) and may be difficult to navigate without specific knowledge of health economic modelling methods. Although larger trials may have involvement of health economists, smaller trials may not which may prevent pre-trial health economic modelling. The software used to develop the models may also present a barrier; representation of the complexity of the causes and consequences of obesity can require certain software that is less widely used. However, the development of user interfaces such as R Shiny (16), which enables a user to interact with the model without needing to directly edit the code, has the potential to make pre-trial health economic modelling more accessible.

The overall aim of the current study was to examine how a health economic model can be used in practice to conduct pre-trial modelling based on change in mechanisms of action. This was divided into three parts. In Part 1, the aim was to estimate the effect of a behaviour change technique on a mechanisms of action to determine if it was feasible to conduct pre-trial modelling of a hypothetical planned intervention based on

behaviour change techniques used. The aim of Part 2 was to examine the impact of interventions scenarios in which there was either a small, medium or large effect on each of the mechanisms of action. The aim of Part 3 was to develop a user interface to the model that would enable a user to investigate the impact of changes in mechanisms of action without needing to change the model code.

6.3 Part 1. Estimating the effect of behaviour change techniques on a mechanisms of action

One potential method of pre-trial modelling of a planned intervention is to estimate the impact on mechanisms of action based on the planned content of the intervention and the behaviour change techniques used. For this, ideally quantitative evidence of the magnitude of impact of a specific behaviour change technique on mechanisms of action is required. Therefore the aim of this part of the study was to investigate the feasibility of estimating the effect of an intervention on a mechanisms of action based on the behaviour change techniques used. For simplicity, the objective was to identify a single behaviour change techniques and associated impact on a mechanism of action. Because dietary restraint, habit strength and autonomous diet self-regulation are the mechanisms in the health economic model, these were the focus on the search.

6.3.1 Method

Linking behaviour change techniques to mechanisms of action

Figure 6.1 shows the process of pre-trial modelling based on specific behaviour change techniques (a) and the methodological steps to test the feasibility of conducting pre-trial modelling in this way (b).

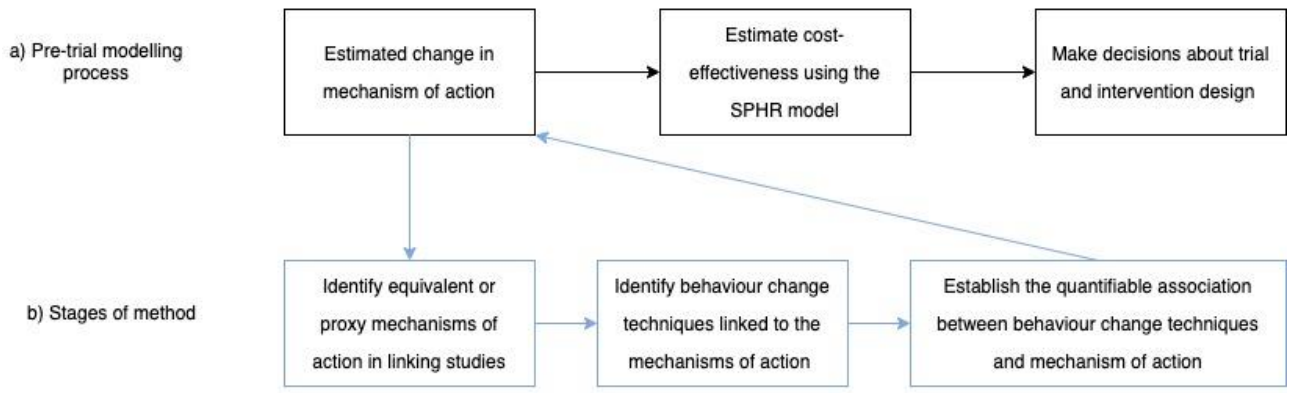

Figure 6.1. Pre-trial modelling process

Current literature was examined to estimate the impact of behaviour change techniques on one more of the mechanisms of action. Understanding the effectiveness of behaviour change techniques has been identified as a gap in the literature. A collection of journal articles (Health Psychology Review) dedicated to behaviour change interventions and mechanisms of action, together indicated that mechanisms are not routinely collected or analysed in primary research studies or in systematic reviews and meta-analyses (17). However, three articles (6-8), identified in a summary of the field of research (17), have aimed to collate research the primary research, theory and expert opinion. These studies were identified as efforts to create "a database of mechanisms of action that can be used to provide better descriptions of intervention mechanism in primary research, and synthesis of findings on intervention mechanisms across studies" (17). The citations of the three linking studies (6-8) were searched for other reviews that summarised studies that attempted to establish the mechanism of an intervention, but no further reviews were identified. Of the three linking studies, two are from the same study team, and examined links between behaviour change techniques and mechanisms of action identified in the literature (8), links between behaviour change techniques and mechanisms of action agreed upon by experts in the field of behaviour change (6). The third paper outlines an intervention mapping approach in which behaviour change methods are defined and linked to determinants of behaviour change (7).

These reviews were used to identify a behaviour change technique that will target one or more of dietary restraint, habit strength and autonomous diet self-regulation and to quantify the impact. There were three stages (Figure 6.1). These three variables (dietary restraint, habit strength and autonomous diet self-regulation) are included in a health economic model, but these specific mechanism of action were not in the linking studies. Therefore the first stage was to identify the mechanisms of actions in the linking studies that are equivalent to, or can be used as proxies, for the three variables in the health economic model. The second stage was to identify the behaviour change techniques that have been linked to these mechanisms of action identified in the first stage. The third stage was to examine the research that the linking studies reference to support the links made between the mechanisms of action to determine if there was a quantitative link that can be used to conduct pre-trial modelling. For the link between a behaviour change technique and mechanisms of action to be used for pre-trial modelling, there needs to be a quantitative association between the two and the effect needs to be translatable to an effect change in the mechanisms of action in the model.

6.3.2 Results and Discussion

The mechanisms of action in the model (habit strength, dietary restraint and autonomous diet self-regulation) were matched to mechanisms of action in the three linking studies (6-8) based on the definitions. Habit was matched to behavioural cueing (6, 8) and habitual, automatic and impulsive behaviours (7). Dietary restraint was matched to behavioural regulation (6, 8) and to methods to change skills, capability, and self-efficacy and to overcome barriers (7). Autonomous diet self-regulation was matched to motivation (6, 8). The mechanisms of action, defined in the linking studies (6-8), that most closely match definitions the mechanisms of action in the model are in Table 6.1.

Table 6.1. Equivalent or proxy mechanisms of action identified in the linking papers (6-8) for the three mechanisms of action in the health economic model (habit strength, dietary restraint and autonomous diet self-regulation)

Mechanisms of action		
Health economic model	Expert consensus study (6), Synthesis of links described in published intervention literature (8)	Intervention mapping approach (7)
Habit strength	Behavioural Cueing: processes by which behaviour is triggered from either the external environment, the performance of another behaviour, or from ideas appearing in consciousness	Habitual, Automatic and Impulsive Behaviours
Dietary restraint	Behavioural Regulation: behavioural, cognitive, and/or emotional skills for managing or changing behaviour;	Change Skills, Capability, and Self-Efficacy and to Overcome Barriers
Autonomous diet self-regulation	Motivation: processes relating to the impetus that gives purpose or direction to behaviour and operates at a conscious or unconscious level	No clear match for mechanisms of action was found.

Behaviour change techniques that were hypothesized to act on each of the mechanism of actions (in columns two and three of Table 6.1) in the three linking studies (6-8) are shown in Table 6.2. Definitions of all behaviour change techniques are in Supplementary Material, Table 6.7. In some cases, the same behaviour change technique was given different labels across the reviews. Where descriptions overlap, these are shown in Supplementary Material, Table 6.7.

Table 6.2. Theorised links between behaviour change techniques and mechanisms of action in the three linking studies; an expert consensus study (6), a synthesis of links described in published intervention literature (8) and an intervention mapping approach (7)

	Habit strength Behavioural Cueing (6,8) Habitual, Automatic and Impulsive Behaviours (7)	Dietary restraint Behavioural Regulation (6,8) Change Skills, Capability, Self-Efficacy (7)	Autonomous diet self-regulation Motivation (6,8)[a]
Behaviour change techniques identified in more than one paper	▪ Prompts/cues (6,8), stimulus control (7) ▪ Habit formation (6,8) ▪ Avoidance/reducing exposure to cues for behaviour (6), cue altering (7)	▪ Reducing negative emotions (6), improving physical and emotional states (7) ▪ Problem solving (6), planning coping responses (7)	▪ Pros and cons (6,8)
Behaviour change techniques in one study only	*Synthesis of links in literature (8)* None *Expert consensus study (6)* Information about antecedents, restructure social environment, prompts/cues, adding objects to environment, restructuring physical environment *Intervention mapping approach (7)* Deconditioning, counterconditioning, implementations intentions, planning coping responses, early commitment, public commitment, training executive function	*Synthesis of links in literature (8)* Self-monitoring, action planning, goal setting, habit reversal, behaviour substitution, discrepancy between behaviour and goals, self-monitoring of outcomes of behaviour, habit formation *Expert consensus study (6)* None *Intervention mapping approach (7)* Guided practice, enactive mastery experiences, verbal persuasion, reattribution training, self-monitoring of behaviour, provide contingent rewards, cue altering, public commitment, goal setting, set graded tasks	*Synthesis of links in literature (8)* Mental rehearsal of successful performance, identity associated with behaviour change, self-incentive *Expert consensus study (6)* Social reward, information about social and environmental consequences, comparative imagining of future outcomes, commitment, goal setting (behaviour), non-specific reward (outcome) *Intervention mapping approach (7)* None

[a]No match for Autonomous diet self-regulation was found in the intervention mapping approach linking paper (7)

Several behaviour change techniques were theorised to act on one or more of the three mechanisms of action. Figure 6.2 shows the behaviour change techniques that were linked with a mechanism of action in more than one of the three linking papers (6-8). In some cases the behaviour change techniques were labelled differently across studies despite having similar descriptions and so both labels are shown. There were six links between a behaviour change technique and a mechanisms of action that were identified more than one linking study. Full definitions for all behaviour change techniques are in Supplementary Material, Table 6.7.

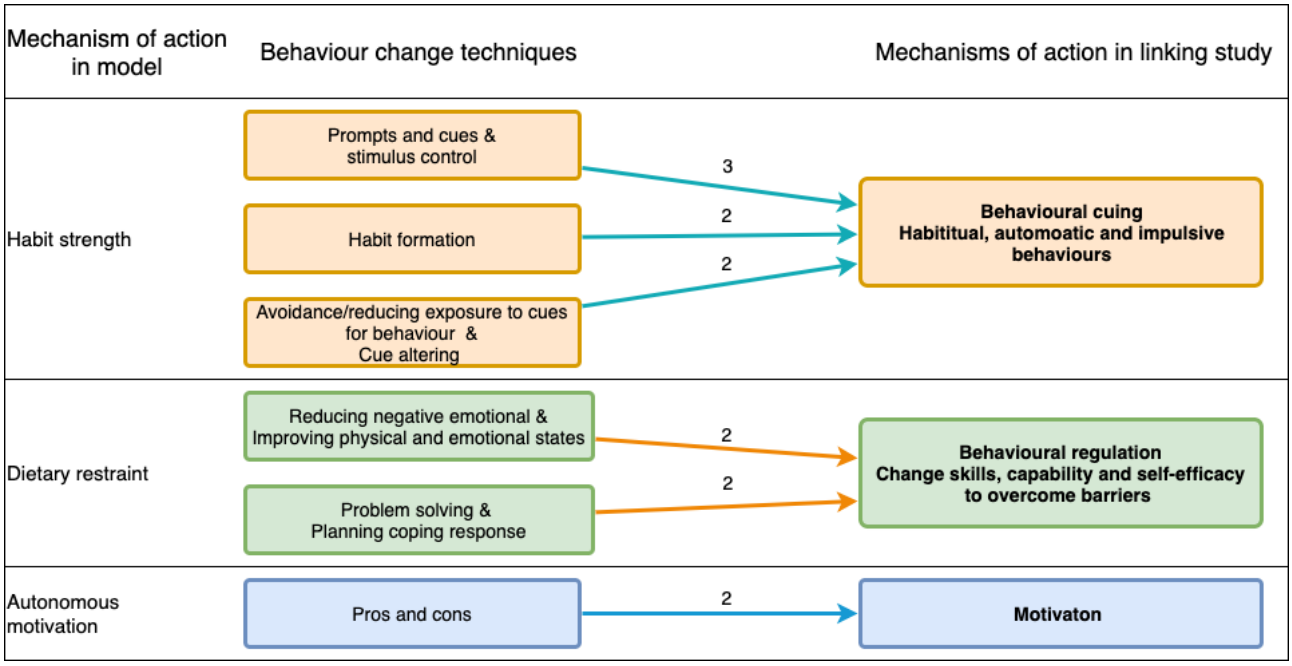

Figure 6.2. Theorised links made between behaviour change techniques and mechanisms of action in linking studies (6, 7)

Habits (represented as behavioural cueing (6, 8) or habitual, automatic and impulsive behaviours (7)) was identified as a mechanism of action for prompts and cues in both the review of the literature (8) and in the expert consensus studies (6). It was also identified as a mechanisms for stimulus control, a behaviour change techniques which has a similar definition to prompts and cues, in the intervention mapping study (7). This was the only link between a behaviour change technique and mechanism of action that was identified by all three linking studies. The details of the empirical evidence sources referenced by the studies linking the prompts and cues to habits are listed in Table 6.3. The evidence supporting the links between behaviour change techniques and mechanisms of action that were identified by two out of the three papers were also examined (Supplementary Material, Table 6.8).

Table 6.3. Studies referenced by linking studies to support the links made between prompts and cues or stimulus response (behaviour change techniques) to behavioural cueing or habitual, automatic and impulsive behaviours (mechanism of action)

Author and year	Behavioural target	Population	Implementation of BCT	Mechanisms of Action	Results (evidence of link)	Quantifiable association
Aruajo-soares et al 2009 (18)	Physical activity	Adolescents (mean age 12)	No intervention	Action planning and coping planning	No main effects for action planning or coping planning were found. The combination of high levels of action planning and coping planning is associated with increases in physical activity.	✗
Chin a Paw et al. 2008 (19)	Consumption of sugar containing beverages	Adolescents (mean age 13)	Posters near food access points and changing canteen assortment	Habit	Attitude and habit strength were significant mediators of the intervention's effect on sugar containing beverages consumption among boys	✗
Maranda et al., 2015 (20)	Improved glycaemic control	Adolescents (mean age 14)	Instructed participants to associate pet care duties with diabetes self-management tasks	Automaticity	No measurement of mechanisms of action	✓
Matei et al., 2015 (21)	Reduce sitting time, increase activity	Adults (60-75 years old)	Offering tips and rationale for undertaking physical activity in a way that would build physical activity habits, planning ahead, tracking progress, "start low, go slow"	Habit formation	No clear pattern in habit scores across the intervention	✗
Prestwich et al. 2009 (22)	Increase exercise frequency	University students	Text message prompts to remind of intentions to exercise	Habits	The intervention with prompts were paired with implementation intervention results in greater behaviour change than implementation intention alone	✗
Vik et al., 2015 (23)	Reducing and breaking up sitting time at home	Children (10-12 years old)	Posters of things to do during breaks, ideas for remembering to take breaks, teacher reminds pupils to get out quickly for recess.	Automaticity	Intervention not effective	✗

In summary, there were six studies referenced by the linking studies (6-8) that linked the behaviour change techniques (labelled as prompts and cues (6, 8) or stimulus control (7)) to habit strength (represented as behavioural cueing (6, 8) or habitual, automatic and impulsive behaviours (7)). Of the six studies (Table 6.3) referenced by the linking studies (6-8), two studies (20, 22) didn't measure the mechanisms of action that the behaviour change techniques was hypothesised to target. In one study the specific mechanisms of action, defined as action and coping planning (18), was associated with physical activity but there was no intervention so this couldn't be linked with any behaviour change technique.

In three studies (19, 21, 23) the mechanisms of action that the intervention was hypothesised to target, were measured. Of these three, there were two studies in which there was no reported impact on the mechanisms of action. These intervention both aimed to reduce sitting time for children (23) or adults (21) but there was no impact on automaticity (23) or habit strength (21) respectively. In the third study, the intervention had a significant impact on habit strength; habit strength was a mediator of a change in consumption of sugar containing beverages among boys (19). In this study it was hypothesised that the intervention would target habits through the use of posters with suggestions for healthier choices near points of purchase and encouraging schools to make adjustments to canteens such as offering smaller portion size (e.g. cans instead of bottles) and restricting access to vending machines. The intervention was associated with a reduction of habit strength for consuming sugar containing beverages which was associated with a lower consumption of sugar containing beverages (in ml/day). Although this study provided evidence of a link between two behaviour change techniques and a mechanisms of action, the aim of the intervention was to decrease habit strength for drinking sugar containing beverages rather than increase the strength of healthy habits. Therefore, translating the impact of the behaviour change techniques (posters and canteen rearrangement) to a change in habit strength in reference to healthy eating habits was not possible to do reliably as the impact on consumption of healthy food was not measured. To translate this reduction in habit strength for a sugar containing beverage to increase in habit strength of healthy eating would require an assumption about how the magnitude of effect of a behaviour change techniques of reducing habit strength for an unhealthy behaviour compared to increasing habit strength of a healthy behaviour.

6.4 Part 2. Pre-trial modelling of interventions scenarios in which there was either a small, medium or large effect on a mechanism of action

The evidence supporting the impact of behaviour change techniques on mechanisms of action is currently limited and therefore estimating the specific magnitude of change in mechanisms of action may be unreliable. The aim of Part 2 was to estimate the impact of small, medium and large changes in each mechanism of action on BMI and long-term costs and QALYs. This could inform the design of an intervention, in particular, by comparing estimated outcomes with expected costs, decisions can be made regarding content and factors influencing budgets.

6.4.1 Method

Testing nine intervention scenarios

Scenarios in which an intervention had a small, medium or large effect on one of each of the mechanisms of action (i.e. habit strength, dietary restraint or autonomous motivation) were tested. The effect size was based on Cohen's d calculation.

The scenarios in which an intervention had a small, medium or large effect on one of each of the mechanisms of action was implemented by altering the coefficients in the mediation analysis of the WRAP trial (Chapter 3) which informed model development (Chapter 4). In the WRAP trial, participants with a BMI of 28 or over were randomly assigned to either a brief intervention (booklet on how to lose weight), a 12-week referral to WW or a 52-week referral to WW. Participants assigned to the 12- and 52-week weight-management programmes lost significantly more weight than the brief intervention at 3 and 12 months. Participants assigned to the 52-week programme lost significantly more weight than those assigned to the 12-week programme and the brief intervention at 12 and 24 months. The full results are reported in Ahern et al (36). In a mediation analysis of this trial data (see Chapter 3), habit strength, dietary restraint and autonomous diet self-regulation mediated the effect of both the 12- and 52-week intervention on change in BMI; increases in habit strength, dietary restraint and autonomous diet-self regulation were associated with decreases in BMI. Both the 12- and 52-week interventions were associated with a greater increase in habit strength and dietary restraint than the brief intervention. Although a decrease in autonomous diet-self regulation was observed in all treatment

groups, the 12- and 52-week interventions was associated with a smaller decrease in autonomous diet self-regulation when compared to the brief intervention.

In the mediation analysis of the WRAP trial, each of the mechanisms of action was fitted to a quadratic curve of score on mechanisms of action across 4 time points (baseline and 3, 12, and 24 months). There were three growth factors, intercept, slope and quadratic for each mechanisms of action. The slope and quadratic factors described the change from baseline, and these were both conditional on age, gender and treatment for all three mechanisms of action. Table 6.4 shows the coefficients for each mechanism of action determined in the original mediation analysis.

Table 6.4. Coefficients for the slope of quadratic for each mechanisms of action and BMI in the original mediation analysis

Coefficients	Habit strength		Dietary restraint		Autonomous motivation	
	Slope	Quadratic	Slope	Quadratic	Slope	Quadratic
Constant	0.835	-0.230	2.681	-0.840	-1.150	0.343
Age	0.003	0.001	0.006	-0.002	0.012***	0.005**
Gender	0.047	-0.023	-0.877***	0.284***	-0.255*	0.093
Treatment (12-week)	0.305*	-0.128**	0.926***	-0.361**	0.265	-0.061
Treatment (52-week)	0.482***	-0.186***	1.494***	-0.507***	0.418*	-0.143*

In the intervention scenarios tested, the treatment coefficients for the mechanisms of action were altered to reflect a small, medium and large changes in the mechanisms of action. Table 6.5 shows the mean treatment coefficients for the slope and quadratic for each intervention scenario. Age and gender coefficients were the same as in the original mediation analysis (Table 6.4). In each scenario, it was assumed that a single mechanism of action was changed. Figure 6.3 shows graphs of the trajectories each of the predicted mechanisms of action in each scenario alongside the trajectory for the brief intervention.

Table 6.5. Treatment coefficient for the slope and quadratic growth factors for each mechanisms of action and each intervention scenario (small, medium and large effect size).

Treatment scenario	Habit strength		Dietary restraint		Autonomous motivation	
	Slope	Quadratic	Slope	Quadratic	Slope	Quadratic
Habit strength						
Small	0.40	-0.13	0	0	0	0
Medium	0.74	-0.20	0	0	0	0
Large	1.12	-0.28	0	0	0	0
Dietary restraint						
Small	0	0	1.03	-0.33	0	0
Medium	0	0	1.99	-0.55	0	0
Large	0	0	3.06	-0.82	0	0
Autonomous motivation						
Small	0	0	0	0	0.38	-0.12
Medium	0	0	0	0	0.70	-0.17
Large	0	0	0	0	1.25	-0.37

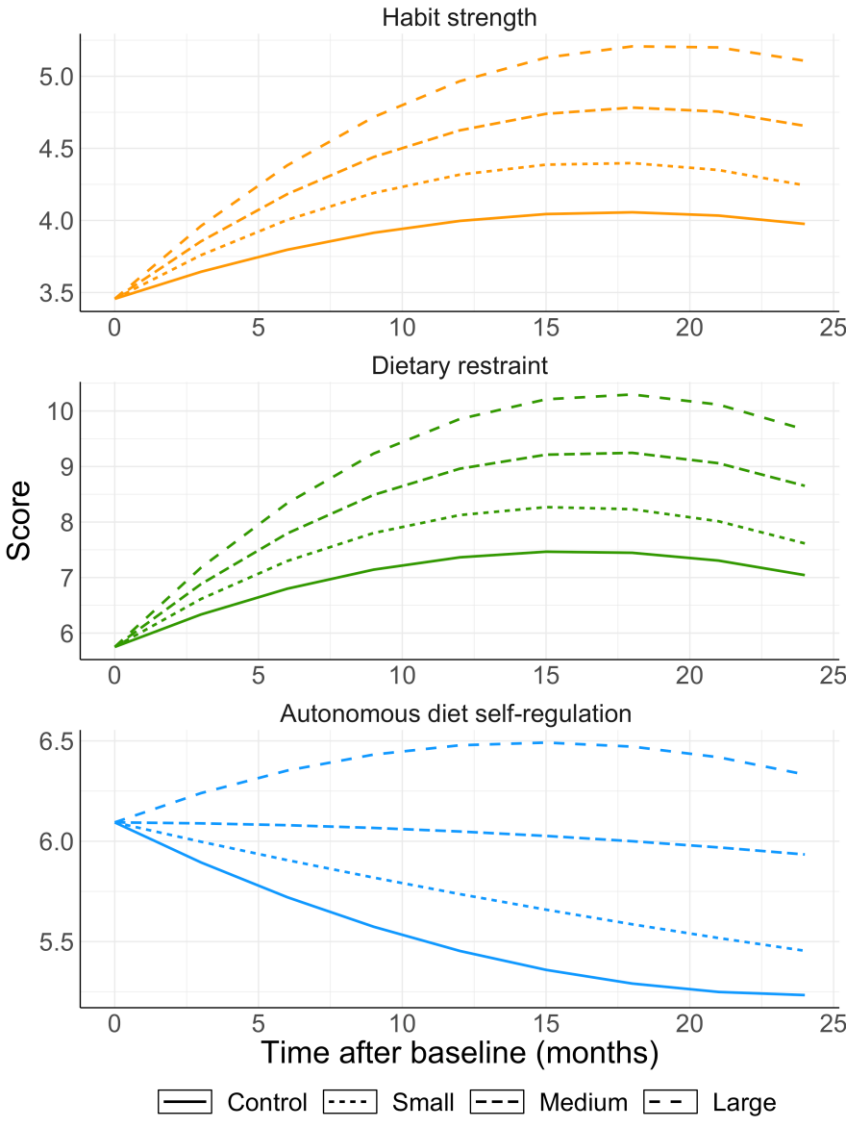

Figure 6.3. Trajectory of mechanisms of action in each intervention scenario

Health economic modelling

The School of Public Health research (SPHR) health economic model was adapted to include the three mechanisms of action (habit strength, dietary restraint and autonomous diet self-regulation) such that change in BMI was partly conditional on the change in these mechanisms of action. Full details of the SPHR health economic model and how this model was adapted to include the three mechanisms of action have been described previously in Chapters 4 and 5. Briefly, using the results from the mediation analysis of the WRAP trial, the relationships between the mechanisms of action and BMI were programmed into the SPHR health economic model such that change in BMI over the first two years is conditional on change in habit strength, dietary restraint and autonomous diet self-regulation as well as baseline demographic factors. There was also a direct effect of the intervention on BMI based on the original mediation analysis (Chapter 3). This allowed the intervention effect to be inputted in the model through change in these three mechanisms of action rather than simply change in BMI. A comparison of inputting intervention effect via change in BMI directly to entering intervention effect as change in mechanisms of action resulted in equivalent estimates of BMI. In summary, this health economic model enables change in habit strength, dietary restraint and autonomous diet self-regulation to be translated into a change in BMI and long-term healthcare-related costs and benefits (measured in Quality Adjusted Life Years; QALYs).

Outcomes

The outcomes of interest of the nine intervention scenarios were BMI, and lifetime costs and QALYs. The costs and QALYS of each scenario were compared to the brief intervention from the WRAP trial and incremental costs and QALYs were calculated. This brief intervention was used as a comparison group as it was the control group in the WRAP intervention and so the change in the mechanisms of action were measured. Justifiable cost was also calculated. The justifiable cost is the amount that can be spent on an intervention with the effect tested in the scenario for the intervention to be cost-effective assuming a certain cost-effectiveness threshold. In the UK, the National Institute for Health and Care Excellence (NICE) threshold, over which treatments are less likely to be recommended for use in the NHS, is typically between £20,000 and £30,000 per QALY and therefore justifiable cost was calculated at these values as well as a willingness to pay of £0 which means that the intervention has to save at least as much as it costs (i.e. intervention is cost saving). Justifiable cost is calculated as the (willingness to pay threshold x incremental QALYs) – Incremental costs.

6.4.2 Results and discussion

The mean BMI at years 1 and 2, costs and QALYs, incremental costs and QALYs and justifiable cost compared to the brief intervention for each scenario are in Table 6.6. In all scenarios, the mean BMI was lower at two years than at baseline which indicates that even a small change in mechanism of action results in a decrease in BMI. Comparing the mechanisms of action, the impact of the small, medium and large effects of autonomous diet self-regulation on BMI are smaller than the equivalent effect sizes in habit strength and dietary restraint. The impact of small, medium and large changes in habit strength on BMI are similar to equivalent effect sizes in dietary restraint. A large change in autonomous diet self-regulation has a similar impact on BMI as a small change in habit strength or dietary strength.

The incremental costs and QALYs of each probabilistic sensitivity analysis are shown on a cost-effective plane in Figure 6.4. The differences in incremental costs and QALYs between the small, medium and large effect size is smaller for autonomous diet self-regulation than for habit strength and dietary restraint. The incremental costs and QALYs for habit strength and dietary restraint are similar. There was slightly more uncertainty in the cost-effectiveness for habit strength compared to dietary restraint and autonomous diet self-regulation.

The findings in Figure 6.4 and Table 6.6, show that even a small intervention effect on any one of the mechanisms of action has a large justifiable cost; the lowest justifiable cost was £425 for a cost saving intervention. Furthermore, the findings indicate that interventions that are able to achieve a large change in mechanisms of action would result in large changes in BMI and high costs savings (up to £1700). Across effect sizes, the largest justifiable costs were associated with changes in habit strength and the lowest justifiable costs were associated with autonomous diet self-regulation. While this indicates that behaviour change techniques that target habit strength and dietary strength should be prioritised, it was assumed that the mechanisms of action change independently and it's not known how increases in autonomous diet-self regulation would impact or be impacted by change in habit strength and dietary restraint. It is also not known from these scenario, how achievable the changes in each of the mechanism are and the cost of implementing behaviour change techniques that could result in the effect sizes in the scenarios. For example, although a large change in autonomous diet self-regulation is similar to a small change in habit, the large change in motivation

may be achieved at a smaller cost. Therefore the justifiable cost can be compared to the expected costs of behaviour change techniques to make decisions about the content of the intervention.

Table 6.6. Change in BMI and costs and QALYs associated with each scenario

Intervention scenarios	Mean BMI			Lifetime NHS & social care Costs (£)	Lifetime QALYs	Incremental versus brief intervention		Justifiable cost (£) at willingness to pay per QALY of:		
	Year 1	Year 2	Change from baseline to year 2			Costs	QALYs	£0 (cost-saving)	£20000	£30000
Brief intervention	33.29	33.73		28,849.15	10.7948					
Habit strength										
Small	32.40	31.96	-2.14	28070.37	10.8621	-778.78	0.0673	778.78	2124.69	2797.65
Medium	31.64	30.45	-2.90	27620.17	10.9038	-1228.98	0.1090	1228.98	3408.06	4497.61
Large	30.80	28.76	-3.74	27148.87	10.9471	-1700.27	0.1522	1700.27	4745.22	6267.69
Dietary restraint										
Small	32.47	32.10	-2.07	28112.83	10.8582	-736.31	0.0634	736.31	2004.69	2638.87
Medium	31.73	30.63	-2.81	27669.40	10.8991	-1179.74	0.1043	1179.74	3266.38	4309.7
Large	30.87	28.89	-3.67	27181.05	10.9443	-1668.1	0.1495	1668.1	4657.51	6152.22
Autonomous diet self-regulation										
Small	32.97	33.09	-1.57	28423.25	10.8294	-425.89	0.0345	425.89	1116.76	1462.2
Medium	32.73	32.62	-1.81	28273.94	10.8435	-575.2	0.0487	575.2	1548.21	2034.72
large	32.29	31.75	-2.25	28003.38	10.8684	-845.77	0.0736	845.77	2316.83	3052.36

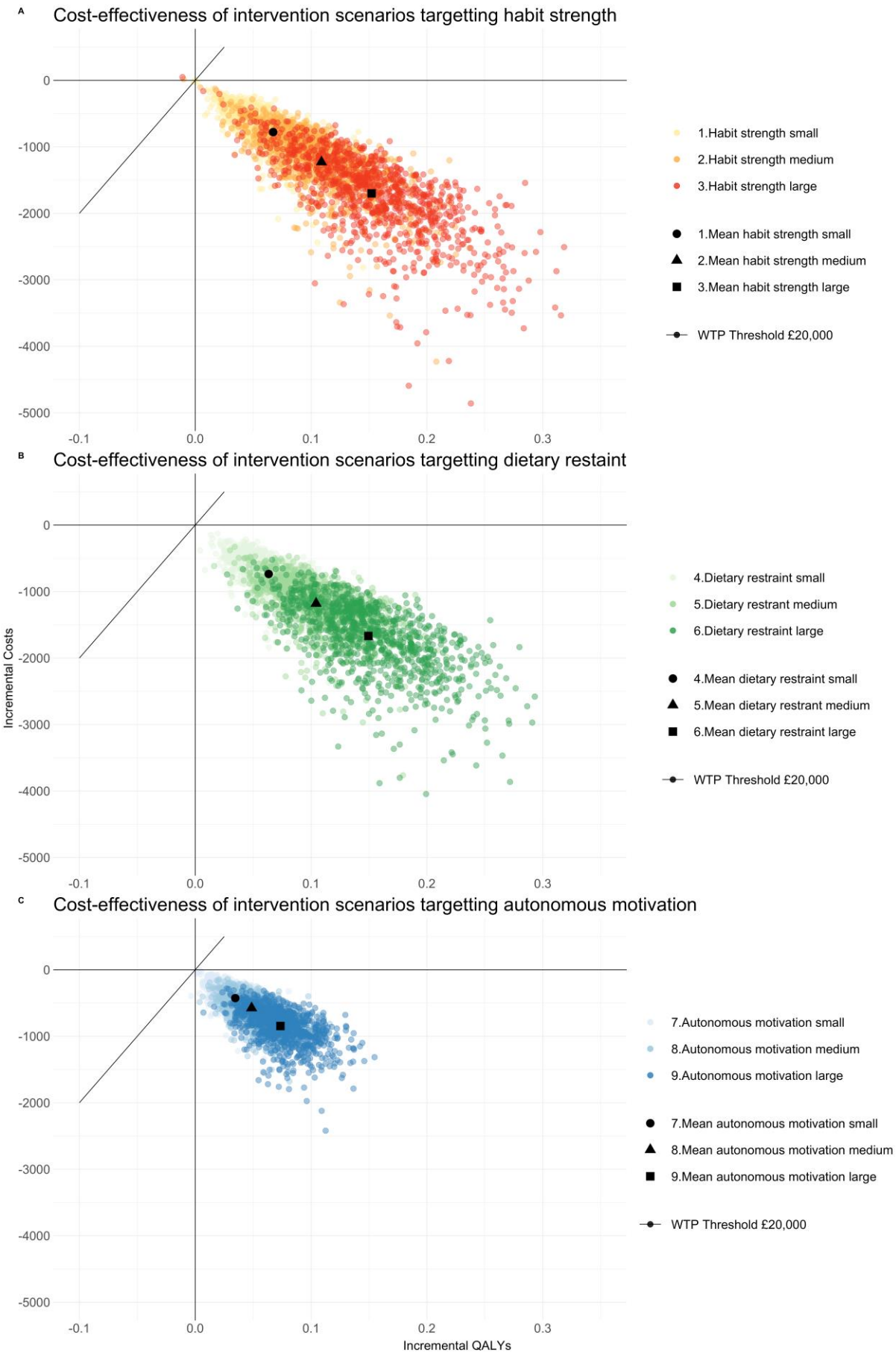

Figure 6.4. Cost-effectiveness plane of the nine scenarios

6.5 Part 3. Developing an R shiny user interface for the SPHR health economic model

Pre-trial health economic modelling is recommended when designing an intervention. However, conducting the health economic modelling may require an understanding of the health economic model and the software used. The model used in Part 2 was the SPHR health economic model and this was developed using R. A recent development in R is the shiny package which enables development of a user interface (16). The user interface allows a user to select a range of inputs and see the outputs. The aim of this part of the study was to develop a user interface for the SPHR health economic model used to conduct the pre-trial modelling outlined in Part 2.

6.5.1 Method

A user interface was created using R Shiny. R Shiny 'apps' have two main parts; a user interface and the server. The user interface allows the user to enter selected inputs and specifies what outputs are displayed. The server part takes those inputs and runs designated functions with these input values and the results generated are then used to form the outputs which are displayed in the user interface.

Modifiable inputs

The user interface enables users to enter change in the three mechanisms of action; habit strength, dietary restraint and autonomous diet self-regulation. In the initial version of the user interface, users were able to use sliders to enter a value for each mechanisms of action. The end year, the length of the time horizon of the model, and the probability sensitivity analysis (PSA) count was also modifiable in this initial version of the user interface. The user was able to select an end year, a number of PSA runs and a value for habit strength, dietary restraint and autonomous diet self-regulation and then run the model using these inputs. However, the model took many hours to run which limited interactivity of the user interface. Furthermore, restrictions on the use and storage of the data and the health economic model prevents it from being stored on an external server, which is required for online publication. Therefore, a second version of the user interface was created which would enable the user to select one of the scenarios that were run in Part 2; i.e. small, medium and large effect sizes in either habit strength, dietary restraint or autonomous diet self-regulation.

Outputs displayed

The outputs displayed are mean BMI trajectory over the first 6 years for the brief intervention and intervention groups (graph); at 6 years it is assumed that the control and intervention groups are following the trajectory that they would have followed in the absence of an intervention. This is the base case assumption in the model and is supported by a meta-analysis which indicated that weight was regained after around 5 years. While there are limitations to this assumption which were discussed in Chapter 2, and alternative assumptions can be made such as those in Chapter 4, the impact of intervention of the mechanisms of action over 2 years was the focus on the scenarios and so the base case assumption was kept the same for simplicity. The total and incremental costs and QALYs are displayed in a table. The incremental costs and QALYs for each PSA was displayed with a cost-effectiveness plane to show the uncertainty around the cost-effectiveness. There were additional figures that show the number of diabetes cases, cardiovascular cases and diabetes complications that were averted as a result of the planned intervention compared to the control intervention. These conditions were chosen as they are the conditions that are impacted most by changes in BMI. The user interface would also provide justifiable cost estimates assuming an ICER of £0 (cost-saving intervention), £20,000 and £30,000 (acceptable ICER in the UK). The interface also has an option to download the PSA results to an excel spreadsheet.

6.5.2 Results and discussion

The R code for first iteration of the user interface is available in a GitHub repository (https://github.com/sebates1/thesis). The second iteration which enables a user to select and view the outcomes of a single scenario is deployed online and can be found here: https://sebates.shinyapps.io/Pre-trial-modelling/ and screenshot are shown in Figures 6.5 to 6.7. The inputs are limited to the scenarios tested in study two and full code for this including the results are stored here: https://github.com/sebates1/thesis. This user interface does not allow users to interact with model directly and so does not satisfy the aim of the study. However, it enables quick interaction with model results without requiring a detailed understanding of the model code and is published online and therefore is accessible to anyone who wants to access it. Although the user interface is limited to pre-trial modelling of three mechanisms of action, it demonstrates how a user interface allows interaction with the results of pre-trial heath economic modelling.

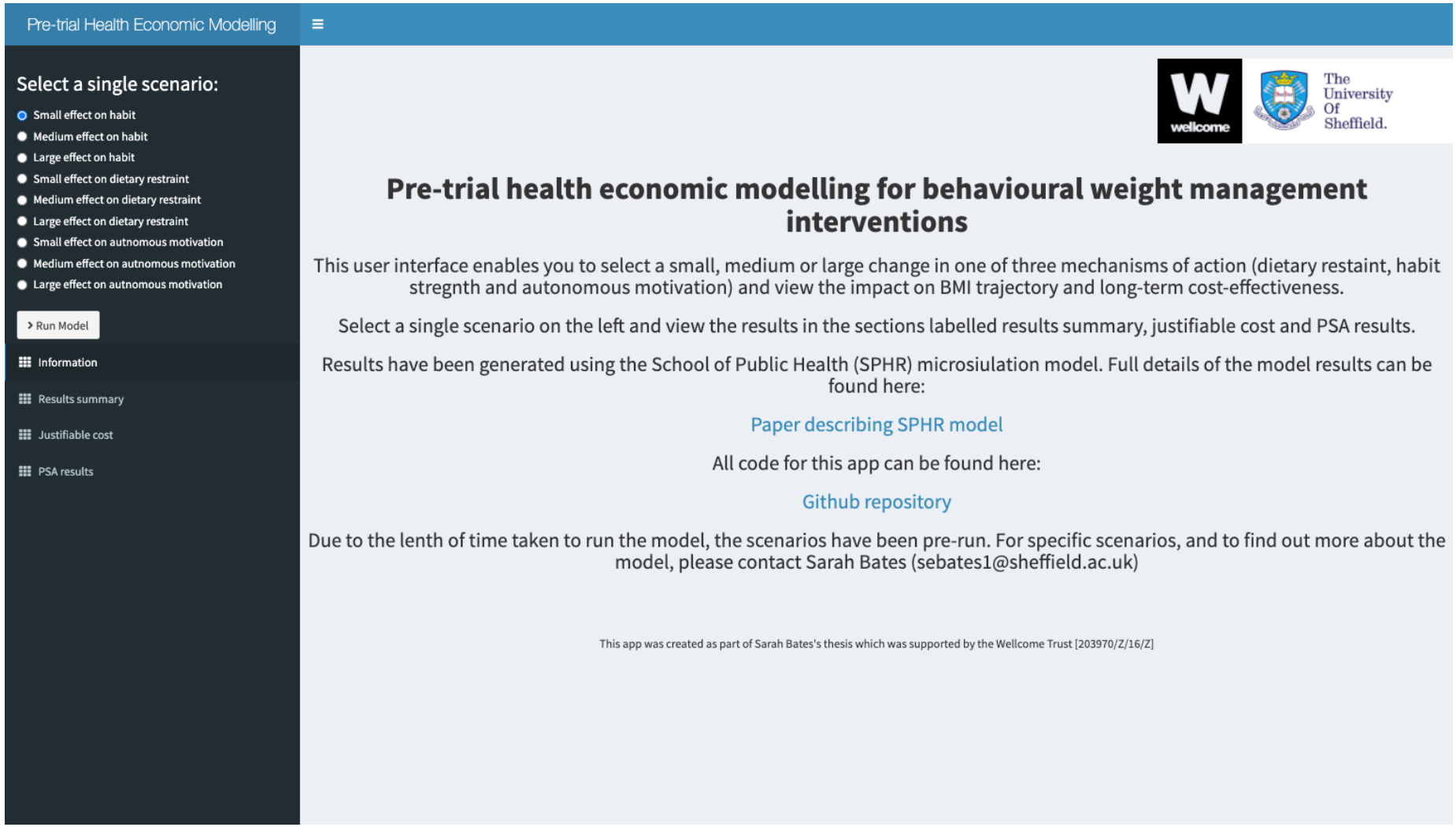

Figure 6.5. Screenshot of front page of user interface

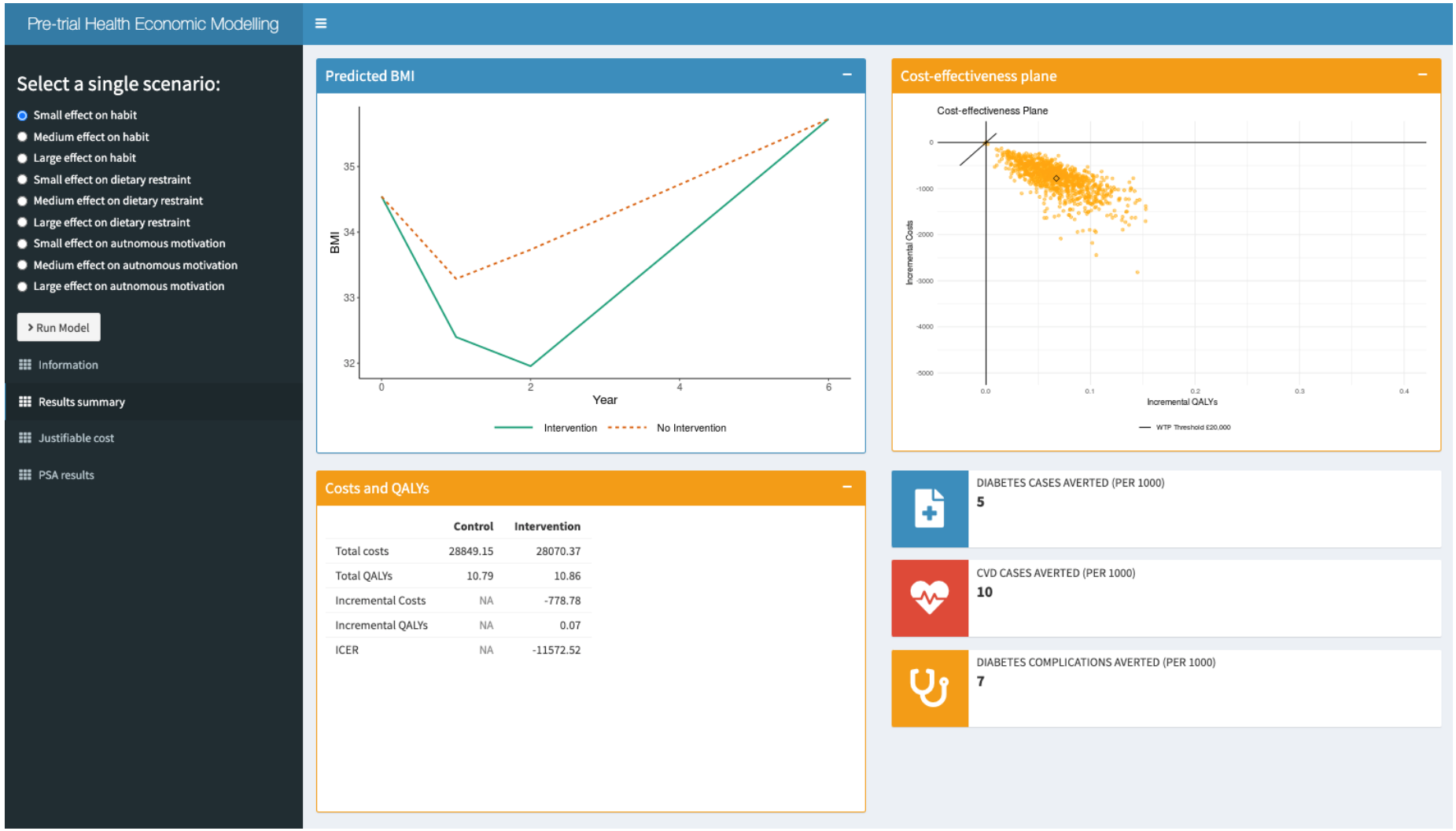

Figure 6.6. Screenshot of results summary part of user interface

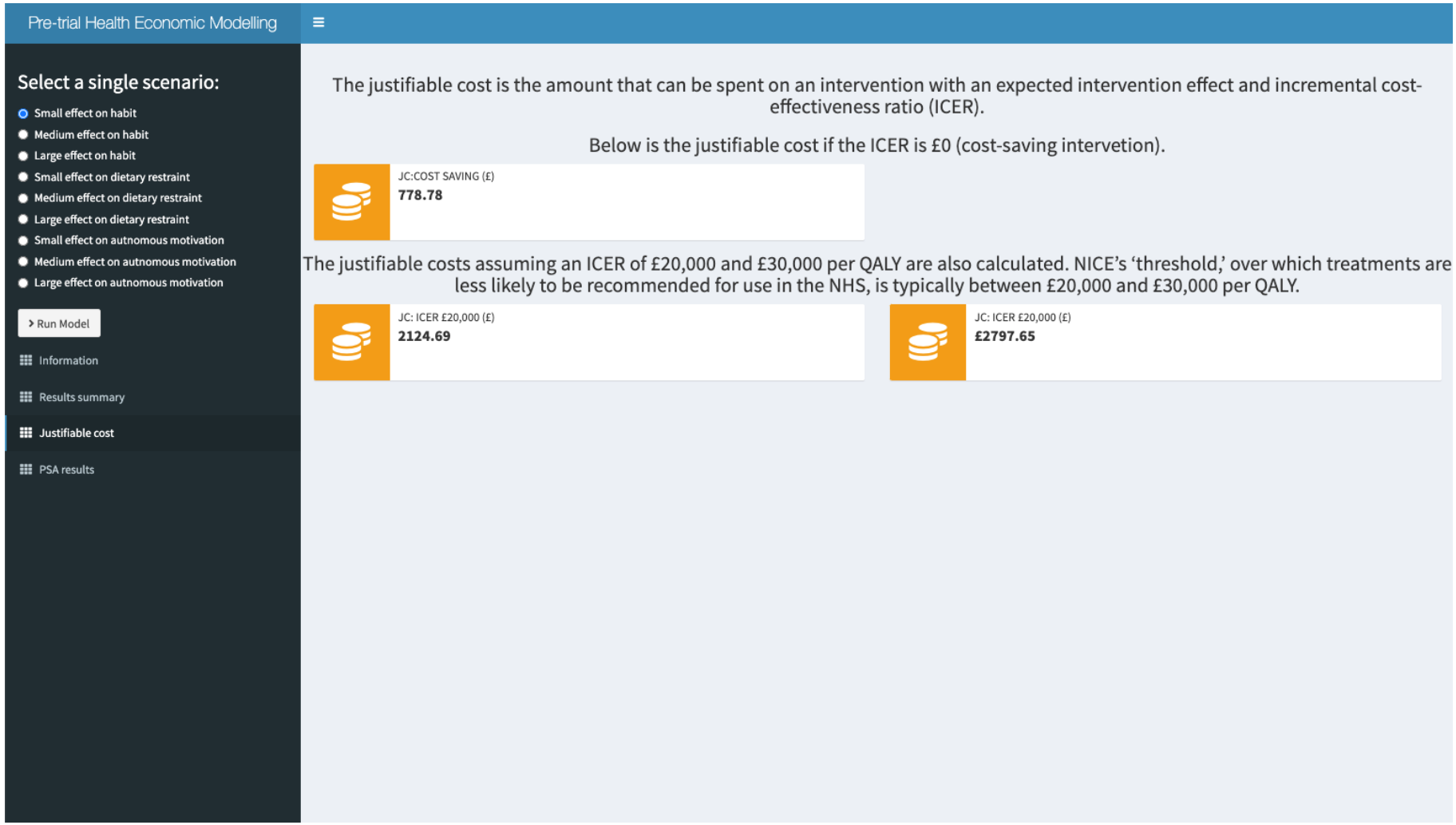

Figure 6.7. Screenshot of justifiable cost part of user interface

6.6 Discussion

6.6.1 Key findings

The overall aim of the current study was to examine the practical feasibility of pre-trial health economic modelling of behavioural weight-management interventions based on change in mechanisms of action. Pre-trial modelling was conducted, and a user interface was created. Estimating a change in a mechanism of action based on the behaviour change technique was limited in the first part of the study, by a lack of quantitative links between behaviour change techniques and mechanisms on action in the literature. However, pre-trial modelling of the hypothetical intervention scenarios, in the second part of the study, in which either habit strength, dietary restraint or autonomous diet self-regulation were successfully targeted in a weight-management intervention scenario indicated that these interventions would be cost saving at costs ranging from £425 (small effect on autonomous diet self-regulation) to £1700 (large effect on habit strength). In the third part of the study, a user interface was generated and published online which enables researchers to view the results of the intervention scenarios and use these to inform the design of an intervention.

6.6.2 Challenges impacting on the feasibility of pre-trial modelling

The first part of the study highlighted the challenges of estimating the impact of an intervention on mechanisms of action based on behaviour change techniques used. First, there are variations in the labels and descriptions for behaviour change techniques and mechanisms of action. In this study a health economic model with three mechanisms of action (habit strength, dietary restraint and autonomous diet self-regulation) was used. However, when examining what behaviour change techniques might impact these three mechanisms of action, the studies that report links between behaviour change techniques and mechanisms of action did not include these three specific mechanisms of action or least they were not labelled in the same way. There were also different labels for similar behaviour change techniques. The inconsistency of labelling and descriptions made it difficult to assess where consensus was reached between linking studies on links between behaviour change techniques and mechanisms of action. This variation in labelling and descriptions has been identified in a recent summary of the behaviour change field (17).

Second, studies that link behaviour change techniques and mechanisms of action are based on qualitative, quantitative and theoretical links made in the literature, but all highlighted that there are few empirical studies that link behaviour change techniques with mechanisms of action quantitatively (7, 8). This reflects the findings of recent reviews (e.g. (17)). In a review of meta-analyses of self-regulation mechanisms in health behaviour change, only four of 66 directly tested the link between a mechanisms of action and the outcome (24) and similarly in a review of meta-analyses examining health behaviours and outcomes linked to cardiovascular disease, none of the 15 reported the role of mechanisms of action (25). Although there are reviews which examine interventions targeting a single theoretical construct such as habit-based intervention, the focus is only on the outcomes of the intervention (e.g. BMI) and the impact on the mechanisms of action often isn't measured (26). Furthermore, interventions often include several behavioural change techniques which makes it challenging to determine the relationship between individual behaviour change techniques and a mechanism of action (17) and often theory is not used or applied in the design of behaviour change interventions which limits opportunities to test theorised links between behavioural change techniques and their mechanisms (27). Finally, there is little consensus across studies that have aimed to link behaviour change techniques and mechanisms of action through analysis of the literature and expert consensus. These limitation have been documented in the literature and limits our understanding of why the interventions work which could be used to inform the design of effective interventions (9, 25). This limitation therefore impacts on the ability to do pre-trial modelling based on specific behaviour change techniques.

A third challenge, identified in the third part of the study, was in creating a user interface with interactivity. The version of the user interface published online simply enables a user to select results of a certain scenario which has already been generate by the model. This is due to the complexity of the model, which means that the time taken to run can exceed 20 hours when running full probability sensitivity analysis. To enable users to interact directly, there will be a long wait until results are available which is likely to limit engagement with the model. Future iterations of this user interface could include an option for the user to enter an email address for the results to be sent to when complete. Although this would prevent the user having to check back to see if the model results are available, it limits the ability to examine various options with quick feedback. In order to be able to return the results within a short timescale (e.g. within a few minutes), some pre-processing is required. In the example developed in the third part of the study, the scenarios tested in second part are

available to view in the user interface, but a greater number of scenarios could be run. The disadvantage of pre-running scenarios is that it's time-consuming to run the model scenarios in advance and even with three mechanism of actions there would be many combinations of different change values which would increase if the model was adapted to include more modifiable factors such as age and gender. Another option would be to create a meta-model which would involve running the model several thousand times and then run a regression with the various parameters as predictors. Although this wouldn't produce exact model results, it would enable an estimate of cost-effectiveness in a short-time frame; quick feedback would likely make the model more functional for pre-trial modelling. This would enable almost immediate return of results similar to the prototype currently published but with greater flexibility. Future research is needed to establish the accuracy of this approach.

6.6.3 Implications

Pre-trial health economic modelling based on change in mechanisms of action can inform theory-based intervention design. Although the pre-trial health economic modelling was limited by difficulties estimating a specific change in mechanism of action based on intervention content in the first part of the study, the use of intervention scenarios in second part can be used to inform intervention design. In this case, the scenarios tested can be used to consider what behaviour change techniques are linked to the mechanisms of action, estimate the cost of implementation of those behaviour change techniques and decide whether the cost is likely to amount to more or less than the justifiable cost. This is more intervention-specific and theory-based than previous methods of pre-trial modelling that have involved estimating the intervention effect based on previous interventions (in Chapter 5) which may have included different content. Part 2 of the study showed that even the scenario with the lowest benefits would be cost-saving at a price of £542. This is higher than the costs of widely available weight-management interventions that reportedly cost around £200 (28, 29). The findings indicate that even small change in mechanisms of action can have a significant impact on BMI and health-related costs. The linking reviews identified in the first part of the study (6-8) could be used to identify what behaviour change techniques may target mechanisms of action and achieve the intervention effects tested in the second part. For example, behaviour change techniques such as using prompts and cues for a desired behaviour, reducing exposure to cues for unhealthy behaviours and planning coping responses have all been linked to habit formation. However, as highlighted in part 1 and in the literature (17), there is a lack of empirical

evidence of the impact of specific behaviour change techniques on specific mechanisms of action which may make deciding on the behaviour change techniques to include in an intervention challenging.

More research is needed to understand the links between behaviour change techniques and mechanisms of action. Based on the knowledge of the behaviour change techniques used in the intervention and the known change in mechanisms of action, plausible scenarios can be estimated within the model and these can be tested to determine which scenarios best explain the observed data. However, mechanisms of action are often not measured at all in studies (25) which may limit estimations. In addition, behaviour change techniques may be combined in different ways and the impact may not always be additive; two behaviour change techniques may impact on a mechanisms of action but the combined impact on mechanisms of action may be more or less than the sum of the impact of the two behaviour change techniques individually. Finally, it is common for interventions to include many behaviour change techniques and so even when a change in mechanisms of action is observed, it can be challenging to determine the impact of individual behaviour change techniques (17).

Ongoing research in this field may make it easier to estimate the impact of behaviour change techniques on mechanism of action. For example, the human behaviour change project aims to extract and synthesise information about the effectiveness of behaviour change interventions (30). This can then be used to make predictions and inform decisions about behavioural interventions used in different situations. It is likely that research examining the associations between the intervention content, context, population and effectiveness could be used to inform pre-trial health economic modelling to provide predictions of cost-effectiveness as well as effectiveness. However, this research is still in the early stages and still relies on the research available and the analyses that have been conducted, which currently does not include much quantitative analysis of links between behaviour change techniques and mechanisms of action as indicated in part 1. Therefore, there is need for more empirical evidence on the links between behaviour change techniques, mechanisms of action and health outcomes. While analysis of existing data on trials of behavioural weight interventions such as the analysis in Chapter 3 provides some insights, there is a need to design and conduct studies with the pathway between behaviour change techniques, mechanisms of action and health outcomes mapped and a plan for testing these pathways to determine whether an intervention works via the pathways as expected.

Understanding links between behaviour change techniques and mechanisms of action may require testing the effect of individual behavioural change techniques or using factorial designs which enables testing of main and interactive effects of behavioural change techniques. More studies that generate evidence about these pathways will enables synthesis of this information which can better inform the design of future intervention as well as pre-trial modelling.

The development of the R Shiny user interface demonstrates the potential use of the SPHR health economic model as a pre-trial modelling tool. These user interfaces allow interaction with the model without needing to understand the full details of the code and therefore are a useful tool for health economists to share their research and demonstrate the impact of altering certain inputs. To make the user interface developed in this study a useful tool in the design of interventions, more research is needed on the factors that influence weight change so that a wider range of interventions scenarios can be tested, and on methods to combat the length of time taken to run the model.

6.6.4 Limitations

The study had some limitations. First, in the original mediation analysis in which the three mechanisms of action had been targeted in an intervention, there was a direct effect of each of the 12- and 52-week intervention on BMI. That is, when the mediators were accounted for the direct effect of the intervention became non-significant but was also positive; such that the intervention was associated with a non-significant increase in BMI. Although this was not statistically significant, it indicated that there may be an unmeasured effect that opposes the benefits of the change in mechanisms of action. It is likely because there are many factors that impact on BMI, and change in BMI, and although the three mechanisms of action mediated the intervention effect, there are many other unmeasured factors. These unmeasured factors could include factors related to the intervention such as change in self-efficacy or wider factors such as availability of healthy food options. In the scenarios used in the second part of the study, it was assumed that there was no direct effect which may mean that the justifiable cost is overestimated. However, it was not possible to reliably estimate any potential opposing impact of the intervention on BMI. When examining the two interventions, there was a greater direct effect for the 12-week intervention than the 52-week intervention suggesting the greater the effect of mechanisms of action results in smaller changes in the direct effect but it’s not clear whether this would be

equal across each of the three mechanisms of action and so translating this to the scenarios which targeted a single mechanisms of action would have been challenging. Recommendation to collect not only data on mechanisms of action but also routine inclusion and coding of appropriate measures of moderators in intervention research (17) may support better understanding of the factors that impact BMI during an intervention, both related and unrelated to the intervention. Second, the change in habit strength, dietary restraint and autonomous self-regulation were correlated in the original mediation analysis but were assumed to be altered independently in the scenarios. This could mean that the impact is under or overestimated; for example, an intervention targeted at dietary restraint may also increase habit strength or negatively impact on autonomous diet self-regulation and this wasn't captured. More research into mechanisms of action and weight change may improve our understanding of the interactions between mechanisms of action and potential unexpected benefits or 'side-effects' of certain behaviour change techniques on mechanisms of actions other than the one targeted. Third, linking studies were used to identify research linking behaviour change techniques to mechanisms of action. Although these were recent and comprehensive reviews, an independent systematic review of the literature targeted at the three mechanisms of action may have identified additional and potentially more relevant studies.

6.6.5 Conclusion

Pre-trial modelling based on expected or observed change in habit strength, dietary restraint and autonomous diet self-regulation can be conducted and has the potential to inform the design of cost-effective interventions. The study highlights the importance of recommendations to clearly state the behaviour change techniques used and mechanisms of action targeted, and to conduct pre-trial modelling. In the current study, pre-trial modelling has been explored based on three mechanisms of action of weight-management interventions, but it can be expanded to other mechanisms of action and behavioural interventions as the understanding of relationships between behaviour change techniques, mechanisms of action and outcomes improves.

6.7 Contribution to thesis

This chapter investigated a potential benefit recognised in Chapter 4, that the adapted model enables pre-trial modelling to be conducted based on expected effect on mechanisms of action. In this chapter, I explored two

methods of doing this. In the first part I explored whether it was possible to use existing knowledge on how behaviour change techniques impact mechanisms of action to estimate a change in mechanism of action. This would enable pre-trial modelling based on the behaviour change techniques used. However, the lack of research linking behaviour change techniques and mechanisms of action prevented estimating a change in mechanism of action based on behaviour change techniques. The second part of the work focusses on examining the impact of different effect size changes on the mechanisms of action. This didn't require a quantitative link between a behaviour change technique and mechanism of action but could still be used to inform the design of interventions; researchers may find it more feasible to estimate a broad approximation of change rather than the specific change as was the goal in part 1. I had originally hoped to conduct pre-trial health economic modelling of the planned intervention evaluated in Chapter 5, by estimating the impact of the planned weight loss maintenance intervention on the mechanisms in the model. Although this couldn't be done due to delays, given the difficult establishing quantitative associations in part 1 of this chapter, estimating the impact of the planned intervention on the mechanisms in the model would likely have been challenging to do reliably as originally planned. However, selecting a scenario or combinations of scenario in part 2 may have enabled a comparisons of justifiable cost based on previous intervention effect (Chapter 5) and justifiable cost based on estimated change in mechanisms of action (Current chapter).

While I recognise that the health economic model developed in Chapter 4 is currently not widely usable for the purpose of pre-trial modelling using the methods demonstrated in this chapter, due to the number of mechanisms of action and the need for more research, the user interface created in part three demonstrates how pre-trial modelling as demonstrated in part 2 could be used to inform the design of trials. This has the potential to contribute to the design of cost-effective interventions.

6.8 References

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6.9 Supplementary Material

Table 6.7. Definition of behaviour change techniques

Behaviour change techniques matched across reviews	
Behaviour change techniques used in Carey and Connell et al studies (6, 8)	Behaviour change techniques in Kok study (7)
Action planning. Prompt detailed planning of performance of the behaviour (must include at least one of context, frequency, duration and intensity). Context may be environmental (physical or social) or internal (physical, emotional or cognitive)	**Implementation intentions**. Prompting making if-then plans that link situational cues with responses that are effective in attaining goals or desired outcomes.
Avoidance/reducing exposure to cues for behaviour. Advise on how to avoid exposure to specific social and contextual/physical cues for the behaviour, including changing daily or weekly routines	**Cue altering**. Teaching changing a stimulus, either consciously or unconsciously perceived, that elicits or signals a behaviour
Behaviour substitution. Prompt substitution of the unwanted behaviour with a wanted/neutral behaviour	**Counterconditioning**. Encouraging the learning of healthier behaviours that can substitute for problem behaviours
Commitment. Ask the person to affirm or reaffirm statements indicating commitment to change the behaviour	**Public commitment**. Stimulating, pledging, promising, or engaging oneself to perform the healthful behaviour and announcing that decision to others.
Goal setting. Set or agree on a goal defined in terms of the behaviour to be achieved	**Goal setting.** Prompting planning what the person will do, including a definition of goal-directed behaviours that result in the target behaviour
Habit formation. Prompt rehearsal and repetition of the behaviour in the same context repeatedly so that the context elicits the behaviour	**Guided practice.** Prompting individuals to rehearse and repeat the behaviour various times, discuss the experience, and provide feedback.
Problem solving. Analyse , or prompt the person to analyse, factors influencing the behaviour and generate or select strategies that include overcoming barriers and/or increasing facilitators	**Planning coping response.** Prompting participants to list potential barriers and ways to overcome these
Prompts/cues. Introduce or define environmental or social stimulus with the purpose of prompting or cueing the behaviour. The prompt or cue would normally occur at the time or place of performance	**Stimulus control.** Encouraging removing cues for unhealthy habits and adding prompts for healthier alternatives
Reducing negative emotions. Advise on ways of reducing negative emotions to facilitate performance of the behaviour	**Improving physical and emotional states**. Prompting interpretation of enhancement or reduction of physiological and affective states, to judge own capabilities

Behaviour change techniques used in Carey and Connell et al studies (6, 8) only

Adding objects to environment. Add objects to the environment in order to facilitate performance of the behaviour

Comparative imagining of future outcomes. Prompt or advise the imagining and comparing of future outcomes of changed versus unchanged behaviour

Discrepancy between behaviour and goals. Draw attention to discrepancies between a person's current behaviour (in terms of the form, frequency, duration, or intensity of that behaviour) and the person's previously set outcome goals, behavioural goals or action plans (goes beyond self-monitoring of behaviour)

Habit reversal. Prompt rehearsal and repetition of an alternative behaviour to replace an unwanted habitual behaviour

Incentive (outcomes). Inform that a reward will be delivered if and only if there has been effort and/or progress in achieving the behavioural outcome

Identity associated with behaviour change. Advise the person to construct a new self-identity as someone who 'used to engage with the unwanted behaviour'

Information about antecedents. Provide information about antecedents (e.g. social and environmental situations and events, emotions, cognitions) that reliably predict performance of the behaviour

Information about social and environmental consequences. Provide information (e.g. written, verbal, visual) about social and environmental consequences of performing the behaviour.

Material incentive (behaviour). Inform that money, vouchers or other valued objects will be delivered if and only if there has been effort and/or progress in performing the behaviour

Mental rehearsal of successful performance. Advise to practise imagining performing the behaviour successfully in relevant contexts.

Non-specific reward (outcome). Arrange delivery of a reward if and only if there has been effort and/or progress in performing the behaviour

Pros and cons. Advise the person to identify and compare reasons for wanting (pros) and not wanting to (cons) change the behaviour

Restructuring physical environment. Change, or advise to change the physical environment in order to facilitate performance of the wanted behaviour or create barriers to the unwanted behaviour (other than prompts/cues, rewards and punishments)

Restructure social environment. Change, or advise to change the social environment in order to facilitate performance of the wanted behaviour or create barriers to the unwanted behaviour (other than prompts/cues, rewards and punishments)

Self-incentive. Plan to reward self in future if and only if there has been effort and/or progress in performing the behaviour

Self-monitoring. Establish a method for the person to monitor and record their behaviour(s) as part of a behaviour change strategy

Self-monitoring of outcomes of behaviour. Establish a method for the person to monitor and record the outcome(s) of their behaviour as part of a behaviour change strategy.

Social reward. Arrange verbal or non-verbal reward if and only if there has been effort and/or progress in performing the behaviour

Behaviour change techniques in Kok study (7) only

Deconditioning. Letting people experience a lack of reinforcement or even negative outcomes of the undesired behaviour.

Early commitment. Having people choose a (larger) delayed reward far in advance.

Enactive mastery experiences. Providing increasingly challenging tasks with feedback to serve as indicators of capability.

Provide contingent rewards. Praising, encouraging, or providing material rewards that are explicitly linked to the achievement of specified behaviours

Reattribution training. Helping people reinterpret previous failures in terms of unstable attributions and previous successes in terms of stable attributions.

Set graded tasks. Setting easy tasks and increase difficulty until target behaviour is performed.

Verbal persuasion. Using messages that suggest that the participant possesses certain capabilities

Table 6.8. Evidence of the links between behaviour change techniques and mechanisms of action based on linking studies (6-8)

Author and year	Behavioural target	Population	Implementation of BCT	Mechanisms of Action	Results (evidence of link)
Problem solving and planning coping response linked to behavioural regulation					
Armitage et al., 2015 (31)	Fruit intake	Healthcare workers	Supported to form implementation intentions to have an extra portion of fruit each day	Meta-cognitive Processing	Participants who formed implementation intentions ate significantly more fruit and engaged in significantly more metacognitive processing at follow-up than participants in the control condition
Aventin et al., 2014 (32)	Reduce unwanted pregnancy	Teenage boys	Increase strength of intention to avoid unplanned teenage pregnancy using interactive video drama and training sessions	Perceived Behavioural Control	Protocol paper – no results reported
Carels et al., 2004 (33)	Physical activity, nutrition, healthier lifestyle	Obese, sedentary, postmenopausal women	Encouraged to strengthen self-control capacity (e.g. increasing effective self-monitoring), reduce or eliminate factors that contribute to self-control depletion (e.g. negative moods), coping strategies and modifying inappropriate or unproductive attempts at self-control.	Self-Control	No differences between groups on self-control or weight change
Cornélio et al., 2013 (34)	Salt intake	Hypertensive women (Brazil)	Use consciousness-raising to increase awareness of the effects of salt consumption on health and blood pressure and counter-condition to decrease automaticity of using salt when cooking	Habit	Protocol paper – no results reported
Cramp et al., 2006 (35)	Physical activity	Adults (mean age 62) with a history of stroke	Exercise sessions adapted to participants dependent on adverse effects	Self-regulatory efficacy/skills	Some changes in muscle strength but mechanism of action was not measured

Author and year	Behavioural target	Population	Implementation of BCT	Mechanisms of Action	Results (evidence of link)
Gwyther et al., 2015 (36)	Self-regulation in drivers	Adults (N=81, aged 18-83)	Setting goals to change driving behaviour, improve feeling of control, consider factors that previously contribute to successful driving, develop action and coping plans	Self-Regulation	The intervention resulted in a marginally significant effect on self-regulation planning behaviour but no change in intentions. Participants in the intervention groups reported meeting the goals set.
Lhakhang et al., 2015 (37)	Hand hygiene behaviours (handwashing)	Young adults (18 to 26 years	Participants encouraged to generate three action plans specifying the timing, frequency, and technique to wash their hands, and three coping plans, which included both barrier identification and problem-solving	Self-Regulation	A self-regulatory module resulted in greater planning and more hand washing than a motivation module. Once both modules had been delivered, there were no significant difference in hand washing frequency between groups.
Martin et al., 2015 (38)	physically active teaching methods	Children aged 8-9	Training teachers in physical active teaching methods and developments of action plans/goal setting	Psychological Capability	Increased physical activity but relationship between intervention and psychological capacity not measured.
Rosenberg et al., 2015 (39)	Reduction in sitting time and increase sit to stand transitions	adults over age 60 with a body mass index over 27 kg/m2	Supported self-efficacy and engage participants in working on their goals in a manner that is supportive of participant values and preferences, given graphical feedback charts depicting their sitting time, standing time, stepping time, and sit-to-stand transitions after each week	Self-Regulation	Siting time decreased but mechanism of action was not measured.
Thoolen et al., 2009 (40)	Diet, Physical Activity and Medication Adherence	patients recently diagnosed with type-2 diabetes	helping patients to set small, concrete and attainable goals, recognise conditions for and barriers to goal achievement generate strategies for solving potential problems in specific situations, formulate necessary	Proactive Coping Skills	Significant impact of intervention on proactive coping skills and BMI. Proactive was a significant predictor of self-management, even when controlling for

Author and year	Behavioural target	Population	Implementation of BCT	Mechanisms of Action	Results (evidence of link)
			actions in the form of specific action plans		baseline self-management, intentions and self-efficacy.
Habit formation linked to behavioural cuing					
Lally et al., 2008 (41)	Eating healthily, physical activity	Adults with high BMI	advice on habit formation and simple recommendations for eating and activity behaviours promoting negative energy balance, together with a self-monitoring checklist	Habit formation	Average automaticity change across 14 behaviours at 12 weeks was significantly correlated with total weight loss.
Maranda et al. 2015 (20)	Reported in Table 6.3 main manuscript				
Matei et al., 2015 (21)	Reported in Table 6.3 main manuscript				
Pros and cons linked to motivation					
Carey et al., 2006 (42)	Reducing alcohol use	Heavy drinking students	Exercise to identify good things/not-so-good things of continuing drinking habit and potential losses and gains of cutting down on drinking.	Motivation	The intervention with the BCT targeting motivation was not effective.
Hardcastle et al., 2012 (43)	Physical Activity	Individuals in a deprived community	focus was on exploring ambivalence and eliciting self-directed change talk. Exploring importance of increasing physical activity and confidence in doing so	Autonomous Motivation	There were increases in physical activity and intrinsic motivation predicted change in vigorous physical activity.
Knittle et al., 2013 (44)	Physical activity	patients with rheumatoid arthritis	patients were encouraged to weigh pros and cons of re-engaging in PA, and make links between a more physically active lifestyle and important long-term goals	Autonomous Motivation	There were significant increases in both physical activity and autonomous motivation over time.

Author and year	Behavioural target	Population	Implementation of BCT	Mechanisms of Action	Results (evidence of link)
Murphy et al., 2010 (45)	Reducing drinking	Heavy drinking students	video depicting potential negative outcomes associated with drinking, quiz about alcohol and its effects on the body.	Motivation	Students who reported greater increases in motivation following the intervention reported greater subsequent drinking reductions but no significant difference between intervention and comparison
Naughton et al., 2013 (46)	Smoking cessation	women with experience of prenatal smoking	Motivational texts (e.g. think about the money you'll save not smoking)	Motivation	The theoretical importance of motivation for behaviour change is highlighted (qualitative study)

This Table further highlights the difficulty of establishing the links between behaviour change techniques and mechanisms of action. In Armitage et al, the behaviour change technique was categorised as problem solving in the linking review. Problem solving was matched to a similar mechanism of action the Kok et al. (2016) study. However when examining this, implementations intentions were used which is a BCT already specified in the Kok study.

CHAPTER 7: GENERAL DISCUSSION

The overarching aim of this thesis was to investigate the feasibility and benefits of including psychological factors in the prediction of BMI trajectories within health economic modelling of behavioural weight management interventions. The research questions addressed in this thesis to contribute towards this aim were:

i. What are the current methods used within health economic models to predict weight trajectories and how have psychological factors been incorporated?
ii. What are the psychological constructs, or changes in constructs, that predict weight trajectories during and following a weight management intervention?
iii. What impact does incorporating these factors in an existing health economic model have on cost-effectiveness outcomes?
iv. How can inclusion of these factors in an existing health economic model facilitate pre-trial modelling for intervention design?

This final chapter presents a summary of the findings of the thesis, the contributions to existing knowledge, implications, limitations and recommendations for future research.

7.1 Key findings

In Chapter 2, the systematic review of health economic models of obesity showed that a range of assumptions were made about the trajectories of weight or body mass index (BMI), from maintaining all weight loss to regaining all weight lost. Psychological factors were not considered in the trajectories of weight or BMI. However, some of the evidence sources used to support assumptions made about trajectories within the health economic models included psychological variables. In some studies, analysis of psychological variables was not reported and in others, analysis was reported but not used in the health economic model.

In Chapter 3, analysis of a trial of an existing weight management intervention (with durations of 12 or 52 weeks) identified three mechanisms of action; dietary restraint, habit strength and autonomous diet self-regulation. The three mechanisms of action mediated the impact of both the 12- and 52-week format

of the intervention on BMI. The 12- and 52-week intervention resulted in greater increases in habit strength and dietary restraint and lower decreases in autonomous diet self-regulation than the brief intervention comparison group. There were larger effect sizes in the 52-week intervention than the 12-week intervention. Increases in habit strength, dietary restraint and autonomous diet self-regulation were associated with decreases in BMI.

In Chapter 4, habit strength, dietary restraint and autonomous diet self-regulation were added to an existing health economic model of obesity. Change in BMI predicted using the change in mechanisms of action was validated against commonly used methods to input intervention effect; namely, inputting mean change in BMI and change in BMI conditional on demographic factors. Inclusion of psychological mechanisms of action enabled subgroup comparisons based on baseline levels of psychological variables and sensitivity analysis of weight trajectories based on psychological theory and research. Subgroup and sensitivity analysis resulted in small differences in cost-effectiveness and therefore would be unlikely to impact on funding decisions for the weight management intervention examined in this thesis. However, these additional analyses indicated that including mechanisms of action would enable further exploration of cost-effectiveness of an intervention which could inform funding decisions for future interventions.

The accurate prediction of BMI indicated the possibility of conducting pre-trial modelling based on the expected impact on relevant mechanisms of action. Pre-trial modelling was conducted in two ways. First, in Chapter 5, using an estimated intervention effect based on the effectiveness of previous interventions indicated £104 was the maximum justifiable cost for a cost-effective weight loss maintenance intervention. To target the limitation that estimated intervention effect was based on previous interventions rather than the content of the planned intervention, conducting theory-based pre-trial modelling specific to a planned intervention and the mechanisms of action targeted was explored in Chapter 6. The adapted model developed in Chapter 4 was used to conduct pre-trial modelling based on expected change in mechanisms of action. Although there were limitations in the evidence linking behaviour change techniques to mechanisms of action restricted pre-trial modelling based on the

specific planned content of the intervention, this research indicated that pre-trial modelling based on mechanisms of action has the potential to the design of cost-effective interventions.

7.2 Contributions to existing knowledge

7.2.1. Mechanisms of action of a behavioural weight management intervention

Dietary restraint, habit strength and autonomous diet self-regulation were found to mediate the intervention effect of both a 12- and 52-week weight management intervention. This finding contributes to existing research in two ways. First, although previous research had already indicated that this open-group weight management intervention is effective and cost-effective (1), the analysis conducted in this thesis adds to an understanding of *how* it is effective; specifically, the pathway through which the intervention impacts on BMI. The interventions resulted in a greater increase in dietary restraint and habit strength and a smaller decrease in autonomous diet self-regulation than the brief intervention comparison group and this was associated with a greater decrease in BMI. This mediation analysis supports previous findings that dietary restraint, habit strength and autonomous self-regulation are associated with weight loss and weight loss maintenance (2-4) and adds to the small number of studies that has identified these as mechanisms of action (5-7). Second, the comparisons of the same intervention with two different durations (12 and 52 weeks) enabled a greater understanding of the impact of the duration of the intervention. In particular, the finding that habit strength was a significant independent mediators of the longer intervention and not the shorter intervention provided support for dual process theories (8). It indicated that the longer intervention may have provided participants with the continued support required to enable behaviours to become more habitual and less reliant of deliberative processes (dietary restraint).

The mediation analysis reported in Chapter 3 has also made a methodological contribution to existing research. To date, very few formal mediation studies that have been conducted to examine the mechanisms of action of weight management interventions. In a review of meditators (self-regulatory and psychological mechanisms) of weight change, physical activity or dietary intake, there were only 10 studies between 2000 and 2015 in which formal mediation analyses were conducted (5). The analysis conducted in the current study not only adds to this small number of mediation studies, but utilised

latent growth curve analysis to disentangle the complex system of interactions between behavioural weight-management interventions, three mechanisms of action and the trajectory of weight change. This method of analyses enabled representation of a nonlinear change in the mechanisms of action and BMI and so can detect relationships that may not be detected when a linear relationship is assumed. This measurement of the non-linear trajectories is particularly important because analysis of weight change that includes a follow-up of a year or more often reveals a trajectory in which BMI decreases and then increases towards the initial weight (9). Furthermore, the latent growth curve analysis method used enabled growth factors to be outcomes dependent on factors such as age or treatment group, and predictors enabling a greater understanding of the factors that impact on trajectories of mechanisms of action and weight change as well as the relationships between the trajectories.

7.2.2. Public health economic modelling methods

Compared to health economic modelling of surgical or pharmacological interventions, modelling of behavioural interventions presents additional challenges because of the wide range of factors that influence health behaviours and therefore incorporating psychological factors to better understand these behaviours has been identified as a priority (10). Despite this, the systematic review (Chapter 2) revealed that psychological factors had not been incorporated into health economic models of obesity. Although there are other reviews of health economic models of obesity (11), the work in this thesis was the first to focus on the assumptions made about weight trajectories, the evidence to support these assumptions and the impact that different assumptions have on cost-effectiveness outcomes. The review also investigated the actual and potential role of psychological factors in health economic models of obesity and highlighted that there are many cases when psychological variables are collected and not analysed or collected and analysed but not used in heath economic models. This indicated that while psychological variables weren't incorporated, there was the potential to do so with available data.

In Chapter 4, change in dietary restraint, habit strength and autonomous diet self-regulation were incorporated into an existing health economic model and, along with demographic factors and baseline BMI, these were used to predict change in BMI over two years. This adapted model with mechanisms of action provided evidence that change in mechanisms of action accurately predicted change in BMI

across treatment groups as well as inputting mean change in BMI or change in BMI conditional on demographic factors and there was some evidence that there was better prediction of lower BMIs. Cost-effectiveness estimates when using the mechanisms of action were not significantly different from the standard methods based on credible intervals. However, incremental costs and QALYs were lower when BMI was conditional on mechanisms of action. Although in this study, this would likely not impact on funding decisions, there is the potential for these differences to have an impact in other evaluations when there is less certainty about the cost-effectiveness of an intervention. This model enabled additional and potentially useful analyses including subgroup analysis based on scores on the mechanisms of action, and sensitivity analysis based on expected long-term change in mechanisms of action. Both of these analyses indicated some differences. Although these were small and not significantly different from the base case scenario in the current study, it showed the potential for these analyses to be conducted and that psychological factors have the potential to impact cost-effectiveness and should be examined. Based on the finding of the systematic review, this is the first time that psychological factors have been incorporated into a health economic model. Although in the case study analysed in Chapter 4 it is unlikely that funding decision would be impacted by the inclusion of these factors, there is the potential for these methods to be informative in evaluations of weight management interventions.

The findings in Chapters 4 and 6 indicated that change in BMI can be predicted using expected change in mechanisms of actions and that pre-trial modelling based on change in mechanisms of action can be conducted. Using the adapted model, an actual or expected change in mechanisms of action can be entered into the model to get an estimate for long-term cost-effectiveness. Medical Research Council (MRC) guidance recommends that researchers, when designing behavioural interventions, 1) outline the behaviour change techniques planned and the mechanisms of actions that are being targeted and 2) conduct pre-trial modelling to examine the likelihood of effectiveness and cost-effectiveness (12). The model adaptation and pre-trial modelling reported in Chapters 4 and 6 demonstrate how following theory-based design recommendations can also directly inform the pre-trial modelling. Pre-trial modelling based on change in mechanisms of action presents an advantage when compared to estimating the intervention effect on BMI based on the change in weight observed in previous

interventions, as previous interventions may comprise different behaviour change techniques and target different mechanism of action.

Adapting the model and attempting pre-trial modelling highlighted a number of challenges that are likely to impact practical implementation of pre-trial modelling based on change in mechanisms of action. These challenges include the length of time the model takes to run which limits the functionality of pre-trial modelling, difficulties mapping the mechanisms of action in this study to those measured in previous studies and lack of research quantitatively linking behaviour change techniques to mechanisms of action. Although these challenges, and the limitations of the model adaptation to a single trial and three mechanisms of action, mean that it is not widely useable for intervention design currently, it represents a starting point towards the development of a model that could be used for pre-trial modelling based on mechanisms of action. Research in the discipline of health psychology that aims to understand the relationships between the content of the intervention, the mechanisms of action and health outcomes could be used to validate the relationships observed between the three mechanisms of action and BMI in Chapter 3 and understand what other mechanisms of action are relevant to weight management. This could inform the design of effective and, facilitated by pre-trial modelling, cost-effective interventions. Pre-trial modelling will be supported by increasing development of public health economic models that incorporate more of the factors that impact on behaviour and ultimately health outcomes (13). Although the work in this thesis has been specific to weight management, research that has examined the associations between content of the intervention, the mechanisms of action and health outcomes in other health areas such as cardiovascular disease prevention (14), could inform the development or adaptation of a wider range of health economic models.

7.3 Implications

7.3.1 Implications for intervention design

The findings indicate that dietary restraint, habit strength and autonomous diet self-regulation are factors that are both modifiable and associated with reductions in BMI and can therefore be recommended as targets for future interventions. Behaviour change techniques that target these variables should be considered when designing weight loss and weight loss maintenance interventions.

In Chapter 3, the behaviour change techniques used in the weight management intervention that may have positively impacted habit strength and dietary restraint as well as the factors across all interventions (brief, 12-week and 52-week interventions) that may have resulted in a decrease in self-regulation were identified. These behaviour change techniques could be used to inform the design of future interventions. In addition, existing research that aims to identify links between behaviour change techniques and specific mechanisms of action in previous literature and by expert consensus was outlined in Chapter 6 (15, 16).

The work in this thesis represents a first step towards enabling pre-trial modelling based on changes in mechanisms of action. This type of pre-trial modelling allows a more theory-based estimation of expected effect and cost-effectiveness rather than using change in weight based on the results of previous trials which may have used different behaviour change techniques as in Chapter 5. Although several limitations were identified when attempting pre-trial modelling, the work presented in this thesis highlights the potential of conducting pre-trial modelling, such as justifiable costs, based on expected impact on mechanisms of action to inform the design of interventions and trials based on the specific planned intervention. Accurate pre-trial modelling will increase the likelihood that interventions that progress to trial will be cost-effective ensuring that funding for the developments of interventions is allocated efficiently. While Chapter 6 demonstrated pre-trial modelling with a limited number of mechanisms of action, development to include more mechanisms of action has the potential to enable pre-trial modelling of a wide range of interventions.

7.3.2. Implications for health economic modelling

Health economic modelling of behavioural interventions

Adding psychological factors to public health economic models has previously been identified as a priority to better explain heterogeneity in behaviour. Specific to obesity, it was hypothesized in this thesis (Chapter 4) that adding these factors had the potential to better predict heterogeneity in the impact of an intervention on weight and cost-effectiveness of an intervention. In Chapter 4, the estimated mean and distribution of BMI post-intervention based on mechanisms of action were not significantly different to those compared to using the mean change in BMI or mean change in BMI conditional on

demographic factors. This indicated that at a population level, all model specification predicted BMI accurately and that change in mechanisms of action was a reliable method of inputting intervention effect

There were no significant differences in cost-effectiveness estimates across the different methods of inputting intervention effect; however, when BMI was either conditional on demographic factors or predicted by mechanisms of action, incremental costs and QALYs were smaller than when the mean change in BMI was used at the intervention effect. Given that both of these methods (demographic adjusted BMI or BMI predicted on mechanisms of action) allow the intervention effect to vary across individuals, these estimates of cost-effective likely represent the better representation of heterogeneity. In the evaluation reported in Chapter 4, it is unlikely that differences in cost-effectiveness between model specifications would impact on decisions regarding funding as in both cases the intervention was estimated to be cost-saving. However, for interventions that are associated with higher costs and/or lower benefits and that are therefore closer to the willingness to pay threshold in the UK, these differences in cost and QALYs estimates may impact on funding decisions. This provides support for allowing intervention effect to vary across individuals. However, it doesn't indicate that predicting BMI based on mechanisms of action provides an advantage over entering BMI conditional on demographic factors.

However, including psychological mechanisms did enable further examination on how these factors at baseline and change in these over time predicted change in BMI. Although in this case, the level of mechanisms of action at baseline did not have a significant impact on cost-effectiveness, there was some evidence of differences in costs and QALYs depending on these values. In the case study presented here, the two interventions were the same other than duration and therefore targeted the same mechanisms of action; the analysis in Chapter 3 indicated that all three interventions, including the brief intervention, showed a similar direction of change in mechanisms of action although with different effect sizes. Therefore, any impact that baseline psychological factors had on the effectiveness of the intervention may have been present across all groups and so would have had little impact on incremental costs and QALYs. Including mechanisms of action in health economic modelling may have a greater

impact on outcomes when comparing interventions that target different mechanisms of action. Including mechanisms of action in the model also allows assumptions to be made about long term change in BMI that were based specifically on the intervention and mechanisms of action rather than the long-term impact of previous, and likely different, weight management interventions. While in Chapter 4, both the 12- and 52-week intervention were cost-effective in all scenarios, there were differences in costs and QALYs which have the potential to impact cost-effectiveness in other evaluations. Together these findings indicate that including psychological mechanisms of action may represent heterogeneity of cost-effective estimates better than using mean change in BMI, allows subgroup analysis based on potentially influential psychological factors and theory-informed sensitivity analysis of differing longer-term weight trajectories. These advantages have the potential to provide additional information about heterogeneity of cost-effectiveness between individuals and interventions which could inform funding decisions as well as the design of future interventions.

Health economic modelling beyond behavioural interventions

A model that includes the role of psychological factors may make it easier (when more developed) to estimate the cost-effectiveness of other interventions such as population-level interventions. The impact of a population or community-level can be hard to measure as, unlike in a randomised controlled trial, it is challenging to collect data on the individuals impacted by the intervention, and it can be difficult to determine the casual pathways given the large number of potential influencing factors. Therefore the effectiveness of the intervention targeting obesity-related behaviours can be difficult to model on individual BMI. However, if the population level intervention can be entered into the model via expected or observed change in mechanisms of action, then the model may be able to capture or estimate the long-term impact. Taxonomies of behaviour change techniques have defined behaviour change techniques that are specific to population level interventions (17); an example is mass media role-modelling, which is described as providing roles models through the mass media to reinforce the desired behaviour (18). These behaviour change techniques can then be linked to mechanisms of action. Given that these types of interventions often can't be tested in a randomised controlled trial and that estimating the intervention effect can be challenging, estimating the impact of the intervention on the mechanism of action may be easier to hypothesize based on behaviour change theory. In addition, when evaluating

the intervention, change in mechanisms of action can be collected through questionnaires and be used instead of, or alongside, BMI. This is likely to be increasingly easy to collect through the use of mobile applications, cheaper than objective measures of BMI which requires a nurse or research worker and may be more reliable than self-reported BMI. Understanding how population-level interventions link to the mechanisms of action on an individual level would also inform how different interventions interact. For example, restructuring the physical environment by reducing the number of fast-food restaurants in an area might reduce the need to engage dietary restraint. If individual interventions, such as the WW intervention analysed in this thesis, improve dietary restraint and a population level intervention reduces the need for dietary restraint, the overall impact and cost-effectiveness of each of the interventions may be enhanced or reduced by the presence of the other.

7.3.3. Opportunities for ongoing multidisciplinary research

Ongoing research in the field of behaviour change science will enable further development of the public health economic modelling. A recent special issue of Health Psychology Review focussed on current research on behaviour change interventions and mechanisms of action (19). An emerging issue identified was that researchers reporting on behaviour change interventions do not routinely conduct tests of the mechanisms of action by which the interventions bring about change. This issue was also identified in this thesis. In Chapter 6, a lack empirical research prevented estimated of a change in mechanisms of action based on a specific behaviour change technique. In the systematic review reported in Chapter 2, in some trials that were cited as an evidence source to inform a health economic model, data on psychological variables were collected but no analysis was reported. Indeed, Chapter 3 was an analysis of a trial in which psychological variables were measured but no analysis had been conducted due to limitations of time and resources. Another issue that was highlighted in this thesis was that it was difficult to link the behaviour change techniques to the mechanisms of action and outcomes due to the multiple techniques used in an intervention (19). Analysing the pathways through which an intervention has an impact on the desired outcomes, and testing the effects of individual behaviour change techniques in isolation or using factorial designs which enable testing of the independent and interactive effects of individual techniques, have been suggested to overcome these limitations (20). Advances in this field based on these recommendations will not only contribute to the development of effective interventions

but, combined with developments in public health economic modelling such as the work reported in this thesis, also cost-effective interventions.

An example of ongoing work that could contribute to further development of the work in this thesis is the human behaviour change project (21). The human behaviour change project aims to create a knowledge-based system that is able to review published reports of behavioural interventions and extract and analyse information using computer science and artificial intelligence (AI) methodologies The project includes the Behaviour Change Intervention Ontology (BCIO); a classification system for intervention-related entities such as the outcome behaviour, behaviour change techniques and mechanisms of action (22). This ontology was in the development stages at the time of writing but parts of the BCIO including the mode of delivery (e.g. group-based, environmental change) (23) and where interventions take place (e.g. geographical location, attributes of the location) (24) have been generated. The human behaviour change project aims to tackle the variation in how behaviour change interventions and related constructs are represented and reported. Consistency in the reporting of interventions would make comparisons between interventions easier and tackle one of the challenges that arose in Chapter 3; that behaviour change techniques were labelled differently in the literature (e.g. (16, 17)) which made it difficult to interpret the strength of evidence supporting the links between specific behaviour change techniques and mechanisms of action.

An aim of the human behaviour change project is to use the ontology and an ontology-based modelling system (OBMS) to develop a system that can make predictions based on the information available in the synthesized literature and generate a confidence score around that prediction (25). The OBMS includes a formal representation of the constructs with behaviour change theories and how these constructs relate to each other and has been used to create a database of 76 published behaviour change theories which can be compared and synthesized. Defining the models in this way allows comparisons between theories of behaviour change and testing of the propositions within existing theories (e.g. the links between different components of the theory) to facilitate generation, and analysis, of evidence to support or contradict the proposition. Consideration should be given to how the development of a tool that will give users an estimate of intervention effect and a confidence score of that estimate can then

be used for pre-trial modelling so that estimates of cost-effectiveness can also inform decision-making. However, as highlighted in the discussion of Chapter 6, this research will rely on the available evidence and a lack of evidence linking behaviour change techniques, mechanisms of action and health outcomes is well documented both in this thesis and in the literature (19). Therefore, conducting analyses to test the pathways between behaviour change techniques, mechanisms of action and health outcomes is a key area of future research. This should include analysis of existing trial data (as conducted in Chapter 3) where data on potential mechanisms of action have been collected but not analysed (as was the case with some trials identified in the systematic review in Chapter 2).

7.4 Limitations

7.4.1. Suitability of mediation analysis for health economic modelling

The mediation analysis was conducted to determine the mechanisms of action of a weight management intervention with the aim of then incorporating these within the health economic modelling and had several advantages including the representation of the non-linear trajectory of BMI. Using mediation analysis was well suited to investigating the mechanisms of action of an intervention and enabled the estimation of change in BMI in a health economic model. One of the potential benefits of including psychological factors is the prediction on long-term change in BMI from short-term change in psychological factors and BMI. In the study used in this thesis, data were collected over two years and analysis conducted in this thesis enabled prediction of BMI based on the trajectory of mechanisms of action over two years. However the analysis was less suited to making predictions long-term predictions of BMI based on short term outcomes, for example, making prediction of BMI at 2 years based on changes in BMI and mechanisms of action over 3 to 12 months. Given that many trials of weight management interventions have short-term follow-up, it would have been useful for health economic modelling to have a method of predicting BMI at 2 years from shorter-term data points. Although piecewise analysis was explored in Chapter 3 to investigate associations between time points in the study, the models had poor fit compared to the single latent growth curve models and so the latter was used for the mediation analysis. Additional data now available for this study may enable piecewise analysis and prediction of change in weight up to 5 years based on short-term changes in BMI and mechanisms of action (more about this in Section 5).

7.4.2. Use of a single trial and health economic model

The analysis in this thesis was based on a single study and an adaptation of a single health economic models which means that the generalisability is limited. The study had a large sample size, examined a widely available intervention, had a follow-up of 2 years and had data on potential mechanisms of action. The health economic model was an individual simulation model which enables estimates of changes in BMI for individuals and so enables the adaptations described in Chapter 4. While there are clear justifications for these choices, it may limit the generalisability of findings. Firstly, the adaptation of the model and pre-trial modelling is limited to the three mechanisms of action and so analysis of interventions targeting different mechanisms of action could not currently be analysed with the model. However, this work represented the first step in incorporating psychological factors and future research should consider how more factors can be incorporated. Furthermore, in order to conduct the health economic modelling based on psychological factors, the simulated baseline population in the health economic analyses conducted in Chapters 4 and 6 was drawn from the WRAP study analysed in Chapter 3. This may mean that the results are not as generalisable to the general population and limits any pre-trial modelling to populations that are similar to the WRAP study population.

7.4.3. Use of theory

The use of secondary data meant that the mechanisms of action were chosen by the original trial team rather than for the purpose of the analysis in this thesis. Using secondary data was a strength of this research as it enabled analysis of 2 years of trial data which would not have been possible in the time scale of the thesis if primary data collection was used. However, the disadvantage is that the data was not collected with consideration of the specific data analysis conducted in this thesis. Furthermore, because the trial was of an existing commercial intervention there wasn't information about whether there were the hypothesized links between the behaviour change techniques and mechanisms of action and what these links were. The potential mechanisms of action that were examined in Chapter 3 were chosen by the original trial team as they were theorised to be the mechanisms of action based on knowledge of the content of the intervention but it is not known what, if any, theory was used in the original design of the intervention. Therefore, theorised links made between behaviour change

intervention and mechanisms of action and to other behaviour change theories in this thesis were retrospective and could not be compared to an existing hypothesis. Future developments of the health economic model adapted in Chapter 4, which may involve analyses of existing trial data as in Chapter 3, should utilise a theory-based approach which involves starting with a conceptual model before then examining the data available (described more in Section 5).

7.4.4. Open research

Access to the trial data analysed in Chapter 3 can be requested from the study team, but is not currently publicly available. The R code for the SPHR health economic model reported on in chapters 4-6 is also not currently publicly available. Enabling the health economic model and data to be open source would mean the methods used are transparent and replicable and would make the model more assessible other researchers who may be able to adapt the code for their own needs and facilitate development of the model. Furthermore, if this model is developed further in the future, it may also enable researchers designing intervention to use this as a tool in intervention design. While the R code of the model itself is not publicly available, much of the code that was developed throughout the thesis for data analysis as well as results of the health economic modelling is available on GitHub (https://github.com/sebates1/thesis).

7.4.5. Role of obesogenic environment

The focus of this thesis has been mainly on the individual without explicit reference to the environment which is a highly influential factor in diet-related behaviours. While the individual intervention here might be encouraging healthy eating, changes in weight will depend on many factors, such as the resources available, opportunities for physical activity, norms in their social group and access to unhealthy or healthy food (26). The role of external factors has been recognised by the UK government who have recently implemented a tax on sugar-sweetened beverages (known as the ‘sugar tax’) (27). Despite the focus on a single individual intervention in this thesis, including mechanisms of action in health economic modelling of obesity-related interventions could also be applicable to population-level interventions. The behaviour change techniques used in population-level interventions will target specific mechanisms of action which could also be incorporated into health economic modelling.

Therefore the inclusion of mechanisms of action in health economic modelling could support the estimation of the long-term impact of population-level interventions. Ongoing research will need to consider how the behaviour change techniques used across a range of interventions, including both individual and population-level interventions, interact and impact on mechanisms of action, to estimate the cost-effectiveness of interventions in isolation and in combination.

7.4.6. Lack of Value of Information Analysis

Collecting more data on model parameters has the potential of reducing uncertainty and therefore the risk of making the wrong funding decision and the consequences related to the that decision. However, gathering more evidence can be costly. The value of information analysis, recommended in good practice recommendations (28), can be used to assess the costs and benefits of gathering this additional evidence and so not conducting this is a limitation of the thesis. The work in this thesis aimed to explore methodological feasibility of including psychological factors into health economic modelling rather than to inform decisions on funding at this stage and therefore estimating the value of having more information about each parameter was not prioritised. Furthermore, the output of the three model specifications explored in Chapter 4 all indicated that while there was uncertainty in the incremental costs and QALYs, there was little decision uncertainty (i.e. the cost-effectiveness of the 12 and 52-week intervention was well within the willingness to pay threshold) suggesting that value of information would likely be low. However, as value of information analysis can inform decisions about resource allocation (28), and because the addition of the psychological variable added some additional uncertainty (Figure 4.4), in any future iterations of this work value of information analysis will be included. Given that psychological variables identified as mechanisms of action have not often been included in health economic models before, estimating the costs and feasibility of collecting additional data on these variables in future studies will inform decision making using this model.

7.5 Future research

The work in this thesis demonstrates the feasibility, benefits and current limitations of incorporating mechanisms of action of a weight management intervention into a health economic model and has highlighted some areas for future research which are detailed in this section

7.5.1 Analysis of mechanisms of action over the longer-term

The WRAP trial, that the mediation analysis in Chapter 3 was based on, followed participants up 5 years after randomisation. I am now working on research in which I aim to extend the analysis conducted in Chapter 3 to examine whether the analysis conducted with the first 2 years of the data reveals the same mechanisms of action when conducted with the additional data point. As well as a repeat of the two-year analysis, the additional time point will allow piecewise analysis. This can be used to investigate the relationships between the potential mechanisms of action and BMI in the intervention phase (0-12 months) and the post-intervention phase (12-60 months) as well as the interaction between phases. This will be particularly beneficial for the health economic modelling because piece-wise analysis can investigate the feasibility of predicting BMI at 5 years based on changes in BMI and mechanisms of action in the intervention phase (0-12 months). Latent class growth modelling is an additional method that could be used alongside the extension of the mediation analyses which can be used to identify clusters of BMI trajectories; for example those who lose weight and regain the weight loss, those who lose weight and maintain weight loss and those continue to lose weight. By identifying any clusters and then examining the difference between these clusters on demographic, health and psychological variables, I aim to increase understanding of the individuals that the intervention does and does not work for.

The 5-year data will also provide an opportunity to examine the validity of the model assumptions regarding weight trajectories, specifically that an individual's weight will return to the estimated weight trajectory they would have followed if they hadn't been on a weight management intervention by 5 years post baseline. Given that long-term follow-up of a weight management intervention is not common (9), the follow-up data will provide an opportunity to compare the estimates of change in over 5 years using the model's assumptions to the actual change in weight. The range of methods used to

predict weight trajectories identified in the systematic review could also be compared to the 5-year follow-up data to determine which method is closest to the value observed in this trial. This may inform the assumptions used in the model, especially as the systematic review revealed that many models assumed a regain over 5 years based on a systematic review which included only one small study that followed participants up for 5 years (9).

7.5.2 Model development

The model comparisons and pre-trial modelling chapters in this thesis highlighted a number of challenges and limitations that would need to be addressed for pretrial modelling to be based on a change in mechanisms of action to better inform cost-effectiveness estimates. The main development that would be required would be to expand the mechanisms of action that are included in the model beyond dietary restraint, habit strength and autonomous dietary self-regulation. This would require consideration of what mechanisms of action are influential in weight management. I would use a framework for developing the structure of public health economic model (13) could be used to guide this process by adapting the steps required to development of this existing health economic model. The steps are outlined below.

i) Involvement of relevant experts

Individuals with relevant expertise, including those that involved in designing behavioural weight management interventions and with clinical expertise in the treatment of obesity, will be identified and involved in model development. Specifically, this will include individuals that have experience that enables them to identify and hypothesize the mechanisms of action that should be included in a health economic model of obesity, the interactions between the mechanisms of action and factors that will make impact the usability of the model for pre-trial modelling.

ii) Develop a conceptual model

The next stage is to describe hypothesized causal relationships between behaviour change techniques, potential mechanisms of actions and BMI. This stage will include identifying which mechanisms of action are most relevant to diet and exercise-related behaviours and agreeing on definitions of these, the

possible positive and negative impact of specific behaviour change techniques on these mechanisms of action and the correlation between changes in the mechanisms of action and BMI. This stage of the work aims to ensure that the development of the model is theory driven rather than data driven. The scope of the model should also be defined when developing the conceptual model. The focus in this thesis has been on an individual interventions and associated behaviour change techniques but ideally a model would enable the evaluation of community and population level interventions such as limiting fast food restaurants or applying fiscal measures nationally such as the sugar tax (27) and the behaviour change techniques used in these. Defining the types of behaviour change techniques that will be evaluated using the model will require further consideration of positive and negative outcomes. For example, in the intervention discussed in this thesis, although higher autonomous diet self-regulation was associated with a higher BMI, there was a decrease in this across all interventions suggesting that the behaviour change techniques used may be having a negative effect on some mechanisms of action.

iii) Identify and source evidence required for the model

The conceptual model developed will be used to identify the data needed for the model and sources of evidence. As identified in Chapter 6 and supported by previous research, there are relatively few formal mediation studies compared to the number of trials of weight management interventions (5). In the systematic review reported in Chapter 2, there were studies that were used as evidence sources for health economic models that had measured psychological variables but hadn't reported analysis on these variables. The analysis conducted in Chapter 3 is an example of this; this analysis may not have occurred if it wasn't part of this PhD thesis. This lack of emphasis on why an intervention works has been identified as a gap in the research and recommendations are that funders focus on mechanisms of action as a priority (19). Conducting mediation analyses and meta-analyses on studies in which potential mechanisms of action have been collected but not analysed would enable a greater understanding of how and why the intervention is, or isn't, effective. This would also make use of data already collected and contribute to ensuring that maximum impact is made from initial data collection. Further investigation is needed to establish the feasibility of doing this in terms of the quantity and quality of data available. In deciding a method of analysis, consideration of how this can be standardised such that the same methods are used across the interventions would be needed. A standardised method which

would be open access may also make it easier for others to conduct analyses that are directly comparable both of existing data sources and moving forward as new data is collected. Detailed and associated code for mediation analysis, would likely compliment the push to outline the behaviour change techniques used and the mechanisms targeted. Further investigation of methodologies would be needed to determine how results would be combined. The findings of ongoing projects such as the human behaviour change project, which aims to collate information on "What works, compared with what, for what behaviours, how well, for how long, with whom, in what setting, and why?" (21), will also be considered as another source of data to inform the health economic model.

iv) Summary

Ultimately, the health economic model developed through steps i-iii could be used as a tool to conduct pre-trial modelling for planned intervention as demonstrated in Chapter 6. Similarly to using standard code and tools to calculate sample size, justifiable cost could be calculated based on planned behaviour change techniques and the expected impact on the mechanisms of action, which would then be linked to BMI and long-term cost-effectiveness. This could also be used to conduct value of information analysis which could inform decision about trial including, the data collected in the trial or sample size. Pre-trial modelling can provide an estimate of the likelihood of cost-effectiveness to inform decisions regarding whether a trial is justified and/or whether changes can be made to the intervention to reduce the cost or increase effectiveness.

7.6 Conclusion

In this thesis, I have identified mechanisms of action of a weight management intervention, incorporated these into a health economic model, showed that BMI trajectories within health economic models can be predicted using mechanisms of action and demonstrated pre-trial modelling based on change in mechanisms of action. This is a starting point for ongoing research that could examine the impact of adding more mechanisms of action to the health economic model to accurately predict BMI trajectories and developing the model as a more useful tool for pre-trial modelling. This thesis is a multidisciplinary piece of work that has demonstrated methods in which research and methods in health psychology can inform health economic modelling and how health economic modelling can in turn inform intervention

design. Despite the limitations discussed, this research is a step towards understanding how psychological factors can be incorporated and the benefits and challenges of doing so. Incorporating psychological mechanisms of action into public health economic modelling has the potential to enhance the design of effective and cost-effective behavioural weight management interventions.

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Appendix 1: Author contributions

Chapter 2: Bates, S., Bayley, T., Norman, P., Breeze, P. and Brennan, A., 2020. A Systematic Review of Methods to Predict Weight Trajectories in Health Economic Models of Behavioral Weight-Management Programs: The Potential Role of Psychosocial Factors. *Medical Decision Making*, *40*(1), pp.90-105.

SB conceived of the idea, developed the search strategy, conducted the search strategy and produced the first draft of the manuscript. TB reviewed 10% of the search results and AB, PN and PB supervised the work and provided feedback on the final version of the manuscript.

Chapter 3: Bates, S., Norman, P., Breeze, P., Brennan, A., & Ahern, A. (2021). Mechanisms of action in a behavioural weight-management programme: latent growth curve analysis. Accepted for publication in *Annals of Behavioral Medicine*.

SB conceived the idea, conducted the analysis and wrote the manuscript. AB, PN and PB supervised the work. AA gave permission for use and provided the data that was used for the analysis. All authors provided feedback on the manuscript.

Chapter 5: Bates, S., Thomas, C., Islam, N., Ahern, A., Breeze, P. , Griffin, S. & Brennan, A. Using Health economic modelling to inform the design and development of an intervention: estimating the justifiable cost of weight loss maintenance in the UK. *Submitted to BMC Public Health.*

SB, AA, SG, AB, PB and CT conceived and planned the study. AA, NI, and SG designed and conducted the meta-analysis for estimated effect of intervention on BMI. SB, PB and CT conducted the health economic modelling. AB supervised the study. SB wrote the first draft of the manuscript.

Appendix 2: Secondary data analysis self-declaration

The University Of Sheffield.

Downloaded: 10/04/2021
Approved: 16/07/2018

Sarah Bates
Registration number: 160103922
School of Health and Related Research
Programme: PhD (Wellcome Trust Funded programme)

Dear Sarah

PROJECT TITLE: Association between psychological variables and BMI
APPLICATION: Reference Number 021946

This letter confirms that you have signed a University Research Ethics Committee-approved self-declaration to confirm that your research will involve only existing research, clinical or other data that has been robustly anonymised. You have judged it to be unlikely that this project would cause offence to those who originally provided the data, should they become aware of it.

As such, on behalf of the University Research Ethics Committee, I can confirm that your project can go ahead on the basis of this self-declaration.

If during the course of the project you need to deviate significantly from the above-approved documentation please inform me since full ethical review may be required.

Yours sincerely

Charlotte Claxton
Departmental Ethics Administrator

Appendix 3: School of Public Health Research (SPHR) model details

This model was described in detail in the supplementary material of a previously published article (Breeze PR, Thomas C, Squires H, Brennan A, Greaves C, Diggle P, Brunner E, Tabak A, Preston L & Chilcott J (2017) Cost-effectiveness of population-based, community, workplace and individual policies for diabetes prevention in the UK. *Diabetic Medicine*, 34(8), 1136-1144) and their description has been used below. Any adaptations that were made for this study are described in the main text. This article was published open access and thus permission were not required to include this work.

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Developing the Conceptual Model

The conceptual model was developed according to a new conceptual modeling framework for complex public health models (1). In line with this framework the conceptual model was developed in collaboration with a project stakeholder group comprising health economists, public health specialists, research collaborators from other SPHR groups, diabetologists, local commissioners and lay members. The initial broad scope for the conceptual model was based on the structure of previous diabetes prevention models used for National Institute for Health and Care Excellence public health guidance (2;3) and discussions with experts in diabetes prevention modeling. The model was further extended to include Dementia as a possible health outcome for individuals aged over 60 years in the model.

Model Structure

We developed an individual patient simulation that estimates individuals' health in yearly cycles until death. The simulation draws baseline demographic and clinical status for individuals sampled from the Health Survey for England (HSE) 2014 (4). The simulation estimates yearly changes in metabolic risk factors based upon the individuals' baseline characteristics. Within each annual cycle the individuals may be screened for hypertension, dyslipidaemia or diabetes during a visit to the General Practitioner (GP). Opportunistic screening is used to determine diabetes diagnosis or the initiation of anti-hypertensive treatment or statins. Baseline characteristics and metabolic risk factors determine the individuals' probability of cardiovascular events, diabetes microvascular complications, cancer, osteoarthritis and depression. Individuals within the model may die in any cycle as a result of cardiovascular disease, cancer or from other causes.

Figure 8 illustrates the sequence of updating clinical characteristics and clinical events that are estimated within a cycle of the model. This sequence is repeated for every annual cycle of the model. The first stage of the sequence updates the age of the individual. The second stage estimates how many times the individual attends the GP. The third stage estimates the change in BMI of the individual from the previous period. In the fourth stage, if the individual has not been diagnosed as diabetic (Diabetes_Dx=0) their change in glycaemia is estimated using the Whitehall II model. If they are diabetic (Diabetes_Dx=1), it is estimated using the UKPDS model. In stages five and six the individual's blood pressure and cholesterol are updated using the Whitehall II model if the individual is not identified as hypertensive or receiving statins. In stage seven, the individual may undergo assessment for diabetes, hypertension and dyslipidaemia during a GP consultation. From stage eight onwards the individual may experience cardiovascular outcomes, diabetes related complications, cancer, osteoarthritis, depression, dementia, and updated cognitive decline associated with dementia diagnosis. If the individual has a history of cardiovascular disease (CVD history=1), they follow a different pathway in stage eight to those without a history of cardiovascular disease (CVD history=0). Individuals with HbA1c greater than 48 mmol/mol (6.5%) are assumed to be at risk of diabetes related complications. Individuals who do not have a history of cancer (Cancer history=0) are at risk of cancer diagnosis, whereas those with a diagnosis of cancer (Cancer history=1) are at risk of mortality due to cancer. Individuals without a history of osteoarthritis or depression may develop these conditions in stages 12 and 13. In stage 14 individuals with dementia have their cognitive status updated and those individuals aged over 60 without a diagnosis of dementia may receive a diagnosis. Finally, all individuals are at risk of dying due non cardiovascular or cancer mortality. Death from renal disease is included in the estimate of other-cause mortality.

The modeling structure and cycle sequence is explained in more detail using a hypothetical patient below:

Consider a white male aged 53 sampled from the baseline population, referred to hereafter as Mr X. Mr X has a series of baseline demographics informed by the baseline population dataset, or imputation if missing. These characteristics influence his future health outcomes in the model. In the first cycle of the model the age of Mr X is 53. In this cycle Mr X's attendance at the GP is generated and recorded within the model dependent upon his age and gender. In the first cycle of the model Mr X's BMI is extracted from his baseline data. The effect of an intervention on BMI in the first 12 months is applied here if required. Similarly baseline values for HbA1c, systolic blood pressure (SBP), total cholesterol, and HDL cholesterol are extracted from his baseline dataset and modified for treatment effect if necessary. If Mr X has attended the GP in this cycle he may receive opportunistic screening for diabetes, hypertension or high cardiovascular risk if he meets certain risk criteria, agreed by the stakeholder group. If he is diagnosed with any of these conditions/risks, treatments are initiated according to current guidelines in the UK for diabetes diagnosis, anti-hypertensive treatment and statin treatment. If Mr X receives any of these treatments his HbA1c, SBP and/or total cholesterol are reduced accordingly.

Having established Mr X's metabolic risk profile the model determines if Mr X experiences any major health events in this first cycle. If Mr X does not have a history of cardiovascular disease (CVD) the model estimates the probability that he has a fatal or non-fatal cardiovascular event in this cycle. The event is determined using a Bernoulli trial. If Mr X has a history of CVD his probability of a progressing to unstable angina, MI, stroke or a fatal event is determined. If Mr X has HbA1c greater than 48 mmol/mol (6.5%) or a diagnosis of diabetes, the probability of foot ulcer, renal disease, amputation and blindness are calculated and evaluated using a Bernoulli trial. If Mr X does not have diabetes he is not at risk of these complications in this cycle.

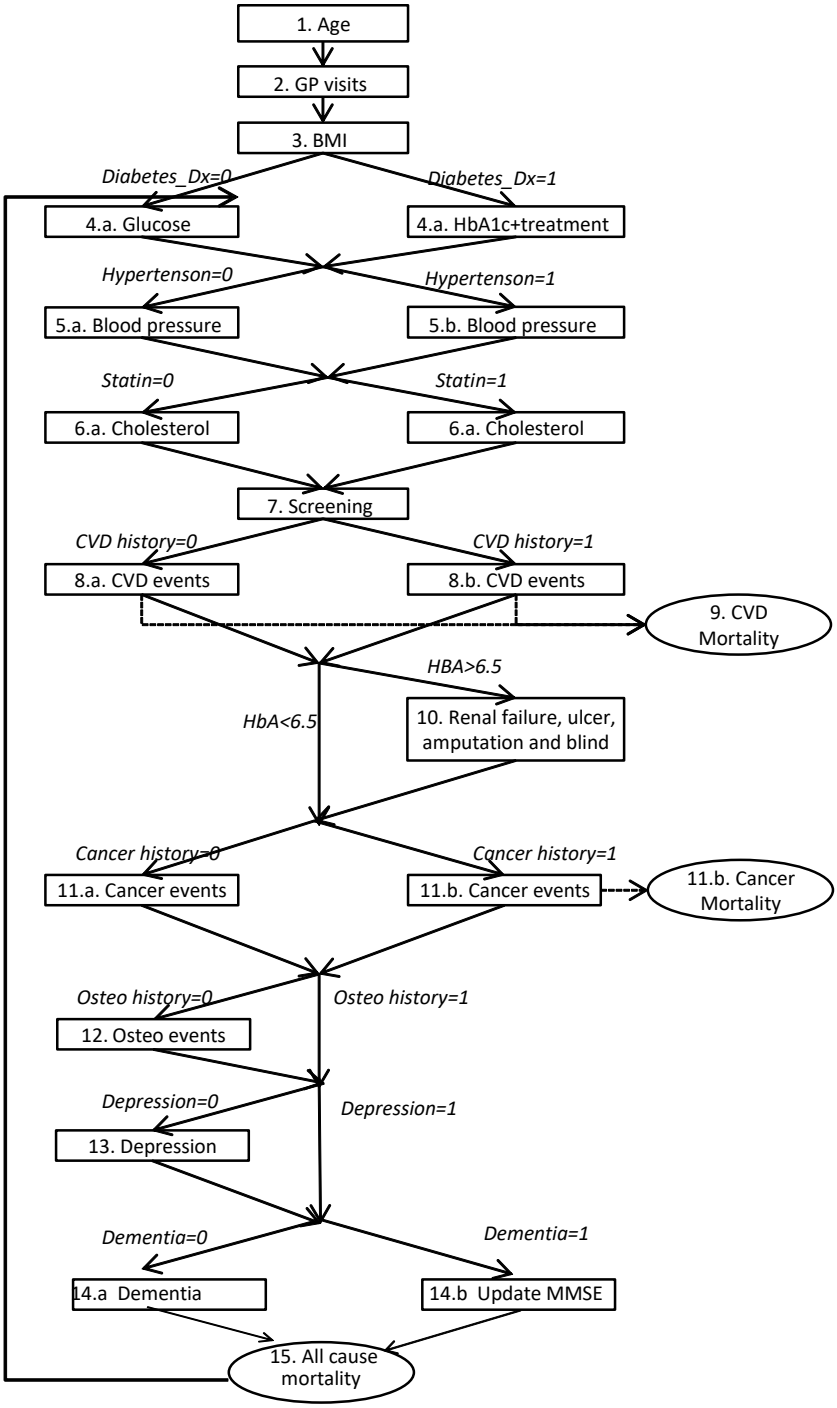
In the next stage of the cycle Mr X may develop breast or colon cancer if he has not already got a history of cancer. The probability of these complications is generated and evaluated in a Bernoulli

trial. If Mr X has a history of cancer, he is at risk of mortality due to cancer in this cycle. If Mr X does not have osteoarthritis the probability of developing this complication is evaluated in this cycle and a diagnosis is given according to a Bernoulli trial. If Mr X has a diagnosis of osteoarthritis his health status for this complication remains unchanged. Similarly, if Mr X does not have depression the probability of developing it is evaluated in this cycle and a diagnosis is given according to a Bernoulli trial. If Mr X has a diagnosis of depression his health status for this complication remains unchanged. If Mr X is over 60 years old and does not have a diagnosis of dementia, he may receive a new diagnosis according to a Bernoulli trial using his current probability of a dementia diagnosis. If Mr X has an existing diagnosis of dementia his MMSE score will be updated to reflect any deterioration in memory and disease severity.

Finally, assuming Mr X has not experienced a fatal event due to CVD or cancer, the probability of death is calculated and evaluated in a Bernoulli trial based on Office of National Statistics life tables combined with hazard ratios for dementia and diagnosis (5). If Mr X remains alive he proceeds to the next cycle. If Mr X dies his health status, costs and QALYs are stored and he is removed from the model.

In the second and subsequent cycles, the model proceeds through a similar sequence of events. However, Mr X firstly ages by the cycle length of one year. A new number of GP visits within the cycle is generated. BMI will increase or decrease according to a trajectory assigned to Mr X at baseline, and intervention effect maintenance if relevant. Similarly, HbA1c, SBP, total cholesterol, and HDL cholesterol all change in this period on a prespecified trajectory and intervention effect. Mr X may undergo opportunistic screening as specified in year one. The sequence of evaluations to determine health events and complications experienced by Mr X in this cycle is the same as described above, however Mr X's metabolic risk factors, treatments, and history are updated with the changes described above.

Figure 8: Model Schematic



Baseline Population Characteristics: Health Survey for England

The model required demographic, anthropometric and metabolic characteristics that would be representative of the UK general population. The Heath Survey for England (HSE) was suggested by the stakeholder group because it collects up-to-date cross-sectional data on the characteristics of all ages of the English population. It also benefits from being a reasonably good representation of the socioeconomic profile of England. A major advantage of this dataset is that includes important clinical risk factors such as HbA1c, SBP, and cholesterol. The characteristics of individuals included in the cost-effectiveness model were based sampled from the HSE 2014 dataset (4). The whole dataset was obtained from the UK Data Service.

Exclusion Criteria

The total sample size of the HSE 2014 was 10,080. Individuals from the HSE dataset who were younger than 16 years (N=2003) were excluded from the sample. This left a final sample size of 8077 individuals.

Summary statistics for the data extracted from the HSE2014 dataset are reported in Table 9.

Table 9: Characteristics of final sample from HSE 2014 (N=8077)

Variable name (description)	Mean	Median	SD	Missing (N)
Age	50.02	49.00	18.63	0
Income	33810	24700	29246	1567
Weight	77.61	75.80	17.26	990
Height	167.7	167.3	9.74	938
BMI	27.52	26.66	5.48	1132
Waist	93.10	92.55	14.39	2818
Hip	105.6	104.1	15.95	2813
Waist-Hip ratio	0.881	0.879	0.092	2832
Total Cholesterol	5.194	5.1	1.104	4176
HDL Cholesterol	1.545	1.5	0.452	4175
HbA1c	5.615	5.4	0.785	4183
SBP	126.2	124.5	17.22	3208
DBP	72.75	72.5	11.07	3408
Total units alcohol	12.6	6.04	21.55	177
Minute vigorous exercise	65.45	30.0	107.66	1170

Minutes walking	89.45	60.00	114.86	1238
EQ-5D	0.8767	1	0.189	187

Table 10: Summary data for categorical (N=8077)

Variable name (description)	Category	N	%
Sex	Male	3588	44.4%
	Female	4489	55.6%
	Missing	0	0%
Economic Activity	In employment	4334	53.7%
	ILO unemployment	315	3.8%
	Retired	2140	26.5%
	Other Inactive	1263	15.6%
	Missing	25	0.3%
Origin	White British	6653	82.4%
	White Irish	76	0.9%
	White other	421	5%
	White and Black Caribbean	32	0.3%
	White and Black African	11	0.1%
	White and Asian	17	0.2%
	Other mixed	44	0.5%
	Indian	198	2%
	Pakistani	146	2%
	Bangladeshi	47	0.6%
	Chinese	44	0.5%
	Other Asian	91	1%
	African	105	1.3%
	Caribbean	73	0.9%
	Other Black	18	0.2%
	Arab	25	0.3%
	Other	44	0.5%
	Missing	32	0.4%
Urban	Urban	3324	41.2%
	Town	273	3.4%
	Village	4480	55.5%
QIMD	0.53-8.49 (least deprived)	1777	22%
	8.49-13.79	1611	20.0%
	13.79-21.35	1557	19.3%
	21.35-34.17	1602	19.8%
	34.17-87.80 (most deprived)	1530	18.9%
Smoking group	Current	1444	17.9%
	Ex-smoker	2033	25.2%
	Never smoke	4535	56.1%
	Missing	65	0.8%
Smoking level	Low smoker	534	6.6%
	Moderate smoker	627	7.8%

	Heavy smoker	276	3.4%
	Don’t know	7	0.1%
	Non-smoker	6570	81.3%
	Missing	63	0.8%
Hypertensive treatment	Yes	1492	18.5%
	No	478	5.9%
	Missing	6107	75.6%
Statins	No	4545	56.3%
	Yes	946	11.7%
	Missing	2586	32.0%
Long term illness 1	15:Stroke	32	0.4%
	16:Heart attack/angina	67	0.8%
	17:Other heart	148	2%
	34:Arthritis/rheumatism	396	4.9%
	Missing	4683	58.0%
Long term illness 2	15:Stroke	14	0.2%
	16:Heart attack/angina	56	0.7%
	17:Other heart	88	1.1%
	34:Arthritis/rheumatism	166	2%
	Missing	6275	77.7%
Long term illness 3	15:Stroke	13	0.2%
	16:Heart attack/angina	8	0.1%
	17:Other heart	30	0.4%
	34:Arthritis/rheumatism	89	1.1%
	Missing	7176	88.8%
Long term illness 4	15:Stroke	6	0.1%
	16:Heart attack/angina	8	0.1%
	17:Other heart	13	0.2%
	34:Arthritis/rheumatism	42	0.5%
	Missing	7623	94.4%
Long term illness 5	15:Stroke	8	0.1%
	16:Heart attack/angina	3	0.04%
	17:Other heart	13	0.2%
	34:Arthritis/rheumatism	15	0.2%
	Missing	7860	97.3%
Long term illness 6	15:Stroke	1	0.01%
	16:Heart attack/angina	2	0.02%
	17:Other heart	2	0.02%
	34:Arthritis/rheumatism	13	0.2%
	Missing	7975	98.7%
Diabetes	Yes	548	6.7%
	No	7525	93.2%
	Missing	4	0.05%

Depression	Yes self reported diagnosis	1107	13.7%
	Yes not self reported diagnosis	401	5.0%
	No	3977	49.2%
	Missing	2592	32.1%
Dementia	Yes self reported diagnosis	11	0.1%
	Yes not self reported diagnosis	7	0.1%
	No	5467	67.7%
	Missing	2592	32.1%
Alcohol Problem	Yes	67	0.8%
	No	61	0.8 %
	Missing	7949	98%

A complete dataset was required for all individuals at baseline. However, no measurements for Fasting Plasma Glucose (FPG) or 2 hour glucose were obtained for the HSE 2014 cohort. In addition, the questionnaire did not collect information about individual family history of diabetes or family history of CVD. These variables were imputed from the Whitehall II dataset (see below) (5;6).

Many individuals were lacking responses to some questions but had data for others. One way of dealing with this was to exclude all individuals with incomplete data from the sample. However, this would have reduced the sample size and representativeness dramatically, which would have been detrimental to the analysis. It was decided that it would be better to make use of all the data available to represent a broad range of individuals within the UK population. With this in mind, we decided to use assumptions and imputation models to estimate missing data.

From this population individuals with a HbA1c above 6% were selected according to the criteria for the Diabetes Prevention Programme. The characteristics of the eligible population entering the model are summarized in Table 11.

Table 11 Diabetes Prevention Programme eligible population from Health Survey for England 2014 (N=2,329) with imputation of missing values

	Number	Percentage	
Male	1042	44.7%	
Non-white	249	10.7%	

IMD 1 (least deprived)	480	20.6%	
IMD 2	509	21.9%	
IMD 3	462	19.8%	
IMD 4	437	18.8%	
IMD 5 (most deprived)	441	18.9%	
Current Smoker	446	19.1%	
Past Smoker	684	29.4%	
Hypertension	615	26.4%	
	Mean	Standard deviation	Median
Age (years)	57.1	17.6	59
BMI (kg/m2)	28.5	5.4	28
Systolic Blood Pressure (mmHg)	129.9	17.7	130
Total Cholesterol (mmol/l)	5.2	1.1	5.2
HDL Cholesterol (mmol/l)l	1.5	0.47	1.5
HbA1c (mmol/l)	6.2	0.15	6.2

HSE 2014 Missing data imputation

Ethnicity

Only a small number of individuals had missing data for ethnicity. In the QRISK2 algorithm the indicator for white included individuals for whom ethnicity is not recorded. In order to be consistent with the QRISK2 algorithm we assumed that individuals with missing ethnicity data were white.

Anthropometric data

Data were imputed using linear regression models to describe patterns observed within the dataset. Simple ordinary least squares (OLS) regression models were used to predict missing data. Missing data were sampled stochastically from the conditional distributions to allow variability in imputed values.

Summary data for each measure confirmed that the data were approximately normally distributed. Covariate selection was made by selecting the anthropometric measure that maximised the Adjusted R-squared statistic, and age and sex were included if the coefficients were statistically significant ($P<0.1$). For height and weight, waist circumference was found to improve model fit.

Metabolic data

Imputation models for metabolic data were developed utilising observations from other measures to help improve their accuracy.

Two imputation models were generated for each of the following metabolic measures: total cholesterol, HDL cholesterol, HbA1c, and SBP. The first imputation method included an alternative metabolic measure to improve precision. The second included only age and/or sex, to be used if the alternative measure was also missing. Simple ordinary least squares (OLS) regression models were used to predict missing data. Summary data for each measure confirmed that the data were approximately normally distributed. Covariate selection was made by selecting the metabolic measure that maximised the Adjusted R-squared statistic, and age and sex were included if the coefficients were statistically significant ($P<0.1$).

Treatment for Hypertension and Statins

A large proportion of individuals had missing data for questions relating to whether they received treatment for hypertension or high cholesterol. The majority of non-responses to these questions were coded to suggest that the question was not applicable to the individual. As a consequence it was assumed that individuals with missing treatment data were not taking these medications.

Anxiety/Depression

Most individuals who had missing data for anxiety and depression did so because the question was not applicable. A small sample N=69 refused to answer the question. We assumed that individuals with missing data for anxiety and depression did not have severe anxiety/depression.

Smoking

Individuals with missing data for smoking status were assumed to be non-smokers, without a history of smoking.

Rheumatoid Arthritis

Indiivduals reporting existing arthritis/rheumatism were assigned to a history rheumatoid arthritis.

Atrial Fibrillation

Individuals reporting "other heart conditions" in response to questions about long-standing illnesses were assumed to have a history of Atrial Fibrillation.

Family history of diabetes

No questions in the HSE referred to the individual having a family history of diabetes, so this data had to be imputed. It was important that data was correlated with other risk factors for diabetes, such as HbA1c and ethnicity. We analysed a cross-section of the Whitehall II dataset to generate a logistic regression to describe the probability that an individual has a history of diabetes conditional on their HbA1c and ethnic origin. The model is described in Table 12.

Table 12: Imputation model for history of diabetes

	Coefficient	Standard error
Intercept	-3.29077	0.4430
HbA1c	0.28960	0.0840
HDL Cholesterol	0.81940	0.1388

History of Cardiovascular disease

Individuals with a history of cardiovascular disease were assigned to a health status of either stable angina, unstable angina, myocardial infarction, or stroke based on responses to health survey for England responses to long standing conditions. Individuals reporting stroke were assigned to stroke,

heart attak/angina to unstable angina and MI at random using distributions estimated in the statins HTA (7).

GP Attendance in the General Population

GP visit frequency was simulated in the dataset for two reasons; firstly to estimate healthcare utilisation for the general population; secondly to predict the likelihood that individuals participate in opportunistic screening for diabetes and vascular risks. It was useful to develop a model of GP attendance to be conditional on characteristics in the cost-effectiveness model that are known to be associated with GP attendance, such as age and comorbidities. A negative binomial model was used to generate count data and a skewed distribution as observed in the dataset.

$$\mu_i = \exp(x_i\beta)$$

The dispersion parameter of the Negative Binomial distribution v_i was sampled from a gamma distribution with mean 1 and variance α based on estimates reported in Table 14. The dose was estimated from the Poisson function.

$$p(Y = y|y > 0, x) = \frac{(v_i\mu_i)^y e^{-(v_i\mu_i)}}{y!}$$

The HSE 2014 did not collect data on GP attendance frequency, therefore an alternative UK survey was sought. The South Yorkshire cohort collected data about the frequency of GP attendance in the past 3 months from a representative cross-section of individuals in South Yorkshire (8). All individuals in the cohort were included in the analysis, including those with diabetes. The characteristics of the study population are reported in Table 58.

Table 58: Characteristics of the first wave of the South Yorkshire Cohort (N=27,806)

	Number	Percentage	
Male	12,155	43.7	
White	26,419	95.0	
Non-smoker	23,158	83.3	
Employed (inc. self-employed)	18,502	66.5	
Long-standing illness (any)	16,664	60.0	
Diabetes	2,000	7.2	
Cardiovascular disease	2,438	8.8	
Hypertension	5,653	20.3	
	Mean	Standard deviation	Median

Age	54.45	17.25	57.00
BMI	26.46	5.05	25.68
EQ-5D (TTO)	0.803	0.253	0.848
GP attendances in past 3 months	2.03	1.83	1.00
BMI Body Mass Index; EQ-5D 5 dimensions Euroqol (health related quality of life index)			

The coefficients of the Negative Binomial model described in Table 14 were used to estimate the first parameter of the Negative Binomial distribution μ_i. Analysis of the South Yorkshire cohort (Table 14) was used to describe GP attendance conditional on age, sex, BMI, ethnicity, and health outcomes. The estimated number of GP visits was multiplied by 4 to reflect the annual number of visits per year. In the probabilistic sensitivity analysis the parameters of the South Yorkshire negative binomial model are sampled from a multivariate normal distribution, using the mean estimates described in Table 14 and covariance matrix in Table 60.

Table 14: GP attendance reported in the South Yorkshire Cohort (N= 18,437)

	Mean	Standard error	Uncertainty Distribution
Age	0.0076	0.0005	MULTIVARIATE NORMAL
Male	-0.1495	0.0159	MULTIVARIATE NORMAL
BMI	0.0110	0.0015	MULTIVARIATE NORMAL
Ethnicity (Non-white)	0.2620	0.0375	MULTIVARIATE NORMAL
Heart Disease	0.2533	0.0289	MULTIVARIATE NORMAL
Depression	0.6127	0.0224	MULTIVARIATE NORMAL
Osteoarthritis	0.2641	0.0238	MULTIVARIATE NORMAL
Diabetes	0.2702	0.0278	MULTIVARIATE NORMAL
Stroke	0.1659	0.0474	MULTIVARIATE NORMAL
Cancer	0.2672	0.0414	MULTIVARIATE NORMAL
Intercept	-0.5014	0.0468	MULTIVARIATE NORMAL
Alpha	0.3423	0.0108	MULTIVARIATE NORMAL

Table 60: Variance-covariance matrix for GP attendance regression

	Age	Male	BMI	Ethnicity (Non-white)	Heart Disease	Depression	Osteoarthritis	Diabetes	Stroke	Cancer	Intercept	Alpha
Age	0.0000											
Male	0.0000	0.0003										
BMI	0.0000	0.0000	0.0000									
Ethnicity (Non-white)	0.0000	0.0000	0.0000	0.0014								
Heart Disease	0.0000	0.0000	0.0000	0.0000	0.0008							
Depression	0.0000	0.0000	0.0000	0.0000	0.0000	0.0005						
Osteoarthritis	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0006					

Diabetes	0.0000	0.0000	0.0000	0.0000	-0.0001	0.0000	0.0000	0.0008				
Stroke	0.0000	0.0000	0.0000	0.0000	-0.0002	-0.0001	0.0000	-0.0001	0.0022			
Cancer	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-0.0001	0.0017		
Intercept	0.0000	0.0000	-0.0001	-0.0002	0.0002	0.0000	0.0002	0.0003	0.0000	0.0001	0.0022	
Alpha	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0010

Longitudinal Trajectories of Metabolic Risk Factors

Two separate sets of statistical analyses of longitudinal cohort studies were used to describe metabolic trajectories for individuals in the model. An analysis of the Whitehall II cohort study (6) was developed to describe correlated longitudinal changes in metabolic risk factors for individuals aged 60 years and younger. An analysis of the Englished Longitudinal Study of Ageing was used to describe trajectories for individuals aged 61 and over. The transition point of 61 years was found to be the age at which there were more data observations for participants in ELSA compared with Whitehall. A summary for each set of metabolic trajectory models are provided below.

Whitehall II Data Analysis

Changes in BMI, latent blood glucose, total cholesterol, HDL cholesterol and SBP were estimated from statistical analysis of the Whitehall II cohort. The growth factors for all 5 risk factors were estimated using parallel latent growth modelling. This enabled the growth factors for BMI to be implemented as covariates for the growth processes of glycaemia, systolic blood pressure, and total cholesterol[1]. The structural assumptions of the analysis are described in more detail below.

In the Whitehall II data analysis it was assumed that individuals have an underlying level of glycaemia, which cannot be observed but can be measured by HbA1c, FPG, and 2-hour glucose. This

[1]The model did not converge when BMI slope was included as a predictor for HDL growth.

underlying propensity for diabetes is referred to as latent glycaemia. The statistical model estimated the unobservable latent glycaemia, and from this identified associations with test results for HbA1c, FPG, and 2-hour glucose. The longitudinal changes in BMI, glycaemia, SBP, total cholesterol and HDL cholesterol could then be estimated through statistical analysis.

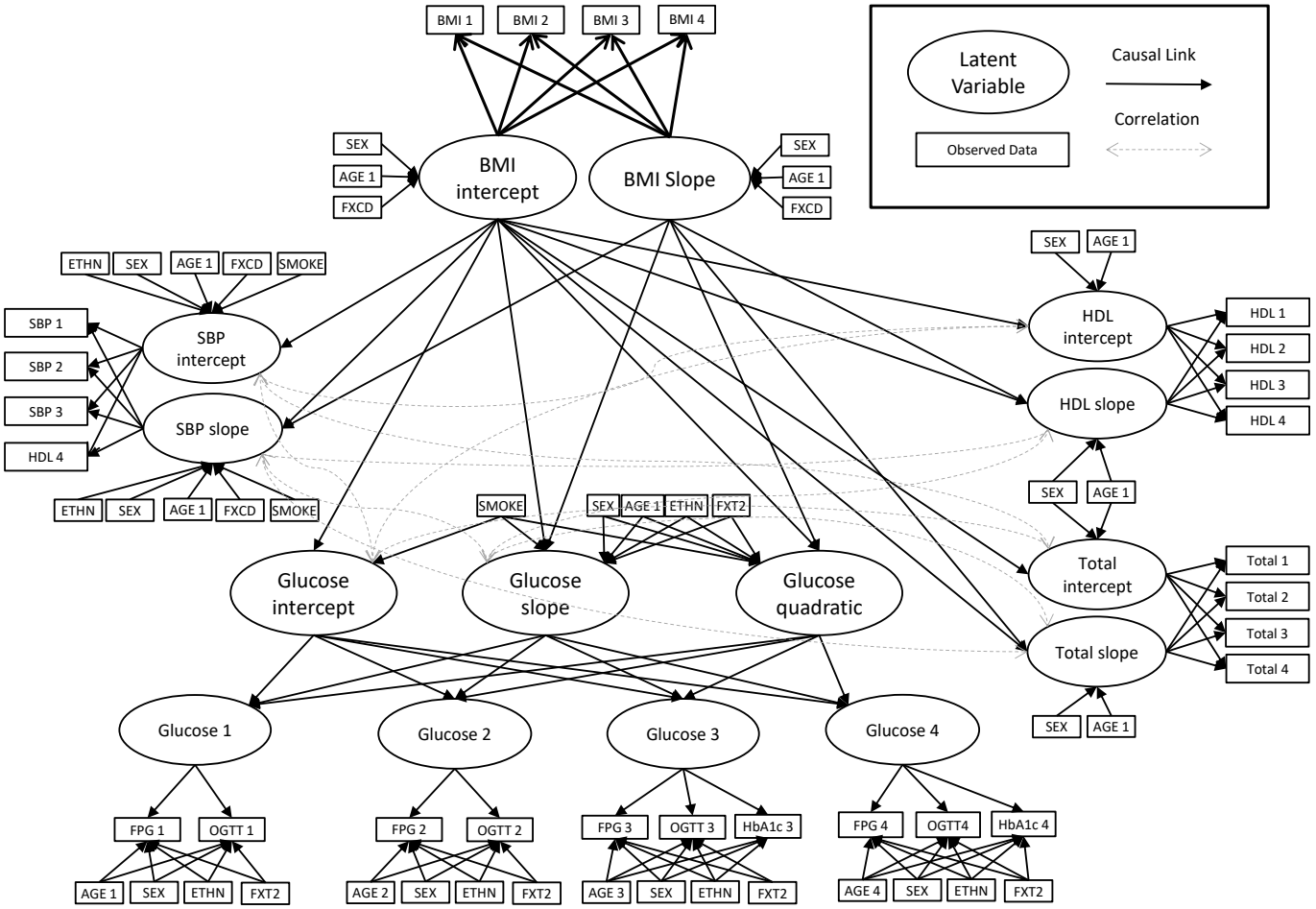
These growth factors are conditional on several individual characteristics including age, sex, ethnicity, smoking, family history of CVD, and family history of type 2 diabetes. We related the effect of changes in BMI to changes in glycaemia, SBP and total cholesterol. However, if an intervention is known to be effective in reducing BMI and the other metabolic risk factors, the Whitehall II model is adjusted to temporarily remove the indirect effect of the intervention through BMI. This ensures that the effectiveness of the intervention is not over-estimated. Unobservable heterogeneity between individual growth factors not explained by patient characteristics was incorporated into the growth models as random error terms. Correlation between the random error terms for glycaemia, total cholesterol, HDL cholesterol and systolic blood pressure was estimated from the Whitehall II cohort. This means that in the simulation, an individual with a higher growth rate for glycaemia was more likely to have a higher growth rate of total cholesterol and SBP.

An advantage of this parallel growth analysis is that it was able to estimate the effect of growth in BMI on the other metabolic risk factors. The statistical analysis also described the correlation between changes in glycaemia, SBP, total cholesterol and HDL cholesterol. As a consequence, the growth factor random error terms were not assumed to be independent and were sampled from a multivariate normal distribution $\boldsymbol{\upsilon} \sim N(0, \Omega)$. Estimates for the covariance matrix are derived from the covariance estimates reported in the statistical analysis.

The baseline observations for BMI, HbA1c, SBP, cholesterol and HDL cholesterol were extracted from the Health Survey for England 2014 in order to simulate a representative sample of the UK

population. The predicted intercept for these metabolic risk factors was estimated using the Whitehall II analysis to give population estimates of the individuals' starting values, conditional on their characteristics. The difference between the simulated and observed baseline risk factors was taken to estimate the individuals' random deviation from the population expectation. The individual random error in the slope trajectory was sampled from a conditional multivariate normal distribution to allow correlation between the intercept and slope random errors.

Figure 9: Path analysis of final statistical analysis of the Whitehall II cohort



ELSA Data Analysis

Changes in BMI, HbA1c, systolic blood pressure, total cholesterol and HDL cholesterol were estimated from a statistical analysis of the ELSA cohort. The changes with age were estimated using independently estimate random coefficient growth models in Stata 13. The growth trajectory models for the metabolic risk factor were estimated under the statistical framework of growth curve modelling (GCM) (9). GCM is an approach to using longitudinal data to estimate shape and rate of change over time. GCM was chosen because it can allow modelling of variability in participants fixed and slope parameters. The growth factors for the metabolic risk factors were assumed to vary between individuals to allow unobservable random effects to describe the heterogeneity in intercept and slope parameters. Assessment of the data indicated that there was significant variance in the intercept (risk factor starting value) and slope (change in risk factor over time) for all metabolic risks. The growth factor models without covariates were specified as.

$$Y_{ij} = (\beta_1 + \zeta_{1j}) + (\beta_2 + \zeta_{2j})t_{ij} + \epsilon_{ij}$$

Where Y describes the observed metabolic risk factor for individual i at time j, β_1 is the population mean intercept, and β_2 population mean slope. The random factors ζ_{1j} and ζ_{2j} describe the random variability across individuals in the intercept and slopes respectively. The statistical models were weighted for selection bias using nurse visit weights for BMI and systolic blood pressure and blood sample weights for Total Cholesterol, HDL Cholesterol and HbA1c supplied by the ELSA dataset to improve the representativeness of the analysis for an English population.

The model assumed that BMI growth was quadratic with age, due to trends observed in the data and in other cohorts (10). HbA1c, systolic blood pressure, total cholesterol and HDL cholesterol were assumed to be linear with time. All model intercepts and slopes were adjusted for sex, smoking status, deprivation and ethnicity. Anti-hypertensive treatment was included as an additional covariate in the systolic blood pressure model. Unfortunately data on statin were not available for any wave except wave 6, therefore we did not include this as a covariate in the analysis. Covariates were included in the final model if the variable was statistical significant with a p-value less than 0.1.

A full list of model parameters estimated from the statistical analysis of the Whitehall II data and ELSA data are presented in Supplementary file 2.

BMI Trajectory

At baseline, BMI estimates from the HSE determine an individual's BMI. If the individual is aged 60 years or less annual changes in BMI are calculated from the Whitehall II study based on population average changes for the individual and a sampled random coefficient factor. From ages 61 and over the ELSA BMI statistical model is used estimate their older age trajectory in BMI. New random coefficient growth factors are estimated based on the covariance structure of the ELSA random intercept and slope. As a consequence, current BMI status is informative in determining the future trajectory of BMI.

Glycaemic Trajectory in Non-Diabetics/undiagnosed Diabetes

At baseline, HbA1c estimates for HbA1c are used to determine an individual's HbA1c and glycaemic status. For individuals aged 60 years or less the Whitehall II study is used to estimate annual changes in HbA1c, and through latent glycaemia FPG, and 2-hr glucose observations. In the Whitehall II analysis we assume that changes in latent glycaemia have a quadratic relationship with time. The Whitehall II models allow random coefficient factors for growth in glycaemia for an individual and measurement error in test results according to estimated parameters from the Whitehall II analysis. For individuals aged 61 and over the ELSA statistical model is used to estimate an individuals linear changes in HbA1c evry year. Random coefficient growth factors are re-estimated using the bivariate covariance structure from the ELSA HbA1c growth model. It is not possible to estimate FPG and 2-hr glucose using the ELSA statistical models.

HbA1c trajectory in type 2 diagnosed diabetics

Following a diagnosis of diabetes in the simulation all individuals experience an initial fall in HbA1c due to changes in diet and lifestyle as observed in the UKPDS trial (11). We have estimated the expected change in HbA1c conditional on HbA1c at diagnosis by fitting a simple linear regression to three aggregate outcomes reported in the study. These showed that the change in HbA1c increases for

higher HbA1c scores at diagnosis. The regression parameters to estimate change in HbA1c are reported in Table 61.

Table 61: Estimated change in HbA1c following diabetes diagnosis

	Mean	Standard error
Change in HbA1c Intercept	-2.9465	0.0444513
HbA1c at baseline	0.5184	0.4521958

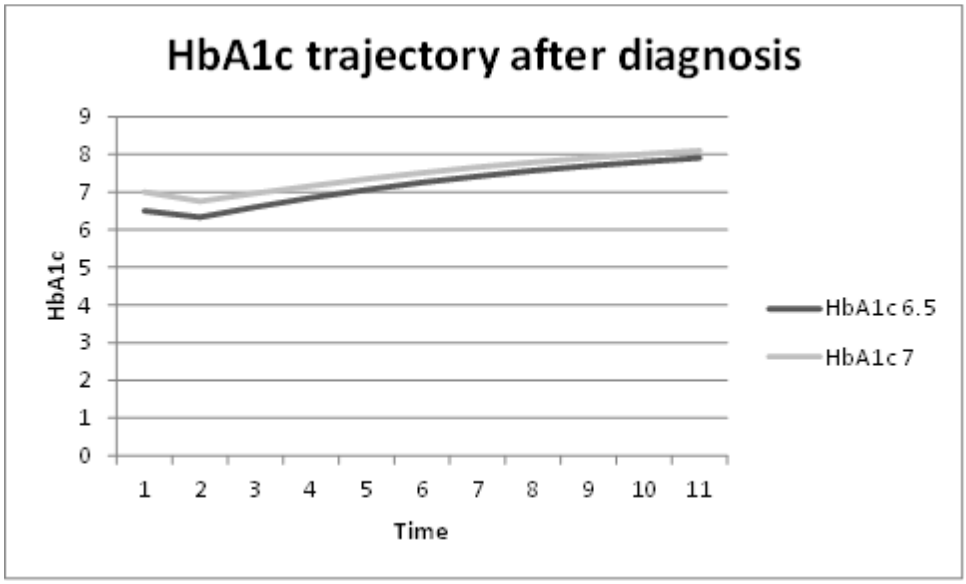
After this initial reduction in HbA1c the longitudinal trajectory of HbA1c is estimated using the UKPDS outcomes model (11) rather than the Whitehall II statistical analysis. The UKPDS dataset is made up of a newly diagnosed diabetic population. As part of the UKPDS Outcomes model, longitudinal trial data were analysed using a random effects model. The coefficients of the model are reported in Table 62.

Table 62: Coefficient estimates for HbA1c estimated from UKPDS data

	Mean Coefficient	Coefficient standard error
Intercept	-0.024	0.017
Log transformation of year since diagnosis	0.144	0.009
Binary variable for year after diagnosis	-0.333	0.05
HbA1c score in last period	0.759	0.004
HbA1c score at diagnosis	0.085	0.004

The model can be used to predict HbA1c over time from the point of diagnosis. The model suggests that HbA1c increases with time. A graph illustrating change in HbA1c over time from two different HbA1c levels at diagnosis is illustrated in Figure 10.

Figure 10: Trajectory of HbA1c estimated from UKPDS longitudinal model



Total Cholesterol and HDL Cholesterol Trajectories in Individuals not receiving Statins

At baseline, an individual's total and HDL cholesterol is determined from the HSE 2014 data. In the simulation, individuals aged 60 years and younger have annual changes in total and HDL cholesterol according to the estimates from the statistical analysis of the Whitehall II cohort. The slope of total and HDL cholesterol are assumed to be linear with time. These growth factors are estimated in the model to be conditional on cholesterol at baseline, age at baseline, sex, and an error parameter to reflect unobservable variability in growth trajectories between individuals. As with latent glycaemia, changes in total cholesterol are also influenced by the trajectory of BMI. For individuals aged 61 and over the ELSA statistical models for Total and HDL cholesterol are used to estimate annual change in cholesterol. As individuals transition between the trajectory models the random coefficient factors are updated allowing current observations to inform the trajectories in Total and HDL cholesterol.

Total Cholesterol and HDL Cholesterol Trajectories in Individuals receiving Statins

During the simulation process, individuals are prescribed statins to reduce their risk of cardiovascular disease. It is assumed within the model that the statins are effective in reducing an individual's total cholesterol, and an average effect is applied to all patients receiving statins. A recent HTA reviewed the literature on the effectiveness and cost-effectiveness of statins in individuals with acute coronary

syndrome (12). This report estimated the change in LDL cholesterol for four statin treatments and doses compared with placebo from a Bayesian meta-analysis. The analysis estimated a reduction in LDL cholesterol of -1.45 for simvastatin. This estimate was used to describe the effect of statins in reducing total cholesterol. It was assumed that the effect was instantaneous upon receiving statins and maintained as long as the individual receives statins. It was also assumed that individuals receiving statins no longer experienced annual changes in total cholesterol. HDL cholesterol was assumed constant over time if patients receive statins.

Non-adherence to statin treatment is a common problem. Two recent HTAs reviewed the literature on continuation and compliance with statin treatment. They both concluded that there was a lack of adequate reporting, but that the proportion of patients fully compliant with treatment appears to decrease with time, particularly in the first 12 months after initiating treatment, and can fall below 60% after five years (7;12). Although a certain amount of non-compliance is included within trial data, clinical trials are not considered to be representative of continuation and compliance in general practice. A yearly reduction in statin compliance used in the HTA analysis is reported in Table 63. It is based on the published estimate of compliance for the first five years of statin treatment for primary prevention in general clinical practice (12). Compliance declines to a minimum of 65% after five years of treatment. It is assumed that there is no further drop after five years.

Table 63: Proportion of patients assumed to be compliant with statin treatment, derived from Table 62 in (12)

Year after statin initiation	1	2	3	4	5
Proportion compliant	0.8	0.7	0.68	0.65	0.65

In the simulation, we assume in the base case that only 65% of individuals initiate statins when they are deemed eligible. However those that initiate statins remain on statins for their lifetime. Those who refuse statins may be prescribed them again at a later date.

SBP Trajectories in Individuals Not receiving Anti-hypertensive treatment

At baseline an individual's SBP is determined from the HSE 2014 data. In the simulation, individuals' aged 60 and younger experience SBP changes every year according to the estimates from the statistical analysis of the Whitehall II cohort. The annual change in SBP is assumed to be linear with time. The growth factors are estimated in the model to be conditional on SBP at baseline, age at baseline, sex, ethnicity, family history of cardiovascular disease, smoking and an error parameter to reflect unobservable variability in growth trajectories between individuals. From ages 61 onwards the ELSA statistical model for systolic blood pressure is used to estimate annual changes. The random coefficient factors are updated using the bivariate covariance matrix for intercept and slope factors.

SBP Trajectories in Individuals receiving anti-hypertensive treatment

During the simulation process, if individuals are identified as having SBP higher than 160mm Hg, or SBP higher than 140mm Hg with comorbid diabetes, cardiovascular disease, or 10 year risk of cardiovascular disease greater than 20%, they will be prescribed anti-hypertensive treatment in line with the National Institute for Health and Care Excellence (NICE) guidelines (13). The change in SBP following initiation of calcium channel blockers was estimated in a meta-analysis of anti-hypertensive treatments (14). This study identified an average change in SBP of -8.4 for monotherapy with calcium channel blockers. In the simulation model it is assumed that this reduction in SBP is maintained for as long as the individual receives anti-hypertensive treatment. Once an individual is receiving anti-hypertensive treatment it is assumed that their SBP is stable and does not change over time, which implicitly assumes that patients continue to be well managed for their hypertension. For simplicity we do not explicitly simulate treatment switching. The assumed zero flat trajectory in systolic blood pressure whilst receiving anti-hypertensives is supported by the analysis of the ELSA dataset in which self-reported use of anti-hypertensives was included as a covariate for age-related change in systolic blood pressure. The analysis found that most of the observed changes in systolic blood pressure were removed if individuals were taking anti-hypertensives.

Metabolic Risk factor screening

We assume that individuals eligible for anti-hypertensive treatment or statins will be identified through opportunistic screening if they meet certain criteria and attend the GP for at least one visit in the simulation period.

1. Individuals with a history of cardiovascular disease;
2. Individuals with a major microvascular event (foot ulcer, blindness, renal failure or amputation);
3. Individuals with diagnosed diabetes;
4. Individuals identified with Impaired Glucose Regulation;
5. Individuals with systolic blood pressure greater than 160mmHg.

Individuals may also be detected for diabetes through opportunistic screening if the following criteria are met.

1. Individuals with a history of cardiovascular disease;
2. Individuals with a major microvascular event (foot ulcer, blindness, renal failure or amputation);
3. Individuals identified with impaired glucose regulation;
4. At baseline individuals are assigned an HbA1c threshold above which diabetes is detected opportunistically, individuals with an HbA1c above their individual threshold will attend the GP to be diagnosed with diabetes. The threshold is sampled from the distribution of HbA1c tests in a cohort of recently diagnosed patients in clinical practice (15).

The base case has been designed to represent a health system with moderate levels of screening for hypertension, diabetes, and dyslipidaemia. Alternative assumptions for more or less intensive opportunistic screening can be assumed.

Diagnosis and Treatment Initiation

It is assumed that there are three, non-mutually exclusive outcomes from the vascular checks or opportunistic screening. Firstly, that the patient receives statins to reduce cardiovascular risk. Secondly, that the patient has high blood pressure and should be treated with anti-hypertensive medication. Thirdly, the model evaluates whether the blood glucose test indicates a type 2 diabetes diagnosis. The following threshold estimates were used to determine these outcomes.

1. Statins are initiated if the individual has greater than or equal to 20% 10 year CVD risk estimated from the QRISK2 2012 algorithm (16).
2. Anti-hypertensive treatment is initiated if systolic blood pressure is greater than 160. If the individual has a history of CVD, diabetes or a CVD risk >20%, the threshold for systolic blood pressure is 140 (13).
3. Type 2 diabetes is diagnosed if the individual has two HbA1c tests greater than 6.5. In the base case it is assumed that FPG and 2-hr glucose are not used for diabetes diagnosis. However, future adaptations of the model could use these tests for diagnosis.

Comorbid Outcomes and Mortality

In every model cycle individuals within the model are evaluated to determine whether they have a clinical event, including mortality, within the cycle period. In each case the simulation estimates the probability that an individual has the event and uses a random number draw to determine whether the event occurred.

Cardiovascular Disease

First Cardiovascular event

Several statistical models for cardiovascular events were identified in a review of economic evaluations for diabetes prevention (17). The UKPDS outcomes model (11;18), Framingham risk equation (19) and QRISK2 (20) have all been used in previous models to estimate cardiovascular events. The Framingham risk equation was not adopted because, unlike the QRISK2 model, it is not

estimated from a UK population. The UKPDS outcomes model would be ideally suited to estimate the risk of cardiovascular disease in a population diagnosed with type 2 diabetes. Whilst this is an important outcome of the cost-effectiveness model, there was concern that it would not be representative of individuals with normal glucose tolerance or impaired glucose regulation. Recent analyses show that the UKPDS over-predicts cardiovascular outcomes in newly diagnosed diabetes patients (21). It was important that reductions in cardiovascular disease risk in these populations were represented to capture the population-wide benefits of public health interventions. The QRISK2 model was selected for use in the cost-effectiveness model because it is a validated model of cardiovascular risk in a up to date UK population and could be used to generate probabilities for diabetic and non-diabetic populations. We considered using the UKPDS outcomes model specifically to estimate cardiovascular risk in patients with type 2 diabetes. However, it would not be possible to control for shifts in absolute risk generated by the different risk scores due to different baselines and covariates. This would lead to some individuals experiencing counterintuitive and favourable shifts in risk after onset of type 2 diabetes. Therefore, we decided to use diabetes as a covariate adjustment to the QRISK2 model to ensure that the change in individual status was consistent across individuals.

The probability of the first cardiovascular event is estimated from the QRISK2 predicted model of cardiovascular disease (20). The QRISK2 is a validated risk prediction algorithm to identify individuals at high risk of cardiovascular disease. The algorithm was developed from UK data and incorporates social deprivation and ethnicity. We accessed the 2012 version from the online QRISK website (22). The QRISK2 equation estimates the probability of a cardiovascular event in the next year conditional on ethnicity, smoking status, age, BMI, ratio of total/HDL cholesterol, Townsend score, atrial fibrillation, rheumatoid arthritis, renal disease, hypertension, diabetes, and family history of cardiovascular disease. Data on all these variables was available from the HSE 2014. Table 64 reports the coefficient estimates for the QRISK2 algorithm. The standard errors were not reported within the open source code. Where possible, standard errors were imputed from a previous

publication of the risk equation (23). Coefficients that were not reported in this publication were assumed to have standard errors of 20%.

Table 64: Coefficients from the 2012 QRISK2 risk equation and estimate standard errors

	Estimated coefficients adjusting for individual characteristics								
	Women		Men			Women		Men	
Covariates	Mean	Standard error	Mean	Mean	Interaction terms	Mean	Standard error	Mean	Standard error
White	0.0000	0.0000	0.0000	0.0000	Age1*former smoker	0.1774	0.035	-3.881	0.776
Indian	0.2163	0.0537	0.3163	0.0425	Age1*light smoker	-0.3277	0.066	-16.703	3.341
Pakistani	0.6905	0.0698	0.6092	0.0547	Age1*moderate smoker	-1.1533	0.231	-15.374	3.075
Bangladeshi	0.3423	0.1073	0.5958	0.0727	Age1*Heavy smoker	-1.5397	0.308	-17.645	3.529
Other Asian	0.0731	0.1071	0.1142	0.0845	Age1*AF	-4.6084	0.922	-7.028	1.406
Caribbean	-0.0989	0.0619	-0.3489	0.0641	Age1*renal disease	-2.6401	0.528	-17.015	3.403
Black African	-0.2352	0.1275	-0.3604	0.1094	Age1*hypertension	-2.2480	0.450	33.963	6.793
Chinese	-0.2956	0.1721	-0.2666	0.1538	Age1*Diabetes	-1.8452	0.369	12.789	2.558
Other	-0.1010	0.0793	-0.1208	0.0734	Age1*BMI	-3.0851	0.617	3.268	0.654
Non-smoker	0.0000	0.0000	0.0000	0.0000	Age1*family history CVD	-0.2481	0.050	-17.922	3.584
Former smoker	0.2033	0.0152	0.2684	0.0108	Age1*SBP	-0.0132	0.003	-0.151	0.030
Light smoker	0.4820	0.0220	0.5005	0.0166	Age1*Townsend	-0.0369	0.007	-2.550	0.510
Moderate smoker	0.6126	0.0178	0.6375	0.0148	Age2*former smoker	-0.0051	0.001	7.971	1.594
Heavy smoker	0.7481	0.0194	0.7424	0.0143	Age2*light smoker	-0.0005	0.000	23.686	4.737
Age 1*	5.0327		47.3164		Age2*moderate smoker	0.0105	0.002	23.137	4.627
Age 2*	-0.0108		-101.2362		Age2*Heavy smoker	0.0155	0.003	26.867	5.373
BMI*	-0.4724	0.0423	0.5425	0.0299	Age2*AF	0.0507	0.010	14.452	2.890
Ratio Total / HDL chol	0.1326	0.0044	0.1443	0.0022	Age2*renal disease	0.0343	0.007	28.270	5.654
SBP	0.0106	0.0045	0.0081	0.0046	Age2*hypertension	0.0258	0.005	-18.817	3.763
Townsend	0.0597	0.0068	0.0365	0.0048	Age2*Diabetes	0.0180	0.004	0.963	0.193
AF	1.3261	0.0310	0.7547	0.1018	Age2*BMI	0.0345	0.007	10.551	2.110
Rheumatoid arthritis	0.3626	0.0319	0.3089	0.0445	Age2*family history CVD	-0.0062	0.001	26.605	5.321
Renal disease	0.7636	0.0639	0.7441	0.0702	Age2*SBP	0.0000	0.000	0.291	0.058
Hypertension	0.5421	0.0115	0.4978	0.0112	Age2*Townsend	-0.0011	0.000	3.007	0.601
Diabetes	0.8940	0.0199	0.7776	0.0175					
Family history of CVD	0.5997	0.0122	0.6965	0.0111					
AF Atrial Fibrillation CVD Cardiovascular disease SBP systolic blood pressure * covariates transformed with fractional polynomials									

The QRISK2 risk equation can be used to calculate the probability of a cardiovascular event including: coronary heart disease (angina or myocardial infarction), stroke, or transient ischaemic attacks, fatality due to cardiovascular disease. The equation estimates the probability of a cardiovascular event in the next period conditional on the coefficients listed in Table 64. The equation for the probability of an event in the next period is calculated as

$$p(Y = 1) = 1 - S(1)^{\theta}$$

$$\theta = \sum_{316} \beta X$$

The probability of an event is calculated from the survival function at 1 year raised to the power of θ, where θ is the sum product of the coefficients reported in Table 64 multiplied by the individual's characteristics. Underlying survival curves for men and women were extracted from the QRISK2 open source file. Mean estimates for the continuous variables were also reported in the open source files.

We modified the QRISK2 assumptions regarding the relationship between IGR, diabetes and cardiovascular disease. Firstly, we assumed that individuals with HbA1c>6.5 have an increased risk of cardiovascular disease even if they have not received a formal diagnosis. Secondly, risk of cardiovascular disease was assumed to increase with HbA1c for test results greater than 6.5 to reflect observations from the UKPDS that HbA1c increases the risk of MI and Stroke (18) . Thirdly, prior to type 2 diabetes (HbA1c>6.5) HbA1c is linearly associated with cardiovascular disease. A study from the EPIC Cohort has found that a unit increase in HbA1c increases the risk of coronary heart disease by a hazard ratio of 1.25, after adjustment for other risk factors (24). We apply this risk ratio to linearly increase risk above the mean HBA1c observed in the HSE 2011 cohort. A linear risk reduction was applied at HbA1c levels below the HSE mean.

The QRISK2 algorithm identifies which individuals experience a cardiovascular event but does not specify the nature of the event. The nature of the cardiovascular event was determined independently. A targeted search of recent Health Technology appraisals of cardiovascular disease was performed to identify a model for the progression of cardiovascular disease following a first event. A Health Technology Assessment (HTA) assessing statins gives age and sex specific distributions of CVD, which were used to assign all QRISK2 events (7). Table 65 reports the probability of cardiovascular outcomes by age and gender. Stakeholders suggested that there may be different relationships between the risk factors and the different types of CVD (e.g. hypertension is more of a risk factor for stroke). However, we decided not to incorporate these differential factors in evaluating the risk of cardiovascular event types into the model due to a lack of evidence.

Table 65: The probability distribution of cardiovascular events by age and gender

	Age	Stable angina	Unstable angina	MI rate	Fatal CHD	TIA	Stroke	Fatal CVD
Men	45-54	0.307	0.107	0.295	0.071	0.060	0.129	0.030
	55-64	0.328	0.071	0.172	0.086	0.089	0.206	0.048
	65-74	0.214	0.083	0.173	0.097	0.100	0.270	0.063
	75-84	0.191	0.081	0.161	0.063	0.080	0.343	0.080
	85+	0.214	0.096	0.186	0.055	0.016	0.351	0.082
Women	45-54	0.325	0.117	0.080	0.037	0.160	0.229	0.054
	55-64	0.346	0.073	0.092	0.039	0.095	0.288	0.067
	65-74	0.202	0.052	0.121	0.081	0.073	0.382	0.090
	75-84	0.149	0.034	0.102	0.043	0.098	0.464	0.109
	85+	0.136	0.029	0.100	0.030	0.087	0.501	0.117

Subsequent Cardiovascular events

After an individual has experienced a cardiovascular event, it is not possible to predict the transition to subsequent cardiovascular events using QRISK2. As with assigning first CVD events, the probability of subsequent events was estimated from the HTA evaluating statins (7). This study reported the probability of future events conditional on the nature of the previous event. Table 66 reports an example of the probabilities within a year of transitioning from stable angina, unstable angina, myocardial infarction (MI), transient ischemic attack (TIA) or stroke for individuals by age group.

Table 66: Probability of cardiovascular event conditional on age and status of previous event (column1)

	Stable angina	Unstable angina 1	Unstable angina 2	MI 1	MI 2	TIA	Stroke 1	Stroke 2	CHD death	CVD death
Age 45										
Stable angina	0.9946	0.0013	0	0.0032	0	0	0	0	0.0009	0
Unstable angina (1st yr)	0	0	0.9127	0.0495	0	0	0	0	0.0362	0.0016
Unstable angina (subsequent)	0	0	0.9729	0.0186	0	0	0	0	0.0081	0.0004
MI (1st yr)	0	0	0	0.128	0.8531	0	0.0015	0	0.0167	0.0007
MI (subsequent)	0	0	0	0.0162	0.978	0	0.0004	0	0.0052	0.0002
TIA	0	0	0	0.0016	0	0.9912	0.0035	0	0.0024	0.0013
Stroke (1st yr)	0	0	0	0.0016	0	0	0.0431	0.9461	0.0046	0.0046
Stroke (subsequent)	0	0	0	0.0016	0	0	0.0144	0.9798	0.0021	0.0021
Age 55										
Stable angina	0.9874	0.0029	0	0.0062	0	0	0	0	0.0035	0
Unstable angina (1st yr)	0	0	0.8859	0.0497	0	0	0	0	0.0617	0.0027
Unstable angina (subsequent)	0	0	0.9548	0.0348	0	0	0	0	0.01	0.0004
MI (1st yr)	0	0	0	0.1152	0.8483	0	0.0032	0	0.0319	0.0014
MI (subsequent)	0	0	0	0.0179	0.9716	0	0.001	0	0.0091	0.0004
TIA	0	0	0	0.0031	0	0.9626	0.0181	0	0.0092	0.007
Stroke (1st yr)	0	0	0	0.0031	0	0	0.0459	0.9288	0.0111	0.0111
Stroke (subsequent)	0	0	0	0.0031	0	0	0.0186	0.9685	0.0049	0.0049
Age 65										
Stable angina	0.976	0.006	0	0.011	0	0	0	0	0.007	0

Unstable angina (1st yr)	0	0	0.8435	0.0488	0	0	0	0	0.1031	0.0046
Unstable angina (subsequent)	0	0	0.9244	0.0632	0	0	0	0	0.0119	0.0005
MI (1st yr)	0	0	0	0.1019	0.8287	0	0.0068	0	0.0599	0.0027
MI (subsequent)	0	0	0	0.0185	0.9634	0	0.0022	0	0.0152	0.0007
TIA	0	0	0	0.0055	0	0.9174	0.0423	0	0.0185	0.0163
Stroke (1st yr)	0	0	0	0.0055	0	0	0.0481	0.8944	0.026	0.026
Stroke (subsequent)	0	0	0	0.0055	0	0	0.0223	0.9514	0.0104	0.0104
Age 75										
Stable angina	0.9681	0.0091	0	0.0158	0	0	0	0	0.007	0
Unstable angina (1st yr)	0	0	0.7789	0.0466	0	0	0	0	0.1671	0.0074
Unstable angina (subsequent)	0	0	0.8733	0.1122	0	0	0	0	0.0139	0.0006
MI (1st yr)	0	0	0	0.0874	0.7849	0	0.0141	0	0.1088	0.0048
MI (subsequent)	0	0	0	0.0178	0.953	0	0.0047	0	0.0235	0.001
TIA	0	0	0	0.008	0	0.8588	0.0828	0	0.0185	0.0319
Stroke (1st yr)	0	0	0	0.008	0	0	0.0446	0.8302	0.0586	0.0586
Stroke (subsequent)	0	0	0	0.008	0	0	0.0246	0.9262	0.0206	0.0206
Age 85										
Stable angina	0.9601	0.0122	0	0.0207	0	0	0	0	0.007	0
Unstable angina (1st yr)	0	0	0.6873	0.0425	0	0	0	0	0.2587	0.0115
Unstable angina (subsequent)	0	0	0.7878	0.1955	0	0	0	0	0.016	0.0007
MI (1st yr)	0	0	0	0.0711	0.7053	0	0.0278	0	0.1875	0.0083
MI (subsequent)	0	0	0	0.016	0.9394	0	0.0091	0	0.034	0.0015
TIA	0	0	0	0.0104	0	0.838	0.0961	0	0.0185	0.037
Stroke (1st yr)	0	0	0	0.0104	0	0	0.0446	0.702	0.1215	0.1215
Stroke (subsequent)	0	0	0	0.0104	0	0	0.0252	0.8894	0.0375	0.0375

Congestive Heart Failure

The review of previous economic evaluations of diabetes prevention cost-effectiveness studies found that only a small number of models had included congestive heart failure as a separate outcome. Discussion with the stakeholder group identified that the UKPDS Outcomes model would be an appropriate risk model for congestive heart failure in type 2 diabetes patients. However, it was suggested that this would not be an appropriate risk equation for individuals with normal glucose tolerance or impaired glucose tolerance. The Framingham risk equation was suggested as an alternative. As described above, switching from the framgingam risk score to the UKPDS was not possible due to differences in covariate selection. The main limitations of this equation is that it is quite old, based on a non-UK population, and include diabetes as a discrete health state rather than on a continuous scale. However, a citation search of this article did not identify a more recent or UK based alternative.

Congestive heart failure was included as a separate cardiovascular event because it was not included as an outcome of the QRISK2. The Framingham Heart Study has reported logistic regressions to estimate the 4 year probability of congestive heart failure for men and women (25). The equations included age, diabetes diagnosis, BMI and systolic blood pressure to adjust risk based on individual characteristics. We used this risk equation to estimate the probability of congestive heart failure in the SPHR diabetes prevention model. Table 67 describes the covariates for the logit models to estimate the probability of congestive heart failure in men and women.

Table 67: Logistic regression coefficients to estimate the 4-year probability of congestive heart failure from the Framingham study

Variables	Units	Regression Coefficient	OR (95% CI)	P
Men				
Intercept		-9.2087		
Age	10 y	0.0412	1.51 (1.31-1.74)	<.001
Left ventricular hypertrophy	Yes/no	0.9026	2.47 (1.31-3.77)	<.001
Heart rate	10 bpm	0.0166	1.18 (1.08-1.29)	<.001
Systolic blood pressure	20 mm Hg	0.00804	1.17 (1.04-1.32)	0.007
Congenital heart disease	Yes/no	1.6079	4.99 (3.80-6.55)	<.001
Valve disease	Yes/no	0.9714	2.64 (1.89-3.69)	<.001
Diabetes	Yes/no	0.2244	1.25 (0.89-1.76)	0.2
Women				
Intercept		-10.7988		
Age	10 y	0.0503	1.65 (1.42-1.93)	<.001
left ventricular hypertrophy	Yes/no	1.3402	3.82 (2.50-5.83)	<.001
Heart rate	100 cL	0.0105	1.11 (1.01-1.23)	0.03
Systolic blood pressure	10 bpm	0.00337	1.07 (0.96-1.20)	0.24
congenital heart disease	20 mm Hg	1.5549	4.74 (3.49-6.42)	<.001
Valve disease	Yes/no	1.3929	4.03 (2.86-5.67)	<.001
Diabetes	Yes/no	1.3857	4.00 (2.78-5.74)	<.001
BMI	kg/m2	0.0578	1.06 (1.03-1.09)	<.001
Valve disease and diabetes	Yes/no	-0.986	0.37 (0.18-0.78)	0.009
*OR indicates odds ratio; CI, confidence interval; LVH, left ventricular hypertrophy; CHD, congenital heart disease; and BMI, body mass index. Predicted probability of heart failure can be calculated as: p = 1/(1+exp(-xbeta)), where xbeta = Intercept + Sum (of regression coefficient*value of risk factor)				

Many of the risk factors included in this risk equation were not simulated in the diabetes model, therefore they could not be included in the model to predict CHD. We adjusted the baseline odds of CHD to reflect the expected prevalence of these symptoms in a UK population.

The proportion of the UK population with left ventricular hypertrophy was assumed to be 5% in line with previous analyses of the Whitehall II cohort (26). The heart rate for men was assumed to be 63.0bpm and for women 65.6bpm based on data from previous Whitehall II cohort analyses (27). The prevalence of congenital heart disease was estimated from an epidemiology study in the North of England. The study reports the prevalence of congenital heart disease among live births which was used to estimate the adult prevalence (28). This may over-estimate the prevalence, because the life expectancy of births with congenital heart disease is reduced compared with the general population. However, given the low prevalence it is unlikely to impact on the results. The prevalence of valve disease was estimated from the Echocardiographic Heart of England Screening study (29).
Using the estimated population values we adjusted the intercept values to account for the population risk in men and women. This resulted in a risk equation with age, systolic blood pressure, diabetes (diabetes diagnosis or HbA1c>6.5), and BMI in women to describe the risk of congestive heart failure for the policy analysis model.

Microvascular Complications

The review of previous economic evaluations identified that the UKPDS data was commonly used to estimate the incidence of microvascular complications (17). This data has the advantage of being estimated from a UK diabetic population. Given that the events described in the UKPDS outcomes model are indicative of late stage microvascular complications, we did not believe it was necessary to seek an alternative model that would be representative of an impaired glucose tolerance population. We adopted a simple approach to modelling microvascular complications. We used both versions of the UKPDS Outcomes model to estimate the occurrence of major events relating to these complications, including renal failure, amputation, foot ulcer, and blindness (11;18). These have the greatest cost and utility impact compared with earlier stages of microvascular complications, so are more likely to have an impact on the SPHR diabetes prevention outcomes.

As a consequence, we assumed that microvascular complications only occur in individuals with HbA1c>48 mmol/mol (6.5%). Whilst some individuals with hyperglycaemia (HbA1c>42 mmol/mol [6.0%]) may be at risk of developing microvascular complications, it is unlikely that they will progress to renal failure, amputation or blindness before a diagnosis of diabetes. Importantly, we did not assume that only individuals who have a formal diagnosis of diabetes are at risk of these complications. This allows us to incorporate the costs of undetected diabetes into the simulation.

The UKPDS includes four statistical models to predict foot ulcers, amputation with no prior ulcer, amputation with prior ulcer and a second amputation (18). In order to simplify the simulation of neuropathy outcomes we consolidated the models for first amputation with and without prior ulcer into a single equation. The parametric survival models were used to generate estimates of the cumulative hazard in the current and previous period. From which the probability of organ damage being diagnosed was estimated.

$$p(Death) = 1 - \exp\left(H(t) - H(t-1)\right) \quad (1.1)$$

The functional form for the microvascular models included exponential and Weibull.

Retinopathy

We used the UKPDS outcomes model v2 to estimate the incidence of blindness in individuals with HbA1c>48 mmol/mol (6.5%) (18). The exponential model assumes a baseline hazard λ, which can be calculated from the model coefficients reported in Table 68 and the individual characteristics for $\boldsymbol{X}$.

$$\lambda = exp(\beta_0 + \boldsymbol{X}\boldsymbol{\beta_k})$$

Table 68: Parameters of the UKPDS2 Exponential Blindness survival model

	Mean coefficient	Standard error	Modified mean coefficient
Lambda	-11.607	0.759	-10.967
Age at diagnosis	0.047	0.009	0.047
HbA1c	0.171	0.032	0.171
Heart rate	0.080	0.039	
SBP	0.068	0.032	0.068
White Blood Count	0.052	0.019	

CHF History	0.841	0.287	0.841
IHD History	0.0610	0.208	0.061
SBP Systolic Blood Pressure; CHF Congestive Heart Failure; IHD Ischaemic Heart Disease			

The age at diagnosis coefficient was multiplied by age in the current year if the individual had not been diagnosed with diabetes, and by the age at diagnosis if the individual had received a diagnosis. The expected values for the risk factors not included in the SPHR model (heart rate and white blood count) were taken from Figure 3 of the UKPDS publication in which these are described (18). Assuming these mean values, it was possible to modify the baseline risk without simulating heart rate and white blood cell count.

Neuropathy

We used the UKPDS outcomes model v2 to estimate the incidence of ulcer and amputation in individuals with HbA1c>48 mmol/mol (6.5%) (18). The parameters of the ulcer and first amputation models are reported in Table 69.

Table 69: Parameters of the UKPDS2 Exponential model for Ulcer, Weibull model for first amputation with no prior ulcer and exponential model for 1st amputation with prior ulcer

	Ulcer		1st Amputation no prior ulcer		1st Amputation prior ulcer		2nd Amputation	
	Logistic		Weibull		Exponential		Exponential	
	Mean	Standard error	Mean	Standard error	Mean	Standard error	Mean	Standard error
Lambda	-11.295	1.130	-14.844	1.205	-0.881	1.39	-3.455	0.565
Rho			2.067	0.193				
Age at diagnosis	0.043	0.014	0.023	0.011	-0.065	0.027		
Female	-0.962	0.255	-0.0445	0.189				
Atrial fibrillation			1.088	0.398				
BMI	0.053	0.019						
HbA1c	0.160	0.056	0.248	0.042			0.127	0.06
HDL			-0.059	0.032				
Heart rate			0.098	0.050				
MMALB			0.602	0.180				
PVD	0.968	0.258	1.010	0.189	1.769	0.449		
SBP			0.086	0.043				
WBC			0.040	0.017				
Stroke History			1.299	0.245				

The exponential model assumes a baseline hazard λ, which can be calculated from the model coefficients reported in Table 69 and the individual characteristics for $\boldsymbol{X}$.

$$\lambda = exp(\beta_0 + \boldsymbol{X\beta})$$

The Weibull model for amputation assumes a baseline hazard:

$$h(t) = \rho t^{\rho-1}\exp(\lambda)$$

where λ is also conditional on the coefficients and individual characteristics at time t.

The logistic model for ulcer is described below.

$$\Pr(y = 1|\mathbf{X}) = \frac{\exp(\mathbf{X\beta})}{1 + \exp(\mathbf{X\beta})}$$

The ulcer and amputation models include a number of covariates that were not included in the simulation. As such it was necessary to adjust the statistical models to account for these measures. We estimated a value for the missing covariates and added the value multiplied by the coefficient to the baseline hazard.

The expected values for the risk factors not included in the SPHR model (heart rate, white blood count, micro-/macroalbuminurea, peripheral vascular disease and atrial fibrillation) were taken from Figure 3 of the UKPDS publication in which these are described (18). In the ulcer model we assumed that 2% of the population had peripheral vascular disease.

The amputation risk model with a history of ulcer was not included in the simulation, but was used to estimate an additional log hazard ratio to append onto the amputation model without a history of ulcer. The log hazard was estimated for each model assuming the same values for other covariates. The difference in the log hazard between the two models was used to approximate the log hazard ratio for a history of ulcer in the amputation model (10.241). The final model specifications are reported in Table 70.

Table 70: Coefficients estimates for Ulcer and 1st Amputation

	Ulcer	1st Amputation	2nd Amputation
	Logistic	Weibull	Exponential

	Mean	Standard error	Mean	Standard error	Mean	Standard error
Lambda	-11.276	1.13	-13.954	1.205	-3.455	0.565
Rho			2.067	0.193		
Age at Diagnosis	0.043	0.014	0.023	0.011		
Female	-0.962	0.255	-0.445	0.189		
BMI	0.053	0.019				
HbA1c	0.160	0056	0.248	0.042	0.127	0.06
HDL			-0.059	0.032		
Stroke			1.299	0.245		
Foot Ulcer			10.241			

Nephropathy

We used the UKPDS outcomes model v1 to estimate the incidence of renal failure in individuals with HbA1c>48 mmol/mol (6.5%) (11). Early validation analyses identified that the UKPDS v2 model substantially overestimated the incidence of renal failure in the SPHR model. The Weibull model for renal failure assumes a baseline hazard:

$$h(t) = \rho t^{\rho-1}\exp(\lambda)$$

where λ is also conditional on the coefficients and individual characteristics at time t. The parameters of the renal failure risk model are reported in Table 71.

Table 71: Parameters of the UKPDS2 Weibull renal failure survival model

	Mean	Standard error
Lambda	-10.016	0.939
Shape parameter	1.865	0.387
SBP	0.404	0.106
BLIND History	2.082	0.551

Cancer

The conceptual model identified breast cancer and colorectal cancer risk as being related to BMI. However, these outcomes were not frequently included in previous cost-effectiveness models for diabetes prevention. Discussion with stakeholders identified the EPIC Norfolk epidemiology cohort study as a key source of information about cancer risk in a UK population. Therefore, we searched publications from this cohort to identify studies reporting the incidence of these risks. In order to obtain the best quality evidence for the relationship between BMI and cancer risk we searched for a recent systematic review and meta-analysis using key terms ‘Body Mass Index’ and ‘Cancer’, filtering for meta-analysis studies.

Breast cancer

Incidence rates for breast cancer in the UK were estimated from the European Prospective Investigation of Cancer (EPIC) cohort. This is a large multi-centre cohort study looking at diet and cancer. In 2004 the UK incidence of breast cancer by menopausal status was reported in a paper from this study investigating the relationship between body size and breast cancer (30). The estimates of the breast cancer incidence in the UK are reported in Table 72.

Table 72: UK breast cancer incidence

	Number of Cases	Person Years	Mean BMI	Incidence Rate of per person-year	Standard error	Reference
UK pre-menopause	102	103114.6	24	0.00099	0.00009	(30)
UK post-menopause	238	84214.6	24	0.00283	0.00004	(30)

A large meta-analysis that included 221 prospective observational studies has reported relative risks of cancers per unit increase in BMI, including breast cancer by menopausal status (31). We included a risk adjustment in the model so that individuals with higher BMI have a higher probability of pre-and post-menopausal breast cancer (31). In the simulation we adjusted the probability of breast cancer according to the difference in the individual's BMI and the average BMI reported in the EPIC cohort. The relative risk and confidence intervals per 5mg/m^2 increase in BMI are reported in Table 73.

Table 73: Relative risk of Breast cancer by BMI

	Mean Relative risk	2.5th Confidence Interval	97.5th Confidence Interval	Reference
UK pre-menopause	0.89	0.84	0.94	(31)
UK post-menopause	1.09	1.04	1.14	(31)

Colorectal cancer

Incidence rates for colorectal cancer in the UK were reported from the European Prospective Investigation of Cancer (EPIC) cohort. The UK incidence of colorectal cancer is reported by gender in a paper from this study investigating the relationship between body size and colon and rectal cancer (32). The estimates of the colorectal cancer incidence are reported in Table 74.

Table 74: UK colorectal cancer incidence

	Number of Cases	Person Years	Mean Age	Mean BMI	Incidence Rate of per person-year	Standard error	Reference

Male	125	118468	53.1	25.4	0.00106	0.0001	(32)
Female	145	277133	47.7	24.5	0.00052	0.0002	(32)

The risk of colorectal cancer has been linked to obesity. We included a risk adjustment in the model to reflect observations that the incidence of breast cancer is increased in individuals with higher BMI. A large meta-analysis that included 221 prospective observational studies has reported relative risks of BMI and cancers, including colon cancer by gender (31). We selected linear relative risk estimates estimated from pooled European and Australian populations. In the simulation we adjusted the incidence of colorectal cancer by adjusting the probability of colorectal cancer by the difference in the individual's BMI and the average BMI reported in the EPIC cohort. The relative risk and confidence intervals per 5mg/m^2 increase in BMI are reported in Table 75.

Table 75: Relative risk of colon cancer by BMI

	Mean Relative risk	2.5th Confidence Interval	97.5th Confidence Interval	Reference
UK pre-menopause	1.21	1.18	1.24	(31)
UK post-menopause	1.04	1.00	1.07	(31)

Osteoarthritis

Stakeholders suggested that diabetes and BMI should be included as independent risk factors for osteoarthritis. Osteoarthritis had not been included as a health state in previous cost-effectiveness models. The stakeholder group requested that BMI and diabetes be included as risk factors for osteoarthritis based on recent evidence (33). A search for studies using key words 'Diabetes', 'Osteoarthritis' and 'Cohort Studies' did not identify a UK based study with diabetes and body mass index included as independent covariates in the risk model. Therefore, the Italian study was used in the model.

A study from the Bruneck cohort, a longitudinal study of inhabitants of a town in Italy reported diabetes and BMI as independent risk factors for osteoarthritis (33).

The cohort may not be representative of a UK cohort. However, the individuals are from a European country, the study has a large sample size and has estimated the independent effects of BMI and diabetes on the risk of osteoarthritis. No UK based studies identified in our searches met these

requirements. The data used to estimate the incidence of osteoarthritis is reported in Table 76. We did not identify any studies that described diabetes risk on a continuous scale.

Table 76: Incidence of osteoarthritis and estimated risk factors

	No cases	Person years	Mean BMI	Incidence rate	Standard error	Reference
No diabetes	73	13835	24.8	0.0053	0.0006	(33)
	Hazard ratio	2.5th	97.5th			Reference
HR Diabetes	2.06	1.11	3.84			(33)
HR BMI	1.076	1.023	1.133			(33)Personal communication

Depression

Depression was not included as a health state in previous cost-effectiveness models for diabetes prevention. However, a member of the stakeholder group identified that a relationship between diabetes and depression was included in the CORE diabetes treatment model (34). Therefore, the references used in this model were used.

Depression was included as a health state in the model. However, the severity of depression was not modelled. Some individuals enter the simulation with depression at baseline according to individual responses in the Health Survey for England 2014 questionnaire. Depression is described in the simulation as a chronic state from which individuals do not completely remit. We did not estimate the effect of depression on the longitudinal changes for BMI, glycaemia, SBP and cholesterol. As a consequence, it was not possible to relate the impact of depression to the incidence of diabetes and cardiovascular risk.

In the simulation, individuals can develop depression in any cycle of the model. The baseline incidence of depression among all individuals without a history of depression was estimated from a study examining the bidirectional association between depressive symptoms and type 2 diabetes (35). Although the study was not from a UK population, the US cohort included ethnically diverse men and women aged 45 to 84 years. We assumed that diagnosis of diabetes and/or CVD increased the

incidence of depression in individuals who do not have depression at baseline. We identified a method for inflating risk of depression for individuals with diabetes from the US cohort study described above (35). The risk of depression in individuals who have had a stroke was also inflated according to a US cohort study (36). Odds of depression and odds ratios for inflated risk of depression due to diabetes or stroke are presented in Table 77.

Table 77: Baseline incidence of depression

Baseline Risk of depression			
	Mean	Standard error	
Depression cases in NGT	336		
Person years	9139		
Odds of depression	0.0382	0.002	
Log odds of depression	-3.266		
Inflated risk for Diabetes			
	Mean	2.5th CI	97.5th CI
Odds ratio of diabetes	1.52	1.09	2.12
Log odds ratio of diabetes	0.419		
Inflate risk of stroke			
Odds ratio of stroke	6.3	1.7	23.2
Log odds ratio stroke	1.8406		
NGT Normal Glucose Tolerance			

Dementia

The risk dementia diagnosis is estimated from risk models estimated from the THIN database (37). The THIN dementia risk score uses data from The Health Improvement Network (THIN) database from across the UK. Routinely collected data was used to predict 5-year risk of recorded diagnosis of Dementia for those aged 60-79 and 80+. The sample size is large and the risk scores are representative of the United Kingdom and diagnosis practices between 2000-2011. The disadvantage of these risk scores are the relatively short follow-up of patients, the low predictive power of the older risk score, and narrow scope to predict dementia diagnosis but not dementia onset.

The parameters for the THIN 60-79 year old and 80-99 risk models are reported in Table 78.

Table 78: THIN dementia risk models

THIN 60-79 Risk Score			THIN 80-99 Risk Score		
Parameter label	mean	Standard error	Parameter label	mean	Standard error
Baseline hazard	0.9969		Baseline hazard	-0.9277	

Age	0.2092	0.0047	Age	0.055	0.0041
Age^2	-0.0034	0.0003	Age^2	-0.005	0.0010
Female	0.1285	0.0278	Female	0.16	0.0286
Calendar Year	0.0448	0.0050	Calendar Year	0.074	0.0056
Townsend quintile 2	0.0134	0.0390	BMI	-0.05	0.0066
Townsend quintile 3	0.1179	0.0392	Anti-hypertensives	-0.249	0.0265
Townsend quintile 4	0.2018	0.0402	Systolic Blood Pressure	-0.006	0.0010
Townsend quintile 5	0.2255	0.0447	Lipid ratio	0.042	0.0495
BMI	-0.0616	0.0038	Past Smoker	-0.178	0.0281
BMI^2	0.0025	0.0003	Smoker	-0.134	0.0485
Anti-hypertensives	-0.1320	0.0296	Alcohol Porblems	0.256	0.1352
Past Smoker	-0.0679	0.0301	Diabetes	0.183	0.0413
Smoker	-0.0866	0.0415	Stroke	0.242	0.0332
Alcohol problems	0.4435	0.0799	Atrial Fibrillation	0.057	0.0383
Diabetes	0.2867	0.0417	Depression	0.4	0.0332
Depression	0.8336	0.0325	Anxiety	0.136	0.0520
Stroke	0.5772	0.0394	NSAIDs use	-0.157	0.0408
Atrial Fibrillation	0.2207	0.0514	Aspirin use	0.092	0.0281
Aspirin use	0.2528	0.0326			

For the SPHR prevention model the 5-year Dementia risk was transformed into 1 year individual probabilities. The Dementia risk scores include fixed and time-varying patient characteristics. As a consequence, it is not possible to use standard methods of transforming probabilities over different time-horizons (38). We used a simple calibration technique to modify the baseline hazard to reflect simulated changes in the populations risk profile over 5 years. We calibrate the simulated 5 year incidence of dementia against the predicted incidence for each age group in the THIN database (37).

For each risk model we simulated 20,000 randomly sampled patients aged 60-79 and 80-95 in 50 model runs. For each sample we repeated simulations multiple times, in each simulation the baseline hazard was adjusted until the incidence of Dementia equalled the THIN risk score prediction based on baseline characteristics. The baseline hazard adjustment was estimated by averaging the adjustments needed for each of the 20 simulation runs to match the THIN prediction. The calibration was designed to calibrate to the predicted incidence, rather than the reported incidence from the THIN dataset to account for any differences in the baseline characteristics of the THIN data and HSE sample. For

example, the mean age for the development cohort of the 60-79 model were 65.6, whereas the mean simulated ages was 70. Age is an important predictor of Dementia incidence so it is important to adjust for differences in baseline age between the observed and simulated data.

The THIN database reports a crude incidence of 1.88 per 1,000 persons years for 60-79 and 16.53 per 1,000 person years for ages 80-99 (column 2 Table 79). The 5 year risk score for individuals sampled from the Health Survey for England reports a 5 year incidence of X (column 3 Table 79). Using the adjustment factor identified by calibration (column 5 Table 79), we simulated a 5 year incidence of X and Y (column 4 Table 79). The adjustment factor is applied to the baseline hazards of the THIN dementia risk scores.

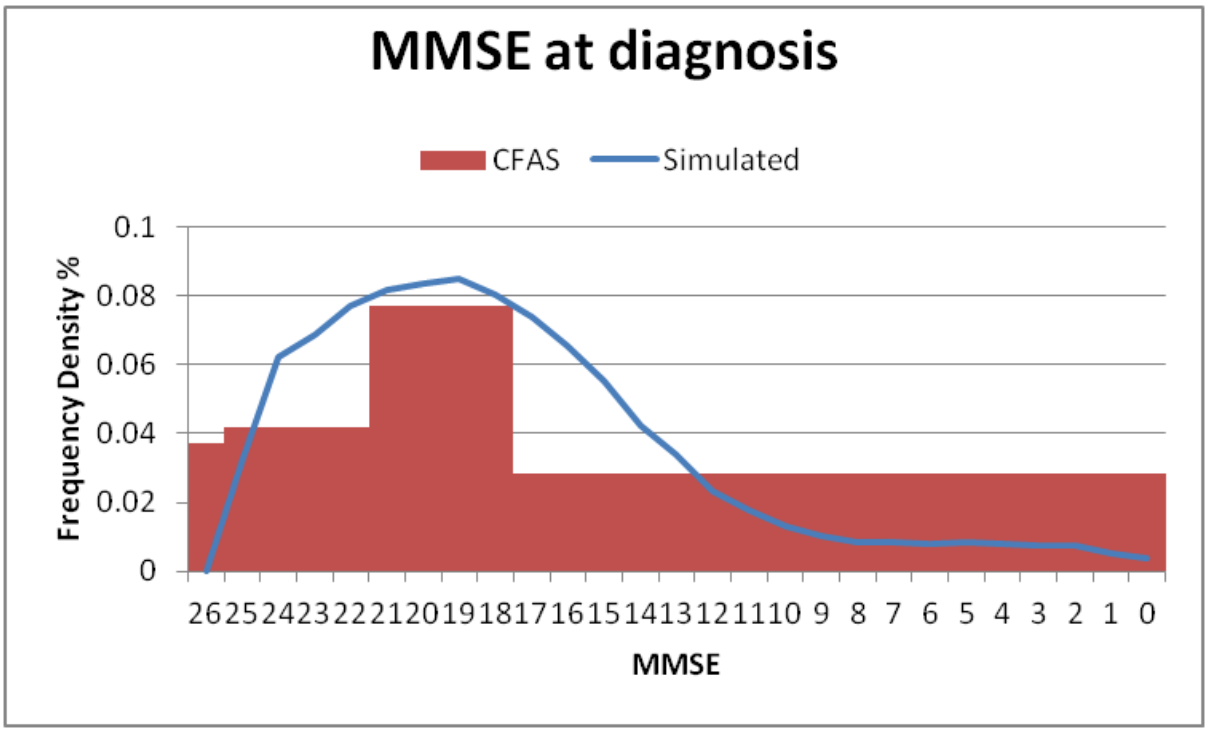
Table 79: Dementia incidence rates used to derive the adjustment factor

	5 year crude incidence from QResearch	5 year risk score for Health Survey for England population	5 year simulated incidence with adjustment factor	Adjustment factor (SE)
THIN risk model 60-79	0.00188	0.00255	0.00255	7.628 (0.104)
THIN risk model 80+	0.01653	0.01523	0.01510	4.557 (0.020)

Dementia Diagnosis

A Swedish registry reporting MMSE scores at dementia diagnosis was identified (39). This study reported a mean MMSE score at diagnosis of 21.2 (SD 5.2). This data was used to generate MMSE scores at diagnosis in the model because it reflects cognitive function in a cohort diagnosed in routine care. In order to generate heterogeneity in cognitive function at diagnosis a Gamma distribution was fitted to this mean and standard distribution and patients MMSE score at diagnosed was sampled from this distribution. Sampled value outside the limits of the MMSE score, assuming a maximum score at diagnosis of 25, were re-sampled from a uniform distribution within these limits. The resulting

distribution was compared against summary data from CFAS for an incident cohort to validate the simulated MMSE scores against this dataset (40).



Disease Progression

Dementia disease progression was characterized by a deterioration in MMSE score. This relatively simple characterization of the disease is sufficient to capture major cost escalations and quality of life deterioration. A more complex structure that explicity models insitutionalisation was considered (41). However, it was concluded that the data on insitutionalisation was out of date. Therefore, the modelling structure was aligned to the most up to date cost estimates for dementia (42).

Changes in MMSE score over time were estimated using data from a recent cost-effectiveness model for Donepezil (43). Although the data are from Canada and are relatively old, the sample size is large and model specification allows for detailed characterization of MMSE decline. The regression allows rate of change in MMSE to be conditional on age at baseline and includes splines to describe a different rate of change at different levels of MMSE. For example, the decline in MMSE slows as the score declines below 9.

Mortality

Cardiovascular Mortality

Cardiovascular mortality is included as an event within the QRISK2 (20) and the probability of subsequent cardiovascular events obtained from an HTA assessing statins (7), as described in the Cardiovascular disease section above.

Cancer Mortality

Cancer mortality rates were obtained from the Office of National statistics (7;44). The ONS report one and five year net survival rates for various cancer types, by age group and gender. Net survival was an estimate of the probability of survival from the cancer alone. It can be interpreted as the survival of cancer patients after taking into account the background mortality that the patients would have experienced if they had not had cancer.

The age-adjusted 5-year survival rate for breast cancer and colorectal cancer were used to estimate an annual risk of mortality assuming a constant rate of mortality. We assume that the mortality rate does not increase due to cancer beyond 5 years after cancer diagnosis. The five year survival rate for breast cancer is 84.3%, which translated into a 3.37% annual probability of death from breast cancer. The five year survival rate for persons with colorectal cancer is 55.3%, which translated into a 11.16% annual probability of death from colorectal cancer.

Other cause Mortality (including diabetes and Dementia risk)

Other cause mortality describes the risk of death from any cause except CVD, and cancer. All-cause mortality rates by age and sex were extracted from the 2014 Office of National Statistics life tables (5;7). The mortality statistics report the number of deaths by ICD codes for 5-year age groups. We subtracted the number of cardiovascular disease,diabetes, dementia, breast and colorectal cancer related deaths from the all-cause mortality total to estimate other cause mortality rates by age and sex (Table 75).

Table 80: All cause and derived other cause mortality from the Office of National statistics

	All cause	All cause	Other cause	Other cause		All cause	All cause	Other cause	Other cause
	Men	Women	Men	Women		Men	Women	Men	Women
1	0.0003	0.0003	0.0003	0.0003	51	0.0030	0.0021	0.0022	0.0015
2	0.0002	0.0001	0.0002	0.0001	52	0.0030	0.0021	0.0022	0.0015
3	0.0001	0.0001	0.0001	0.0001	53	0.0030	0.0021	0.0022	0.0015
4	0.0001	0.0001	0.0001	0.0001	54	0.0030	0.0021	0.0022	0.0015
5	0.0001	0.0001	0.0001	0.0001	55	0.0030	0.0021	0.0022	0.0015
6	0.0001	0.0001	0.0001	0.0001	56	0.0030	0.0021	0.0022	0.0015
7	0.0001	0.0001	0.0001	0.0001	57	0.0030	0.0021	0.0022	0.0015
8	0.0001	0.0001	0.0001	0.0001	58	0.0030	0.0021	0.0022	0.0015
9	0.0001	0.0001	0.0001	0.0001	59	0.0030	0.0021	0.0022	0.0015
10	0.0001	0.0001	0.0001	0.0001	60	0.0030	0.0021	0.0022	0.0015
11	0.0001	0.0001	0.0001	0.0001	61	0.0030	0.0021	0.0022	0.0015
12	0.0001	0.0001	0.0001	0.0001	62	0.0030	0.0021	0.0022	0.0015
13	0.0001	0.0001	0.0001	0.0001	63	0.0030	0.0021	0.0022	0.0015
14	0.0001	0.0001	0.0001	0.0001	64	0.0030	0.0021	0.0022	0.0015
15	0.0001	0.0001	0.0001	0.0001	65	0.0030	0.0021	0.0022	0.0015
16	0.0002	0.0001	0.0002	0.0001	66	0.0030	0.0021	0.0022	0.0015
17	0.0003	0.0001	0.0003	0.0001	67	0.0030	0.0021	0.0022	0.0015
18	0.0004	0.0002	0.0004	0.0002	68	0.0030	0.0021	0.0022	0.0015
19	0.0005	0.0002	0.0004	0.0002	69	0.0030	0.0021	0.0022	0.0015
20	0.0004	0.0002	0.0004	0.0002	70	0.0030	0.0021	0.0022	0.0015
21	0.0004	0.0002	0.0004	0.0002	71	0.0030	0.0021	0.0022	0.0015
22	0.0004	0.0002	0.0004	0.0002	72	0.0030	0.0021	0.0022	0.0015
23	0.0005	0.0002	0.0005	0.0002	73	0.0030	0.0021	0.0022	0.0015
24	0.0005	0.0002	0.0005	0.0002	74	0.0030	0.0021	0.0022	0.0015
25	0.0005	0.0002	0.0005	0.0002	75	0.0030	0.0021	0.0022	0.0015
26	0.0006	0.0002	0.0006	0.0002	76	0.0030	0.0021	0.0022	0.0015
27	0.0006	0.0003	0.0006	0.0002	77	0.0030	0.0021	0.0022	0.0015
28	0.0006	0.0003	0.0006	0.0003	78	0.0030	0.0021	0.0022	0.0015
29	0.0006	0.0003	0.0006	0.0003	79	0.0030	0.0021	0.0022	0.0015
30	0.0007	0.0003	0.0006	0.0003	80	0.0030	0.0021	0.0022	0.0015
31	0.0007	0.0004	0.0007	0.0003	81	0.0030	0.0021	0.0022	0.0015
32	0.0007	0.0004	0.0007	0.0003	82	0.0030	0.0021	0.0022	0.0015
33	0.0008	0.0005	0.0007	0.0004	83	0.0030	0.0021	0.0022	0.0015
34	0.0008	0.0005	0.0008	0.0004	84	0.0030	0.0021	0.0022	0.0015
35	0.0010	0.0005	0.0009	0.0004	85	0.0030	0.0021	0.0022	0.0015
36	0.0010	0.0006	0.0009	0.0005	86	0.0030	0.0021	0.0022	0.0015
37	0.0011	0.0006	0.0010	0.0005	87	0.0030	0.0021	0.0022	0.0015
38	0.0012	0.0007	0.0011	0.0006	88	0.0030	0.0021	0.0022	0.0015
39	0.0013	0.0008	0.0012	0.0006	89	0.0030	0.0021	0.0022	0.0015
40	0.0015	0.0008	0.0012	0.0006	90	0.0030	0.0021	0.0022	0.0015
41	0.0016	0.0009	0.0013	0.0007	91	0.0030	0.0021	0.0022	0.0015
42	0.0016	0.0010	0.0013	0.0008	92	0.0030	0.0021	0.0022	0.0015
43	0.0018	0.0011	0.0015	0.0008	93	0.0030	0.0021	0.0022	0.0015
44	0.0019	0.0012	0.0016	0.0009	94	0.0030	0.0021	0.0022	0.0015
45	0.0022	0.0013	0.0017	0.0010	95	0.0030	0.0021	0.0022	0.0015
46	0.0022	0.0014	0.0018	0.0010	96	0.0030	0.0021	0.0022	0.0015
47	0.0024	0.0016	0.0019	0.0011	97	0.0030	0.0021	0.0022	0.0015

48	0.0025	0.0017	0.0020	0.0012	98	0.0030	0.0021	0.0022	0.0015
49	0.0028	0.0018	0.0023	0.0013	99	0.0030	0.0021	0.0022	0.0015
50	0.0030	0.0021	0.0022	0.0015	100	0.0030	0.0021	0.0022	0.0015

The rate of other cause mortality by age and sex was treated as the baseline hazard. Following input from stakeholders, an increased risk of mortality was assigned to individuals with diabetes using data from a published meta-analysis (45). This study used data from 820,900 people from 97 prospective studies to calculate hazard ratios for cause-specific death, according to baseline diabetes status (45). Cause of death was separated into vascular disease, cancer and other cause mortality. From this study we estimated that individuals with a diagnosis of diabetes have a fixed increased risk of other cause mortality (Hazard ratio 1.8 (95% CI 1.71-1.9)). The estimates reported in the meta-analysis include increased risk of death from renal disease, therefore mortality from renal disease was not simulated separately to avoid double counting of benefits.

Mortality risk increases with the onset of dementia. As a consequence, all cause mortality was inflated after diagnosis of dementia. The hazard ratio of mortality was estimated from analysis of two United States cohorts (46). Participants were recruited to the studies without known dementia at baseline and received annual clinical evaluation and brain donation at death. The analysis included 2566 persons over 8 years and found a hazard ratio of death with all dementia of 4.54 (CI 3.54-5.83) for ages 75-84 and 2.77 (CI 2.37-3.23) for ages 85 and older . These hazard ratios were applied in the model to all cause mortality to describe mortality at younger ages 60-84 and older 85+ ages.

Mortality rates for individuals with diabetes and undiagnosed diabetes are also at increased risk of mortality, which is applied to all cause mortality. Given the correlation between risk factors of diabetes and dementia, and the high prevalence of multi-comorbidities in later life, it is necessary to adjust mortality risk for individuals with both dementia and diabetes. We believe that applying both mortality hazard ratios would over-estimate the mortality burden in these patients. In the model the higher hazard ratio for Dementia is applied.

Direct Health Care Costs

At any given time period of the model individuals can have multiple health complications that incur direct healthcare costs. Some of the health states are mutually exclusive; however an individual can accrue multiple complications within the model. Each health state is associated with an average cost, which is accrued by all individuals for every time period for which the state is indicated. Resource use for each comorbidity is added together and no savings are assumed to be made from the use of the same resources for two or more comorbidities for an individual.

In some instances we have adopted costs and prices from old studies. We have inflated all prices and costs to 2014/15 prices using inflation indices reported in the Personal Social Services Research Unit (PSSRU) (47). This documents health related inflation up to 2013/14 prices. The retail price index was used to inflate costs to 2014/15 prices.

Primary care and community care costs were sought from the Personal Social Services Research Unit (PSSRU) (47), and secondary care costs from UK reference costs (48). Drug costs were obtained from the British National Formulary (49). In most instances costs for long term health outcomes were sought from recent Health Technology Appraisals as this was thought to be the best source of evidence for costs and resource use by disease area in the UK. If an HTA appraisal was not identified, searches for good quality cost-effectiveness analyses for the relevant disease area were conducted to identify the appropriate UK costs.

GP attendance

The costs of each visit to a General Practitioner were estimated at £46.95 from the Personal Social Services Research Unit (PSSRU) (47).

Diabetes diagnosis incurred a cost of £14 in line with costs used for a previous evaluation of a Diabetes Prevention Programme (3).

Recent guidelines for hypertension have recommended that hypertension be confirmed with ambulatory blood pressure monitoring (ABPM) (13). The cost of ABPM assessment is included in the cost of diagnosis (£53.40) (50), however, we assume that the test does not alter the initial diagnosis. The cost of identifying individuals to receive statins is assumed to be negligible because cases are detected using existing cardiovascular risk programmes used by the GP.

Diabetes

We were advised by stakeholders to model a simplified diabetes treatment pathway. It was recommended that a single annual cost of prescriptions be applied to all patients diagnosed with diabetes. Initially we explored this as an option but concluded that the timing of more costly treatments for type 2 diabetes is important because treatment costs will be discounted. The model assesses interventions that lower HbA1c and so have the potential to impact on the level of treatment required.

We decided to implement a three stage treatment regimen as a trade-off between model simplicity and capturing key cost differences between the interventions. At diagnosis all patients are prescribed low cost treatments, such as Metformin and Sulfonylurea. We chose Metformin, 500mg/day to describe the average cost of these medications. If HbA1c increases above a threshold the individual is prescribed the more expensive Gliptins in addition to Metformin. The individual continues to receive Metformin plus Gliptins for a period of time until they require insulin. A summary of unit costs used for diabetes maintenance is detailed in Table 81.

Table 81: Unit costs used for diabetes maintenance

Resource	Unit cost	Standard error	Source
Nurse at GP	£25.52	2.5	(47)
Health care assistant	£3.40	0.34	(47)
Urine sample	£1	0.1	(48)
Eye screening	£24.31	5.86	(51)
HbA1c	£3	0.3	(48)
Lipids	£1	0.1	(48)
Liver function	£1	0.1	(48)
B12	£1	0.1	(48)

Metformin Monotherapy

Cost estimates from the British National Formulary indicate that the cost of Metformin is approximately £19 per annum, using a combination of standard and modified release tablets (49). The use of blood glucose self-monitoring strips was described in a recent UK based study in which 36% of patients used monitoring strips at a mean weekly consumption of 3.1 (52) for individuals prescribed Metformin only, at a cost of 20p per strip as reported in the BNF.

Other resource use costs and resource utilisation assumptions for diabetics receiving Metformin monotherapy are detailed in Table 82.

Table 82: Drug costs and resource utilisation costs for low cost diabetes monotherapy

Resource	Assumption for costs	Unit cost	Source	Inflation	Annual utilisation	Source	Cost per year
Metformin	500mg *bid* standard (85% of patients) or modified release (15%) tablets	£18.83 per annum	(49)	1	1	Assumption	£18.83
Nurse at GP	Nurse advanced per surgery consultation with qualifications	£25.52	(47)	1	1	Stakeholder workshop	£25.52
Health care assistant	Clinical support worker patient work 10 mins	£3.40	(47)	1	1	Stakeholder workshop	£3.40
Urine sample	Biochemistry	£1	(48)	1	3	Stakeholder workshop	£1
Eye screening	Optometrist test 2006 price	£18.39	(51)	1.322	1	Stakeholder workshop	£24.31
HbA1c	Haematology	£3	(48)	1	1	Stakeholder workshop	£3.00
Lipids	Chemistry	£1	(48)	1	1	Stakeholder workshop	£1.00
Liver function	Chemistry	£1	(48)	1	1	Stakeholder workshop	£1.00
B12	Chemistry	£1	(48)	1	1	Stakeholder workshop	£1.00
							£79.06

The cost of diabetes in the year after diagnosis is assumed to be greater than subsequent years because the individual will receive more contact time whilst their diabetes is being controlled. The additional costs of diabetes in the year after diagnosis are reported in Table 83.

Table 83: Drug costs and resource utilisation costs for the first year after diabetes diagnosis

Resource	Assumption for costs	Unit cost	Source	Inflation	Annual utilisation	Source	Cost per year
Nurse at GP	Nurse advanced per surgery consultation with qualifications	£25	(47)	1	1	Stakeholder workshop	£51.03
Health care assistant	Clinical support worker patient work 10 mins	£3.40	(47)	1	2	Stakeholder workshop	£6.80
Urine sample	Biochemistry	£1	(48)	1	2	Stakeholder workshop	£2
HbA1c	Haematology	£3	(48)	1	2	Stakeholder workshop	£6.00
Lipids	Chemistry	£1	(48)	1	2	Stakeholder workshop	£2.00
Liver function	Chemistry	£1	(48)	1	2	Stakeholder workshop	£2.00
B12	Chemistry	£1	(48)	1	2	Stakeholder workshop	£2.00
Smoking Cessation	Nicotine replacement therapy	£103	(47)	1	0.3*	Stakeholder workshop	£30.90
							£103
* Assumed 20% smoking prevalence and 50% uptake of smoking cessation services							

Metformin plus Gliptins

Simulated individuals experience an annual increase in HbA1c. Gillett et al. (2012) assume that individuals switch to dual treatment if HbA1c increases above 7.4% (53). Within the model, the individual is switched to a dual treatment in the first annual cycle in which HbA1c exceeds 7.4%. For costing purposes the second drug to be added to Metformin was Sitagliptin, which is reported in the British National Formulary to cost £1.21 per day (49). Belsey et al. (2009) report that 48% of patients used monitoring strips at a mean weekly consumption of 3.3 (52). Table 84 reports the other resource use costs and utilisation assumptions for diabetics receiving Metformin plus Gliptins.

Table 84: Drug costs and resource utilisation costs for Metformin and Gliptins

Resource	Assumption for costs	Unit cost	Source	Inflation	Annual utilisation	Source	Cost per year
Sitagliptin	100mg per day	£1.21	(49)	1	360	Assumption	£434
Metformin	500mg *bid* standard (85% of patients) or modified release (15%) tablets	£18.83 per annum	(49)	1	1	Assumption	£18.83
Self-monitoring strips	50 strip pack Active®	£0.20	(49)	1	82.20	(52)	£16.36
Nurse at GP	Nurse advanced per surgery consultation with qualifications	£25.52	(47)	1	1	Stakeholder workshop	£25.52
Health care assistant	Clinical support worker patient work 10 mins	£3.40	(47)	1	1	Stakeholder workshop	£3.40

Urine sample	Biochemistry	£1	(48)	1	1	Stakeholder workshop	£1
Eye screening	Optometrist test 2006 price	£18.39	(51)	1.322	1	Stakeholder workshop	£24.31
HbA1c	Haematology	£3	(48)	1	1	Stakeholder workshop	£3.00
Lipids	Chemistry	£1	(48)	1	1	Stakeholder workshop	£1.00
Liver function	Chemistry	£1	(48)	1	1	Stakeholder workshop	£1.00
B12	Chemistry	£1	(48)	1	1	Stakeholder workshop	£1.00
							£529

Insulin plus Oral Anti-diabetics

The second major treatment change is assumed to be initiation of insulin. Gillett et al. (2012) assumed that individuals switch to insulin if HbA1c increases above 8.5% (53). Within the model the individual is switched to insulin in the first annual cycle at which HbA1c exceeds 8.5%. The insulin Glargine was chosen to represent insulin treatment in the UK and is consistent with Gillett et al. (2012) (53). The total resource use and costs of this health state are reported in Table 85 & Table 86.

Table 85: Costs of insulin treatment

	Price	Source
Glargine	£628.44	(54)(2006 prices)
Oral anti-diabetics	£43.68	(54) (2006 prices)
Reagent test strips	£221.43	(54) (2006 prices)
Hypoglycaemic rescue	£23.43	(54) (2006 prices)
Pen delivery devices	£54.79	(54) (2006 prices)
Sharps	£68.82	(54) (2006 prices)
Total cost per year	£1,013.51	

Table 86: Drug costs and resource utilisation costs for insulin and oral anti-diabetics

Resource	Assumption for costs	Unit cost	Source	Inflation (2013)	Annual utilisation	Source	Cost per year
Insulin treatment costs	Total annual cost	£1,013.51	(54)	1.322	NA	N/A	£1376
Nurse at GP	Nurse advanced per surgery consultation with qualifications	£25.52	(47)	1	3	Stakeholder workshop	£76.55
Health care assistant	Clinical support worker patient work 10 mins	£3.40	(47)	1	3	Stakeholder workshop	£10.21
Urine sample	Biochemistry	£1	(48)	1	3	Stakeholder workshop	£3.00
Eye screening	Optometrist test 2006 price	£18.39	(47)	1.322	1	Stakeholder workshop	£24.31
HbA1c	Haematology	£3	(48)	1	3	Stakeholder workshop	£9.00

Lipids	Chemistry	£1	(48)	1	3	Stakeholder workshop	£3.00
Liver function	Chemistry	£1	(48)	1	3	Stakeholder workshop	£3.00
B12	Chemistry	£1	(48)	1	3	Stakeholder workshop	£3.00
							£1503

Statins

We assumed that individuals who are prescribed statins receive a daily dose of 40mg of generic Simvastatin. The British National Formulary reports a cost of approximately 7p per day (49). The individual remains on statins for the rest of their life. Table 87 reports the derived annual costs for statins. We assumed that individual's cholesterol is monitored whilst on statins and patients receive two lipid tests per year. The cost of GP attendance was not included in the cost of statins to avoid double counting of GP attendance.

Table 87: Annual treatment costs of statins

	Assumption for costs	Unit cost	Source	Inflation	Annual utilisation	Cost per year
Statins	Simvastatin 20mg	£0.0728	(49)	1	360	£26.59
Statins	Lipid tests	£1	(48)	1	2	£2
						£28.59

Anti-hypertensives

A search of the literature did not identify any recent publications of anti-hypertensive prescriptions in the UK. As a consequence the best estimates of cost of anti-hypertensive treatment dated from 2004. These were inflated to current prices (47). Due to the number of different anti-hypertensive treatments available and possibilities for combination therapies, using the cost from this study of prescriptions was preferred to using costs directly from the BNF.

Table 88: Annual cost of anti-hypertensive prescription expenditure per patient

	Price	Inflation	Cost per year	Standard error	Source
Anti-hypertensive prescriptions	£144	1.322	£195.94	19.59	(55)

Cardiovascular Events

Costs for coronary heart disease disease were obtained from a 2009 HTA for high dose lipid-lowering therapy unless otherwise stated (12). The costs of stroke were obtained from a study estimating costs from the Oxford vascular cohort (56). Table 89 describes the costs and resource use assumptions that were used for this study. It also reports the health states to which we have applied each cost in the

model. The costs of congestive heart failure were estimated from the UKPDS costing study for complications related to diabetes (57). The unit costs for cardiovascular events are detailed in Table 90.

Table 89: Resources use assumptions and costs for cardiovascular outcomes

	Resource assumptions	**Cost (2009)**	**Cost (2014/15)**	**Health States applied**
Unstable Angina year 1	Secondary care costs: 100% hospitalisation, 50% revascularisation procedure, three outpatient appointments). Primary care costs (three GP visits) and medications.	£3880	£4,674	UANG1
MI year 1	Secondary care costs: 100% hospitalisation, 50% revascularisation procedure, three outpatient appointments). Primary care costs (three GP visits) and medications.	£3996	£4,813	MI1
Subsequent ACS care costs	Secondary care costs (one outpatient appointment). Primary care costs (three GP visits) and medications.	£340	£410	SANG, UANG, MI
Stroke year 1	Costs of first year post stroke (56)	£10,524	£12,677	STRO1
Stroke subsequent costs	Average costs in years 2-5 following stroke (56).	£1,444	£1,740	STRO2
Transient Ischemic Attack	Hopsital costs from 5 year study	£2,260	£2,723	TIA
Fatal CHD	Palmer et al. (58). Assumed that 50% of fatalities incurred cost.	£592	£713	
Fatal non cardio-vascular event	Youman et al. (59). Assumed 50% fatalities incurred cost.	£3688	£4,443	
	Source	**Cost (2012)**	**Cost (2014/15)**	
Congestive heart failure year 1	UKPDS (57)	£3,191	£3,091	
Congestive heart failure subsequent years	UKPDS (57)	£1,473	£1,818	

Table 90: Unit costs for Cardiovascular cost estimates taken from HTA report (12)

Unit Cost	Mean	Inflation	Mean (2014/15)	Standard error	Distribution
Unstable Angina hospital: EB05SZ	£1059	1.2045	£1275	127.6	GAMMA
Revasc. Hospital mixture of HRG codes	£5011.81	1.2045	£6037	604	GAMMA
MI Hospital: EB107	£1290.88	1.2045	£1555	156	GAMMA
First Outpatient	£137.28	1.2045	£165	16.5	GAMMA
Subsequent appointment	£91.37	1.2045	£110	11.0	GAMMA
GP visit year1	£102	1.2045	£123		CONSTANT
GP visit year 2	£91.37	1.2045	£110		CONSTANT
Fatal CHD (Palmer (58) Inflated)	£591.52	1.2045	£713	71	GAMMA
Fatal stroke (Youman (59) inflated)	£3688.23	1.2045	£4443	444.3	GAMMA

Glytrin Spray	£10.47	1.2045	£12.61		CONSTANT
Isosorbide mononitrate	£11.24	1.2045	£13.54		CONSTANT
Verapamil	£41.98	1.2045	£50.57		CONSTANT
Atenolol	£30.24	1.2045	£36.42		CONSTANT
Aspirin	£6.65	1.2045	£8.01		CONSTANT
Ramipril	£75.09	1.2045	£90.45		CONSTANT
ARB	£210.27	1.2045	£253		CONSTANT
Clopidogrel	£460.27	1.2045	£554		CONSTANT

Renal Failure

The cost of renal failure was estimated for the UK using relevant published studies. A recent costing study reported the costs of dialysis types (60). The prevalence of dialysis and transplants were taken from a second study reporting the prevalence of renal failure in the UK in 2008 (61). The cost of renal transplantation was taken from a costing study investigating the cost-effectiveness of renal transplantation (62). The overall cost was estimated as a weighted average of the treatment outcomes. All costs were inflated to 2014/15 prices.

Table 91: Unit costs for renal failure

	Cost (£)	Source	Inflation	Cost (2014/15)	Standard error	Proportion
Haemodialysis with overheads	34,236	(60)	1.2282	£42,049	4204.9	0.469
Automated peritoneal dialysis (APD)	22,160	(60)	1. 2282	£27,217	2721.7	0.045*
Continuous ambulatory peritoneal dialysis (CAPD)	16,074	(60)	1. 2282	£19,742	1974.2	0.045*
Transplant	17,000	(62)	1.3918	£23,660	2366	0.442
Immunosuppressants annual cost	5000	(62)	1. 39184	£6,959	695.9	
* Assumed 50% split of peritoneal dialysis types						

Foot Ulcers

A search of the literature did not identify any studies for foot ulcer for the UK or a health system comparable to the UK. The cost of foot ulcers was estimated from a US Cost of Illness study (63). We acknowledge that this is a limitation of the analysis, because US costs may not be representative of

care in the UK. The costs were converted from dollars to pounds using Purchasing Power Parities reported by the OECD (64). The costs were also inflated to UK 2014/15 prices.

Table 92: Estimated cost of foot ulcers

Resource component	Not Infected	With Cellulitis	With Osteomyelitis
Prevalence	0.874	0.09	0.036
Mean cost per patient	$178.97	$472.73	$876.52
Mean cost per patient (2014/15 £)	£168	£443	£822
Standard error	16.8	44.3	82.2
Total Cost PPP (2014/15 £)			£216

Amputation

The cost of amputation in the first year of surgery and subsequent years has been reported in a UKPDS costing study(65). The costs were extracted and inflated to 2014/15 prices. The cost of amputation in the first year was £12,254 (standard error £3130) and in subsequent years was £3,403 (standard error £732).

Blindness

The cost of blindness in the first year of surgery and subsequent years has been reported In a UKPDS costing study (65). The costs were extracted and inflated to 2014/15 prices. The cost of blindness in the first year was £2,067 (standard error £940) and in subsequent years was £1,260 (standard error £138).

Cancer

The cost of breast and colorectal cancer is estimated as a one-off fixed cost at diagnosis in the model. This simplifying assumption means that the cost of cancer treatment is independent of survival. We acknowlegde that this assumption will affect the timing of costs because all costs are imposed in the first year and subject to less discounting. However, we anticipate that the impact on overall outcomes will not be substantial. A large proportion of costs are will be incurred in the first year of treatment (surgery, chemotherapy, radiotherapy). Costs in subsequent years will be lower for patients who

achieve remission and survival will be short in patients who relapse. Therefore, the costs are likely to be skewed to the early years post diagnosis.

A recent appraisal for cancer screening estimated the overall cost of breast cancer as a weighted average depending on the prognosis at diagnosis to be £10,452 in 2006/7 prices and £13,818 when inflated to 2014/15 prices (66).

The cost of colorectal cancer was taken from a screening appraisal which reported the lifetime costs of colorectal cancer according to the Dukes stage of the tumour (67). The appraisal also reported the proportion of cancers identified at each stage, which allowed us to estimate the weighted average cost of colorectal cancer. Table 93 reports the overall cost of colorectal cancer by stage of disease at diagnosis.

Table 93: Estimated cost of colorectal cancer

Resource component	Dukes' Stage A	Dukes' Stage B	Dukes' Stage C	Stage D
Number of patients	3241.92	9,431.04	7,662.72	8,841.60
Prevalence	0.111	0.323	0.263	0.303
Mean cost per patient	£7,250.84	£12,441.41	£19,076.90	£11,945.78
Price Inflation				1.296
Mean cost per patient (2014/15)	£10,091	£17,315	£26,550	£16,626
Standard error (2014/15)	£1,009	£1,732	£2,655	£1,663
Total Cost (2014/15)				£18,729

Osteoarthritis

The annual cost of osteoarthritis were estimated in a report in 2010 (68). In this report the authors estimated the expected cost of osteoarthritis from three previous costing studies. The costs include GP attendance, nurse consultations, replacement surgery, help at home and prescription medications. The estimated annual cost of osteoarthritis was £783 in 2008. In the study 93% of the costs were attributable to direct medical costs and 7% to social care. Therefore, cost of direct medical care in 2014/15 prices at £896.

Depression

Depression is modelled as a chronically recurrent disorder, with patients experiencing further depressive episodes after remission. In the model it is assumed that patients continue to incur costs of depression following an initial diagnosis. These costs reflect ongoing resource use to deal with relapse and prevention of relapse.

A recent trial to prevent secondary depressive episodes collected comprehensive cost data from a sample of individuals with depression (69). The resource uses identified in the control arm were extracted to estimate the costs of depression. The costs from this data (inflated to 2014/15 prices) were not implemented directly into the SPHR diabetes prevention model as this would have over-estimated the number of GP visits. The model already accounts for GP attendance due to depression. Therefore, a revised estimate of the cost of depression, excluding GP consultation was estimated using updated unit costs. The resource use estimates and revised unit cost estimates used to generate a cost of depression excluding GP utilisation are reported in Table 94.

Table 94: Depression utilisation of services and total estimated cost

	Assumption for costs	Unit cost	Source	Inflation	Annual utilisation	Source	Cost per year
Practice nurse at surgery	GP nurse face to face assume 10 mins	£8.83	(70)	1.0206	1.52	(69)	£13.70
Practice nurse at home visit	GP nurse face to face assume 30 mins	£26.50	(70)	1.0206	0.02	(69)	£0.54
Practice nurse telephone	GP nurse face to face assume 10 mins	£8.83	(70)	1.0206	0.11	(69)	£0.99
Health visitor	Health visitor per hour visit 30 mins	£35.50	(70)	1.0206	0.05	(69)	£1.94
District nurse	Community nurse 30 mins	£24.50	(70)	1.0206	0.01	(69)	£0.38
Other nurse	GP nurse face to face assume 10 mins	£8.83	(70)	1.0206	0.13	(69)	£1.17
HCA phlebotomist	Clinical support worker 10 mins	£4.17	(70)	1.0206	0.31	(69)	£1.05
Other primary care	Advanced nurse with qualifications	£25.00	(70)	1.0206	0.19	(69)	£4.85
Out of hours	Inflated of trial costs	£25.39	(69)	1.2045	0.23	(69)	£6.18
NHS direct	Inflated of trial costs	£23.90	(69)	1.2045	0.09	(69)	£2.28
Walk-in centre	Inflated of trial costs	£36.70	(69)	1.2045	0.21	(69)	£8.15
Prescribed medications	Inflated of trial costs	£9.09	(69)	1.2045	7.74	(69)	£74.42
Secondary care	Emergency Medicine, Any Investigation	£109.00	(71)	1	0.26	(69)	£21.06
							£136.71

Dementia

Cost of Diagnosis

A one off cost of diagnosis is incurred in the first year of the disease to account for the costs associated with assessing and diagnosing patients. The most recent cost study of Dementia for the UK estimated the cost of Dementia diagnosis at £650 in 2012/13 prices (42) inflated to £687.82.

Ongoing healthcare costs

The direct health care costs of dementia to the NHS were estimated in an Alzheimers UK report in 2014. The costs were estimated from a modelling study based on PSSRU aggregeate long term care model and PSSRU dementia care model. The report describes costs of care for patients with dementia in 2013 £. Full details of the costing model are reported elsewhere. Table 95 reports the costs of dementia for individuals in community or residential care according to MMSE cognitive score. In the model it is assumed that healthcare costs are met entirely by the NHS. These costs are applied in the model to patients with a dementia diagnosis on an annual basis.

Table 95: Average annual direct healthcare dementia costs

	Healthcare costs		Proportion of patients residential care	Total cost	Total Costs 2014/15 £
	Community	Residential			
Mild (MMSE 21-26)	2,751	4,504	10.4%	2932	3103
Moderate (MMSE 10-20)	2,695	9,438	76.2%	7837	8293
Severe (MMSE 0-9)	11,258	8,689	76.2%	9300	9841

Social Care costs

In this analysis the social care costs refer to the public and private costs incurred with social care as a consequence of a diagnosis with either stroke or dementia. Social care costs associated with the other health outcomes of the model are not included in this estimate. This is likely to under-estimate the overall cost of social care in the population. However, reliable social care costs for other conditions are very hard to obtain because they are less commonly incurred in the prevalent patient population and more likely to be attributed to other factors or ageing more generally.

Osteoarthritis

The annual cost of osteoarthritis were estimated in a report in 2010 (68). The estimated annual cost of osteoarthritis was £783 in 2008. In the study 93% of the costs were attributable to direct medical costs and 7% to social care. Therefore, cost of social care costs in 2014/15 prices at £65.

Stroke

The community costs in the first year following stroke were estimated from the South London Stroke Register (72). The average number of days at day centres, nursing homes, residential home, sheltered accommodation and were used to estimate the social care costs.

	Mean number of days	Source	Unit cost per day	Source	Total cost
Day Centre	3.9	(72)	£59	(47)	254.38
Nursing Home	16.9	(72)	£75	(47)	1,265.09
Residential Home	8.5	(72)	£101	(47)	857.29
Sheltered Home	8.1	(72)	£65	(47)	526.50
				Total cost	2878.97

Dementia

The social care costs of dementia were estimated in an Alzheimers UK report in 2014 (42). The costs were estimated from a modelling study based on PSSRU aggregeate long term care model and PSSRU dementia care model. The report describes costs of care for patients with dementia in 2013 £. Table 95 reports the costs of dementia for individuals in community or residential care according to MMSE cognitive score. We used estimates from the Alzheimers UK report to estimate the pubic and private social care costs of dementia in line with the methods used in this report. We do not include the productivity costs of informal carers or other public costs in the model. These costs are applied in the model to patients with a dementia diagnosis on an annual basis.

Table 96: Average annual dementia costs

	Healthcare costs		Proportion of patients residential care	Total cost	Total Costs 2014/15 £
	Community	Residential			
Mild (MMSE 21-26)	3,121	24,737	10.4%	5362	5674
Moderate (MMSE 10-20)	7,772	25,715	76.2%	21455	22703
Severe (MMSE 0-9)	10,321	25,874	76.2%	22176	23466

Utilities

Baseline Utility

Baseline utilities for all individuals in the cohort were extracted from the HSE 2011. The tariffs for the responses to the 3 level EQ-5D were derived from a UK population study (73). Utility was assumed to decline due to ageing independent of health status. In the simulation, utility declines by an

absolute decrement of 0.004 per year. This estimate is based on previous HTA modelling in cardiovascular disease (7).

Utility Decrements

The utility decrements for long term chronic conditions were applied to the age adjusted EQ-5D score. In consultation with stakeholders, we assumed that a diagnosis of diabetes was not associated with a reduction in EQ-5D independent of the utility decrements associated with complications, comorbidities or depression. Cardiovascular disease, renal failure, amputation, foot ulcers, blindness, cancer, osteoarthritis and depression were all assumed to result in utility decrements. The utility decrements are measured as a factor which is applied to the individual's age adjusted baseline. If individuals have multiple chronic conditions the utility decrements are multiplied together to give the individual's overall utility decrement from comorbidities and complications, in line with current NICE guidelines for combining comorbidities (74).

Due to the number of health states it was not practical to conduct a systematic review to identify utility decrements for all health states. A pragmatic approach was taken to search for health states within existing health technology assessments for the relevant disease area or by considering studies used in previous economic models for diabetes prevention. Discussions with experts in health economic modeling were also used to identify prominent sources of data for health state utilities. Two sources of data were identified for diabetes related complications. A recent study from the UKPDS estimated the impact of changes in health states from a longitudinal cohort (75). They estimated the impact of myocardial infarction, ischaemic heart disease, stroke, heart failure, amputation and blindness on quality of life using seven rounds of EQ-5D questionnaires administered between 1997 and 2007. This data was used to estimate the utility decrement for amputation and congestive heart failure. The absolute decrement for amputation was converted into utility decrement factors that could be multiplied by the individuals' current EQ-5D to estimate the relative effect of the complication. Blindness was included in the statistical model used for this analysis however the UKPDS analysis reported an increase in health state utility following a diagnosis with blindness.

Discussions with the authors highlighted that this was due to treatment following formal classification with blindness and it was decided that this increase in health state utility should not be included in the cost-effectiveness model.

Utility decrements for renal failure and foot ulcers were not available from the UKPDS study described above. A study by Coffey et al. (2000) was used to estimate utility decrements for renal failure and foot ulcers (76). In this study, 2,048 subjects with type 1 and type 2 diabetes were recruited from specialty clinics. The Self-Administered Quality of Well Being index (QWB-SA) was used to calculate a health utility score.

A meta-analysis of utility values for diabetes and diabetes related complications estimated utility decrements for amputation, ulcer, end stage renal failure and blindness (77). The study pooled utility measures using different health state valuation measures in a meta-analysis. Pooling health state utility values is problematic because of the fact that different valuation methods and different preference-based measures (PBMs) can generate different values on exactly the same clinical health state (78).There were not sufficient studies in the meta-analysis to adjust for the effects of health state valuation measure on the result. This is a limitation of the analysis and we decided that it was preferable to use estimates from single studies.

Utility decrements for cardiovascular events were taken from an HTA assessing statins to reflect the utility decrements in all patients (7) rather than using the UKPDS, which is only representative of a diabetic population. The study conducted a literature review to identify appropriate utility multipliers for stable angina, unstable angina, myocardial infarction and stoke. We used these estimates in the model and assume that transient ischaemic attack is not associated with a utility decrement in line with this HTA.

We identified a systematic review of breast cancer utility studies following consultation with colleagues with experience in this area. The review highlighted a single burden of illness study with a broad utility decrement for cancer (79), rather than utilities by cancer type or disease status. This study was most compatible with the structure of the cost-effectiveness structure. Within this study 1823 cancer survivors and 5469 age-, sex-, and educational attainment-matched control subjects completed EQ-5D questionnaires to estimate utility with and without cancer.

The utility decrement for osteoarthritis was taken from a Health Technology Assessment that assessed the clinical effectiveness and cost-effectiveness of glucosamine sulphate/hydrochloride and chondroitin sulphate in modifying the progression of osteoarthritis of the knee (80).

A review of cost-effectiveness studies highlights the scarcity of studies of health-related quality of life in depression (81). The utility studies identified in the review described depression states by severity and did not adjust for comorbid conditions. Furthermore, the valuations were variable between studies suggesting poor consistency in the estimations. Therefore, it was difficult to apply these in the model. We decided to use a study which had used the EQ-5D in an RCT, for consistency with our utility measure (82). They report an average post treatment utility of 0.67, from which we estimated the utility decrement compared with the average utility reported in the HSE dataset. The decrement was then converted into a relative utility reduction.

The quality of life impact of dementia is estimated from a study by Jonsson and colleagues (83). These utility values were idenfied and used in the most recent NICE HTA for Alzheimer disease (41). A systematic review of health state utilities for alzheimers disease discusses differences in health related quality of life in different settings (84). It is often assumed that patients in institutional settings will be more disabled and have poorer quality of life. However, the studies that compared utility between settings did not identify a statistically significant difference. Therefore, we only related utility to MMSE.

Table 97 reports the multiplicative utility factors that are used in the model to describe health utility decrements from comorbid complications. The mean absolute decrement estimated in each study is reported alongside the baseline utility for each study. The utility factor was estimated by dividing the implied health utility with the comorbidity by the baseline utility.

Table 97: Utility decrement factors

	Mean Absolute decrement	St. error absolute decrement	Baseline Utility	Multiplicative Utility Factor	Source
Foot ulcer	-0.099	0.013	0.689	0.856	Coffey (76)
Amputation	-0.172	0.045	0.807	0.787	UKPDS (75)
Blind				1.00	Assumption
Renal failure	-0.078	0.026	0.689	0.887	Coffey (76)
Stable Angina				0.801	Ward HTA (7)
Unstable Angina y1				0.770	Ward HTA (7)
Unstable Angina y2				0.770	Ward HTA (7)
Myocardial Infarction y1				0.760	Ward HTA (7)
Myocardial Infarction y2				0.760	Ward HTA (7)
Transient Ischaemic Attack				1.000	Ward HTA (7)
Stroke y1				0.629	Ward HTA (7)
Stroke y2				0.629	Ward HTA (7)
Breast Cancer	-0.060	0.008	0.791	0.913	Yabroff (79)
Colorectal Cancer	-0.060	0.008	0.791	0.913	Yabroff (79)
Osteoarthritis	-0.101	0.069	0.791		Black HTA (80)
Depression	-0.116		0.791	0.875	Benedict (82)
Congestive Heart Failure	-0.101	0.032		0.875	UKPDS (75)
MMSE 26-30			0.690		Jonsson (83)
MMSE 21-25	-0.05		0.690	0.93	Jonsson (83)
MMSE 15-20	-0.19		0.690	0.725	Jonsson (83)
MMSE 10-14	-0.20		0.690	0.710	Jonsson (83)
MMSE 0-9	-0.36		0.690	0.478	Jonsson (83)
UKPDS baseline utility 0.807; HSE baseline 0.7905					

Probabilistic Sensitivity Analysis

Probabilistic sensitivity analysis (PSA) was enabled in the model to describe the uncertainty in parameter inputs of the model and how this translates into uncertainty in the outcomes of the model. A suitable distribution was selected for each parameter, based upon its mean and standard error. A full list of data inputs into the model and the distribution selected is provided in supplementary file 2. Random sampling simultaneously across all input parameter distributions allowed parameter

uncertainty to be quantified. 5000 different random samples of parameter values were selected, and each was applied to a different random cohort of 20,000 individuals. Therefore, the characteristics of patients varied between model runs to ensure that the result was not biased by the baseline characteristics of the individuals. For each PSA sample, the model was run and results compiled. Given the large number of parameters in the model and thus the capacity for error, a thorough process of checking that mean sampling values corresponded to mean parameter values was undertaken to ensure that the results were as accurate as possible.

Model Validation

The SPHR model has undergone a thorough process of error checking and internal and external validations. Validation of the model to predict metabolic data, diabetes and cardiovascular disease have been reported elsewhere. Here we describe the validation tests used to compared metabolic outcomes with the ELSA data and dementia outcomes with published literature. The validation tests covered four main themes.

1. The evaluate the metabolic trajectory models with inclusion of the ELSA statistical models in individuals aged 61 and over.
2. To evaluate the average rate of decline in MMSE scores.
3. To evaluate the short term incidence of dementia.
4. To evaluate the incidence of long-term outcomes related to older age including coronary heart disease, stroke, dementia and mortality.
5. To evaluate life expectancy following dementia diagnosis.

Unfortunately, it was not possible to identify external data sources to validate all four themes. Therefore, summary statistics are presented for 1 and 2, with discussion in relation to some relevant data due to a lack of directly comparable statistics from the published literature. Statistics relating to themes 3 and 4 are directly compared against three published studies summarising data from CFAS and the preDIVA randomised controlled trial (40;89;90).

Metabolic trajectories

The simulated metabolic trajectories with ELSA statistical models for individuals aged 61 and over are illustrated and compared against the simulated metabolic trajectories with the Whitehall II only for all patients and in 10 year age groups. Figure 11 illustrates the trajectories for all patients. The analysis indicates a shallower trajectory for BMI, HbA1c, Total and HDL cholesterol. The trajectory for systolic blood pressure is mostly unaffected by the inclusion of ELSA data.

Figure 11: Metabolic trajectories for all patients with and without the ELSA statistical models

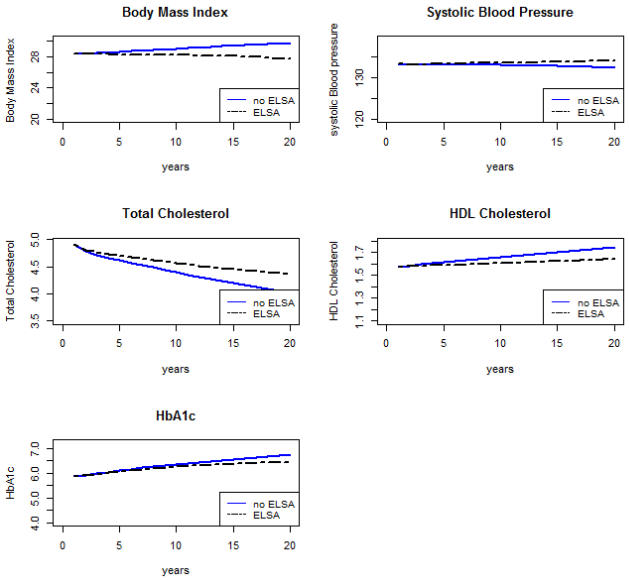


Figure 12 and Figure 13 illustrate the metabolic trajectoriesby 10 year age groups. The trajectories by 10 year age groups follow similar patterns in which the long term trajectories are shallower with the inclusion of the ELSA data. In the 60-70 year old group the rate of decline in BMI is greater with the ELSA statistical models.

Figure 12: Ages 50-60

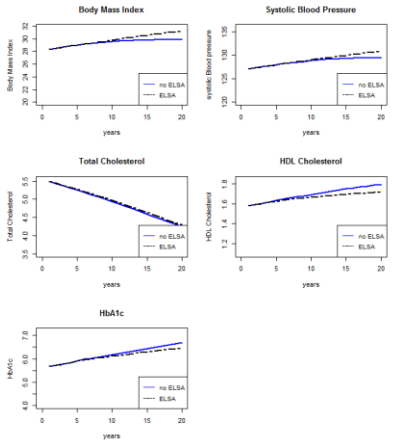
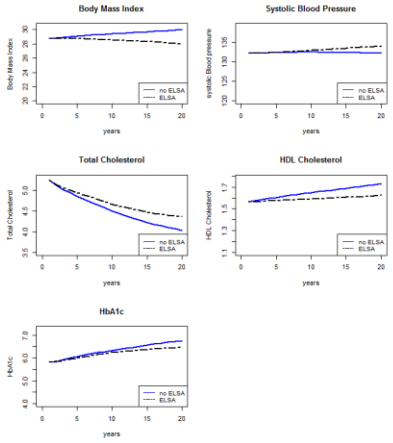


Figure 13: Ages 60-70



Short term Dementia Incidence

We compare the modelled dementia incidence with rates reported in the Congitive Function and Ageing Survey (90). The CFAS study reports dementia incidence after 2 years disaggregated by age and gender. Figure 14 and Figure 15 illustrate how the simulation model incidence of dementia compares with the CFAS data. The graphs show that the incidence in men is underestimated at younger ages, but fit relatively well in older age. Whereas the incidence for women fits well at younger age and slightly underestimates in older ages. The model reproduces the substantial increase in risk for women over the age of 80 observed in the data.

Figure 14: Comparison of dementia incidence in men between CFAS and simulation

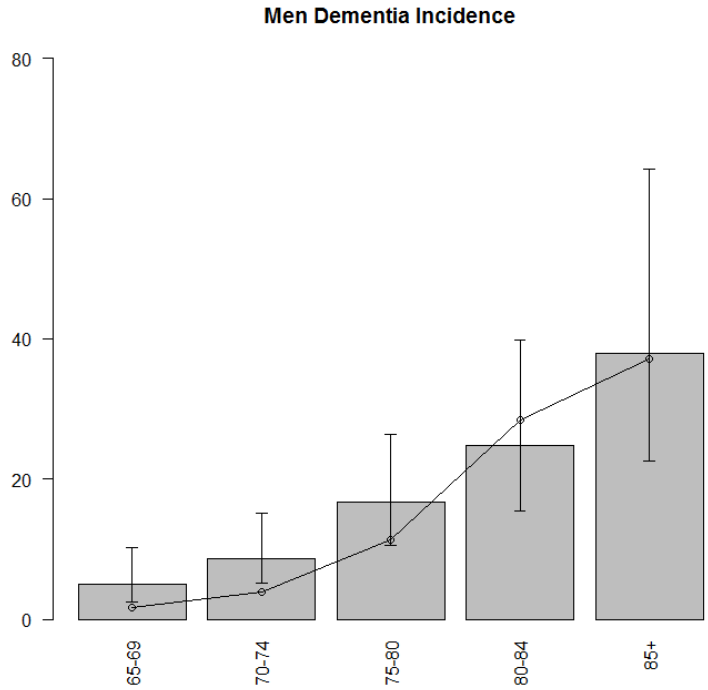
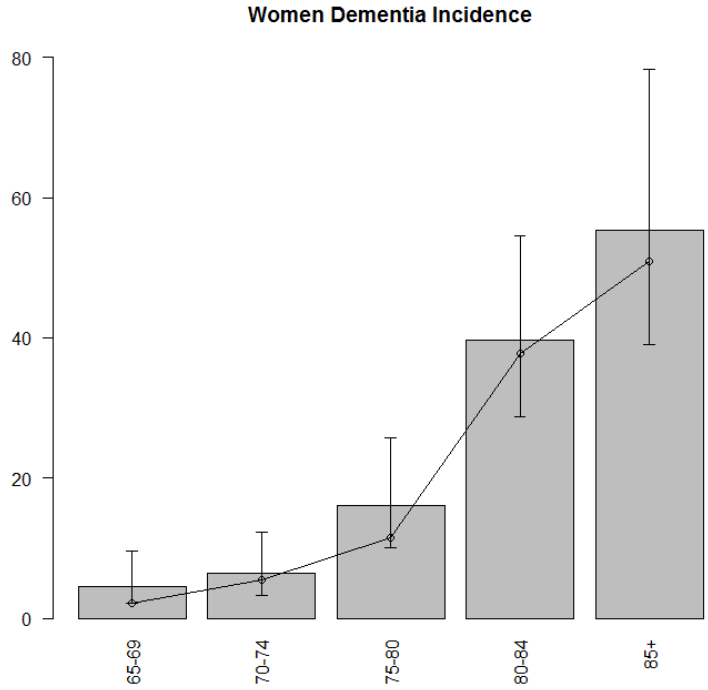


Figure 15: Comparison of dementia incidence in women between CFAS and simulation



Long-Term Outcomes

The pre-DIVA trial collected long term data on the incidence of dementia, coronary heart disease, stroke, cardiovascular mortality and all cause mortality (89). The participants were recruited if aged 70-78 and the population included a mean age of 74.5. The participants were followed for 6 years. We simulated a population of 20,000 individuals from the Health Survey for England 2014 aged 70-78 for 6 years to record health outcomes reported in the PreDIVA trial.

	Pre-DIVA control arm N (%)	Simulation %
All cause dementia	112/1601 (7%)	5.8%
Cardiovascular event	228/1307 (4%)	3.3%
Myocardial Infarction	57/1339 (8%)	7.5%
Stroke including TIA	102/1341 (8%)	4.7%
Cardiovascular death	60/1425 (4%)	11.6%
All cause mortality	269/1634 (16%)	5.8%

Life expectancy

Life expectancy for individuals with dementia is estimated from the CFAS cohort to be 4.5 years with a mean age at onset of 84. The simulated life expectancy for individuals following dementia diagnosis in the model was 3.8 years with a mean age at diagnosis of 87. We would expect the age at onset in the CFAS

group to be younger than the age of diagnosis in a population diagnosed in usual care, which accouts for the lower life expectancy in the simulation.

Cost-Effectiveness Outcomes

In order to compare the cost-effectiveness result with previous model specifications we have estimated the incremental outcomes for 20-years with differential discount rates of 6% for costs and 1.5% for QALYs. This enables us to compare the results with the previous cost-effectiveness outcomes generated for the our previous analyses. The results show that the incremental costs and QALYs are slightly higher in the new model specification, with a more up to date baseline population, mortality rate and inclusion of ELSA metabolic trajectories.

Table 98: Comparison of 20-year cost-effectiveness outcomes

	Targeting Strategy (Incremental results vs. Do Nothing)	
	PHE work	DPP no Dementia
Net Benefit (£20000 willingness to pay)	£701	£994
Incremental Health care cost (per person)	-£75	-£101
Incremental Cardiovascular cost (per person)	-£69	-£97
Incremental QALYs (per person)	0.0388	0.045
Incremental Life Years (per 1000 people)	35	47
Incremental Diabetes diagnoses (per 1000 people)	-7	-13
Incremental CVD events (per 1000 people)	-3	-4

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Appendix 4: Data Inputs and Uncertainty distributions

GP Attendance in the General Population

In the probabilistic sensitivity analysis the parameters of the South Yorkshire negative binomial model are sampled from a multivariate normal distribution, using the mean estimates described in Table 14 and covariance matrix in Table 60.

Table 99: GP attendance reported in the South Yorkshire Cohort (N= 18,437) (1)

	Mean	Standard error	Uncertainty Distribution
Age	0.0076	0.0005	MULTIVARIATE NORMAL
Male	-0.1495	0.0159	MULTIVARIATE NORMAL
BMI	0.0110	0.0015	MULTIVARIATE NORMAL
Ethnicity (Non-white)	0.2620	0.0375	MULTIVARIATE NORMAL
Heart Disease	0.2533	0.0289	MULTIVARIATE NORMAL
Depression	0.6127	0.0224	MULTIVARIATE NORMAL
Osteoarthritis	0.2641	0.0238	MULTIVARIATE NORMAL
Diabetes	0.2702	0.0278	MULTIVARIATE NORMAL
Stroke	0.1659	0.0474	MULTIVARIATE NORMAL
Cancer	0.2672	0.0414	MULTIVARIATE NORMAL
Intercept	-0.5014	0.0468	MULTIVARIATE NORMAL
Alpha	0.3423	0.0108	MULTIVARIATE NORMAL

Table 100: Variance-covariance matrix for GP attendance regression

	Age	Male	BMI	Ethnicity (Non-white)	Heart Disease	Depression	Osteo-arthritis	Diabetes	Stroke	Cancer	Intercept	Alpha
Age	0.0000											
Male	0.0000	0.0003										
BMI	0.0000	0.0000	0.0000									
Ethnicity (Non-white)	0.0000	0.0000	0.0000	0.0014								
Heart Disease	0.0000	0.0000	0.0000	0.0000	0.0008							
Depression	0.0000	0.0000	0.0000	0.0000	0.0000	0.0005						
Osteoarthritis	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0006					
Diabetes	0.0000	0.0000	0.0000	0.0000	-0.0001	0.0000	0.0000	0.0008				
Stroke	0.0000	0.0000	0.0000	0.0000	-0.0002	-0.0001	0.0000	-0.0001	0.0022			
Cancer	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-0.0001	0.0017		
Intercept	0.0000	0.0000	-0.0001	-0.0002	0.0002	0.0000	0.0002	0.0003	0.0000	0.0001	0.0022	
Alpha	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0010

Whitehall II Statistical Model of Metabolic Trajectories

The parameters derived from the Whitehall II statistical model of metabolic trajectories are described in Table 101, Table 102 and Table 103.

Table 101: Coefficient estimates for metabolic risk factor parallel growth models

	Parameter Description	Estimated Mean	Standard error	p-value
BMI Intercept				
α_{10}	Population mean BMI intercept	2.2521	0.045	<0.001
$\boldsymbol{\gamma_{10}}$	Age at baseline coefficient for BMI intercept	0.0056	0.001	<0.001
	Sex coefficient for BMI intercept	-0.0311	0.012	0.009
	Family history of CVD coefficient for BMI intercept	-0.0079	0.012	0.515
υ_{10}	Random error term for BMI intercept	0.1165	0.003	<0.001
BMI linear slope				
α_{11}	Population mean BMI linear slope	0.6409	0.042	<0.001
$\boldsymbol{\gamma_{11}}$	Age at baseline coefficient for BMI linear slope	-0.0084	0.001	<0.001
	Sex coefficient for BMI linear slope	-0.0285	0.011	0.009
	Family history of CVD coefficient for BMI linear slope	-0.0155	0.010	0.117
υ_{11}	Random error term for BMI linear slope	0.0222	<0.001	<0.001
BMI quadratic slope				
α_{12}	Population mean BMI quadratic slope	-0.2007	0.023	<0.001
$\boldsymbol{\gamma_{12}}$	Age at baseline coefficient for quadratic slope	0.0026	<0.001	<0.001
	Sex coefficient for quadratic slope	0.0089	0.006	0.147
	Family history of CVD coefficient for quadratic slope	0.0104	0.006	0.061
ε_1	Random error term for BMI	0.0104	<0.001	<0.001
Glyc Intercept				

α_{20}	Population mean glyc intercept	0	NA	NA
$\boldsymbol{\gamma_{20}}$	Smoker coefficient for glyc intercept	-0.1388	0.029	<0.001
τ_{20}	Association between BMI intercept and glyc intercept	0.2620	0.024	<0.001
υ_{20}	Random error term for glyc intercept	0.0851	0.008	<0.001
Glyc linear slope				
α_{21}	Population mean glyc linear slope	-0.4255	0.071	<0.001
$\boldsymbol{\gamma_{21}}$	Sex coefficient for glyc linear slope	0.1486	0.045	0.001
	Ethnicity coefficient for glyc linear slope	-0.0218	0.081	0.786
	Family history of T2DM coefficient for glyc linear slope	-0.0512	0.054	0.345
	Smoker coefficient for glyc linear slope	0.1796	0.066	0.007
τ_{21}	Association between BMI intercept and glyc linear slope	0.0821	0.024	0.001
τ_{22}	Association between BMI linear slope and glyc linear slope	0.1984	0.073	0.007
υ_{21}	Random error term for glyc linear slope	0.0222	0.011	0.053
Glyc quadratic slope				
α_{22}	Population mean glyc quadratic slope	0.1094	0.025	<0.001
$\boldsymbol{\gamma_{22}}$	Sex coefficient for glyc quadratic slope	-0.0855	0.027	0.002
	Ethnicity coefficient for glyc quadratic slope	0.0899	0.049	0.067
	Family history of T2DM coefficient for glyc quadratic slope	0.0633	0.033	0.052
	Smoker coefficient for glyc quadratic slope	-0.0390	0.040	0.330
υ_{22}	Random error term for glyc quadratic slope	0.0107	0.003	0.002
ε_2	Glyc measurement error	0.0707	0.005	<0.001
SBP Intercept				

α_{30}	Population mean SBP intercept	0.6934	0.021	<0.001
$\boldsymbol{\gamma_{30}}$	Age at baseline coefficient for SBP intercept	0.0043	<0.001	<0.001
	Sex coefficient for SBP intercept	0.0380	0.004	<0.001
	Smoking coefficient for SBP intercept	-0.0243	0.006	<0.001
	Ethnicity coefficient for SBP intercept	0.0078	0.007	0.300
	Family history of CVD coefficient for SBP intercept	0.0061	0.004	0.160
$\boldsymbol{\tau_{31}}$	Association between BMI intercept and SBP intercept	0.1080	0.006	<0.001
υ_{30}	Random error term for SBP intercept	0.0085	0.00	<0.001
SBP linear slope				
α_{31}	Population mean SBP linear slope	-0.0227	0.021	0.278
$\boldsymbol{\gamma_{31}}$	Age at baseline coefficient for SBP linear slope	0.0024	<0.001	<0.001
	Sex coefficient for SBP linear slope	-0.0004	0.004	0.927
	Smoking coefficient for SBP linear slope	0.0205	0.005	<0.001
	Ethnicity coefficient for SBP linear slope	0.0224	0.007	0.001
	Family history of CVD coefficient for SBP linear slope	-0.0013	0.004	0.748
$\boldsymbol{\tau_{31}}$	Association between BMI intercept and SBP linear slope	-0.0396	0.006	<0.001
	Association between BMI linear slope and SBP linear slope	0.2325	0.019	<0.001
υ_{31}	Random error term for SBP linear slope	0.0024	<0.001	<0.001
ε_3	SBP measurement error variance	0.0093	<0.001	<0.001
TC Intercept				
α_{40}	Population mean TC intercept	2.9956	0.176	<0.001
$\boldsymbol{\gamma_{40}}$	Age at baseline coefficient for TC intercept	0.0456	0.003	<0.001
	Sex coefficient for TC intercept	0.0660	0.036	0.070

τ_{40}	Association between BMI intercept and TC intercept	0.4459	0.049	<0.001
υ_{40}	Random error term for TC intercept	0.8960	0.025	<0.001
TC linear slope				
α_{41}	Population mean TC linear slope	2.1216	0.128	<0.001
$\boldsymbol{\gamma_{41}}$	Age at baseline coefficient for TC linear slope	-0.0316	0.002	<0.001
	Sex coefficient for TC linear slope	-0.2677	0.026	<0.001
τ_{41}	Association between BMI intercept and TC linear slope	-0.4808	0.035	<0.001
τ_{42}	Association between BMI linear slope and TC linear slope	0.9802	0.108	<0.001
υ_{41}	Random error term for TC linear slope	0.1583	0.011	<0.001
ε_4	TC measurement error variance	0.3426	0.006	<0.001
HDL Intercept				
α_{50}	Population mean HDL intercept	2.4124	0.054	<0.001
$\boldsymbol{\gamma_{50}}$	Age at baseline coefficient for HDL intercept	0.0032	0.011	<0.001
	Sex coefficient for HDL intercept	-0.3710	0.001	<0.001
τ_{51}	Association between BMI intercept and HDL intercept	-0.3514	0.015	<0.001
υ_{50}	Random error term for HDL intercept	0.0827	-0.040	<0.001
HDL linear slope				
α_{51}	Population mean HDL linear slope	0.1241	0.034	<0.001
$\boldsymbol{\gamma_{51}}$	Age at baseline coefficient for HDL linear slope	0.0020	0.001	<0.001
	Sex coefficient for HDL linear slope	0.0041	0.007	0.558
$\boldsymbol{\tau_{51}}$	Association between BMI intercept and HDL linear slope	-0.0400	0.010	<0.001
υ_{51}	Random error term for HDL linear slope	0.0090	0.001	<0.001

ε_5	HDL measurement error variance	0.0333	0.001	<0.001

Table 102: Coefficient estimates for latent glycaemic measurement model

	Parameter Description	Estimated Mean	Standard error	p-value
μ_0	FPG intercept	4.2903	0.089	<0.001
θ_{01}	Glycaemic factor to FPG	1	NA	NA
θ_{02}	Age to FPG	0.0031	0.001	0.022
θ_{03}	Sex to FPG	0.2129	0.021	<0.001
θ_{04}	Ethnicity to FPG	0.0100	0.037	0.786
θ_{05}	Family history of diabetes to FPG	0.1168	0.025	<0.001
ε_0	FPG measurement error variance	0.1649	0.007	<0.001
μ_1	2-hr Glucose intercept	0.5707	0.223	0.011
θ_{11}	Glycaemic factor to 2-hr glucose	2.4384	0.078	<0.001
θ_{12}	Age to 2-hr glucose	0.0716	0.003	<0.001
θ_{13}	Sex to 2-hr glucose	-0.1411	0.058	0.014
θ_{14}	Ethnicity to 2-hr glucose	0.3047	0.100	0.002
θ_{15}	Family history of diabetes to 2-hr glucose	0.3496	0.068	<0.001
ε_1	2-hr measurement error variance	2.3679	0.054	<0.001
μ_2	HbA1c intercept	4.4769	0.073	<0.001
θ_{21}	Glycaemic factor to HBA1c	0.5074	0.016	<0.001
θ_{22}	Age to HBA1c	0.0101	0.001	<0.001
θ_{23}	Sex to HBA1c	-0.0457	0.001	<0.001
θ_{24}	Ethnicity to HBA1c	0.1854	0.030	<0.001
θ_{25}	Family history of diabetes to HBA1c	0.0563	0.020	0.004
ε_2	HbA1c measurement error variance	0.1166	0.003	<0.001

Table 103: Covariance matrix $\boldsymbol{\Omega}$ for individual random error

	v_{10}	v_{11}	v_{20}	v_{21}	v_{22}	v_{30}	v_{31}	v_{40}	v_{41}	v_{50}	v_{51}
v_{10}	0.1165										
v_{11}	0.0095	0.0131									
v_{20}	<0.0010	<0.0010	0.0851								
v_{21}	<0.0010	<0.0010	0.0222	0.0209							
v_{22}	<0.0010	<0.0010	<0.0010	<0.0010	0.0107						
v_{30}	<0.0010	<0.0010	0.0080	<0.0010	<0.0010	0.0085					
v_{31}	<0.0010	<0.0010	<0.0010	0.0018	<0.0010	<0.0017	0.0024				
v_{40}	<0.0010	<0.0010	0.0324	<0.0010	<0.0010	0.0031	<0.0010	0.8960			
v_{41}	<0.0010	<0.0010	<0.0010	-<0.0012	<0.0010	<0.0010	0.0066	-0.2229	0.1583		
v_{50}	<0.0010	<0.0010	-0.0118	<0.0010	<0.0010	0.0010	<0.0010	0.0273	<0.0010	0.0827	
v_{51}	<0.0010	<0.0010	<0.0010	-0.0059	<0.0010	<0.0010	0.0020	<0.0010	0.0159	0.0061	0.0090

HbA1c trajectory in individuals diagnosed with type 2 diabetes

The input parameters for the initial reduction in HbA1c and long term trend in HbA1c following diagnosis, derived from analysis of the UKPDS outcomes model (2), are reported in Table 61 and Table 105 respectively.

Table 104: Estimated change in HbA1c in first year following diabetes diagnosis

	Distribution	Parameter 1	Parameter 2	Central estimate
Change in HbA1c Intercept	NORMAL	-2.9465	0.0444513	-2.9465
HbA1c at baseline	NORMAL	0.5184	0.4521958	0.5184

Table 105: Estimated change in HbA1c following diabetes diagnosis over long term

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate
Longitudinal HbA1c for diabetes intercept	NORMAL	-0.024	0.017	-0.024

Longitudinal HbA1c for diabetes log(time since diagnosis)	NORMAL	0.144	0.009	0.144
Longitudinal HbA1c for diabetes Second year	NORMAL	-0.333	0.05	-0.333
Longitudinal HbA1c for diabetes lag HbA1c	NORMAL	0.759	0.004	0.759
Longitudinal HbA1c for diabetes HbA1c at diagnosis	NORMAL	0.085	0.004	0.0896

Systolic blood pressure and cholesterol trajectory following treatment

The changes in systolic blood pressure and total cholesterol following treatment with anti-hypertensives or statins and statin uptake are reported in Table 106.

Table 106: Treatment effects following treatment

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate	Source
Simvastatin treatment effects	NORMAL	-1.45	0.11	-1.45	(3)
Anti-hypertensive treatment effect	NORMAL	-8.4	0.638	-8.4	(4)
Statin Uptake	UNIFORM	0.65	(0.4-0.9)	0.65	(5)

Metabolic Risk Factor screening

The distribution for the HbA1c threshold at which opportunistic screening for type 2 Diabetes is initiated even if the individual does not have a history of cardiovascular disease, microvascular disease or identified impaired glucose regulation is reported in Table 107.

Table 107: Threshold for HbA1c opportunistic diagnosis

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate	Source

HbA1c at diagnosis	NORMAL	8.1	0.073	8.1	(6)

Comorbid Outcomes and Mortality

Cardiovascular disease

The parameter distributions for men and women based on the QRISK2 model (7) are reported in Table 108.

Table 108: Input parameters of the QRISK2 risk model

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate
QRISK female ethnicity 2	NORMAL	0.2163	0.0537	0.2163
QRISK female ethnicity 3	NORMAL	0.6905	0.069	0.6905
QRISK female ethnicity 4	NORMAL	0.3423	0.1073	0.3423
QRISK female ethnicity 5	NORMAL	0.0731	0.1071	0.0731
QRISK female ethnicity 6	NORMAL	-0.0989	0.0619	-0.0989
QRISK female ethnicity 7	NORMAL	-0.2352	0.1275	-0.2352
QRISK female ethnicity 8	NORMAL	-0.2956	0.1721	-0.2956
QRISK female ethnicity 9	NORMAL	-0.1010	0.0793	-0.1010
QRISK female smoke 2	NORMAL	0.2033	0.0152	0.2033
QRISK female smoke 3	NORMAL	0.48200	0.0220	0.4820
QRISK female smoke 4	NORMAL	0.6126	0.0178	0.6126
QRISK female smoke 5	NORMAL	0.7481	0.0194	0.7481
QRISK female age 1	NORMAL	5.0373	1.0065	5.0327
QRISK female age 2	NORMAL	-0.0108	0.0022	-0.0108
QRISK female bmi	NORMAL	0.4724	0.0423	0.4724
QRISK female cholesterol	NORMAL	0.6375	0.0143	0.6375
QRISK female sbp	NORMAL	0.0106	0.0045	0.0106
QRISK female townsend	NORMAL	0.060	0.0068	0.060

QRISK female fibrillation	NORMAL	1.3261	0.0310	1.3261
QRISK female RA	NORMAL	0.3626	0.0319	0.3626
QRISK female Renal	NORMAL	0.7636	0.0639	0.7636
QRISK female Hypertension	NORMAL	0.5421	0.0115	0.5421
QRISK female diabetes	NORMAL	0.8940	0.0199	0.8940
QRISK female family history cvd	NORMAL	0.5997	0.0122	0.5997
QRISK female age1 * smoke 1	NORMAL	0.1774	0.0355	0.1774
QRISK female age 1 * smoke 2	NORMAL	-0.3277	0.0655	-0.3277
QRISK age1 * smoke 3	NORMAL	-1.1533	0.2307	-1.1533
QRISK female age 1 * smoke 4	NORMAL	-1.5397	0.3079	-1.5397
QRISK female age 1 * atrial fibrillation	NORMAL	-4.6084	0.922	-4.6084
QRISK female age 1 * renal	NORMAL	-2.6401	0.5280	-2.6401
QRISK female age 1 * hypertension	NORMAL	-2.2480	0.4496	-2.2480
QRISK female age 1 * diabetes	NORMAL	-1.8452	0.3690	-1.8452
QRISK female age 1 * bmi	NORMAL	-3.0851	0.6170	-3.0851
QRISK female age 1 * family history cvd	NORMAL	-0.2481	0.0496	-0.2481
QRISK female age 1 * sbp	NORMAL	-0.0132	0.0026	-0.0132
QRISK female age 1 * town	NORMAL	-0.0369	0.0074	-0.0369
QRISK female age 2 * smoke 1	NORMAL	-0.0053	0..0001	-0.0053
QRISK female age 2 * smoke 2	NORMAL	-0.0005	0.0001	-0.0005
QRISK female age 2 * smoke 3	NORMAL	-0.0105	0.0021	-0.0105
QRISK female age 2 * smoke 4	NORMAL	-0.0155	0.0031	-0.0155
QRISK female age 2 * fibrillation	NORMAL	-0.0507	0.0101	-0.0507
QRISK female age 2 * renal	NORMAL	0.0343	0.0069	0.0343

QRISK female age 2 * hypertension	NORMAL	0.0258	0.0051	0.0258
QRISK female age 2 * diabetes	NORMAL	0.0180	0.0036	0.0180
QRISK female age 2 * bmi	NORMAL	0.0345	0.0069	0.0345
QRISK female age 2 * family history cardiovascular	NORMAL	-0.0062	0.0012	-0.0062
QRISK female age 2 * sbp	NORMAL	-0.000029	0.000006	-0.000029
QRISK female age 2 * townsend	NORMAL	-0.0011	0.0002	-0.0011
QRISK female 1 year survival	CONSTANT	0.9983	NA	NA
QRISK male ethnicity 2	NORMAL	0.3163	0.0425	0.3163
QRISK male ethnicity 3	NORMAL	0.6092	0.0547	0.6092
QRISK male ethnicity 4	NORMAL	0.5958	0.0727	0.5958
QRISK male ethnicity 5	NORMAL	0.1142	0.0845	0.1142
QRISK male ethnicity 6	NORMAL	-0.3489	0.0641	-0.3489
QRISK male ethnicity 7	NORMAL	-0.3604	0.1094	-0.3604
QRISK male ethnicity 8	NORMAL	-0.2666	0.1538	-0.2666
QRISK male ethnicity 9	NORMAL	-0.1208	0.0734	-0.1208
QRISK male SMOKE 2	NORMAL	0.2033	0.0152	0.2033
QRISK male SMOKE 3	NORMAL	0.4820	0.0220	0.4820
QRISK male SMOKE 4	NORMAL	0.6126	0.0178	0.6126
QRISK male SMOKE 5	NORMAL	0.7481	0.0194	0.7481
QRISK male age 1	NORMAL	47.316	9..4630	47.316
QRISK male age 2	NORMAL	-101.236	20.247	-101.236
QRISK male bmi	NORMAL	0.5425	0.0299	0.5425
QRISK male cholesterol	NORMAL	0.14425	0.0022	0.14425
QRISK male sbp	NORMAL	0.0081	0.0046	0.0081
QRISK male townsend	NORMAL	0.0365	0.0048	0.0365

QRISK male fibrillation	NORMAL	0.7547	0.1018	0.7547
QRISK male RA	NORMAL	0.3089	0.0445	0.3089
QRISK male renal	NORMAL	0.7441	0.0702	0.7441
QRISK male hypertension	NORMAL	0.6965	0.011	0.6965
QRISK male age 1 smoke 1	NORMAL	-3.8805	0.7761	-3.8805
QRISK male age 1 smoke 2	NORMAL	-16.703	3.3406	-16.703
QRISK male age 1 smoke 3	NORMAL	-15.3738	3.5291	-15.3738
QRISK male age 1 smoke 4	NORMAL	-17.6453	3.5291	-17.6453
QRISK male age 1 fibrillation	NORMAL	-7.0146	1.4056	-7.0282
QRISK male age 1 renal	NORMAL	-17.015	3.4029	-17.015
QRISK male age 1 hypertension	NORMAL	33.9625	6.7925	33.9625
QRISK male age 1 diabetes	NORMAL	12.7886	2.5577	12.7886
QRISK male age 1 bmi	NORMAL	3.2680	0.6536	3.2680
QRISK male age 1 fxcd	NORMAL	-17.9219	3.5844	-17.9219
QRISK male age 1 sbp	NORMAL	-0.1511	0.030	-0.1511
QRISK male age 1 town	NORMAL	-2.5502	0.5100	-2.5502
QRISK male age 2 SMOKE 1	NORMAL	7.9709	1.5942	7.9709
QRISK male age 2 SMOKE 2	NORMAL	23.6859	4.7372	23.6859
QRISK male age 2 SMOKE 3	NORMAL	23.1371	4.6274	23.1371
QRISK male age 2 SMOKE 4	NORMAL	26.8674	5.3735	26.8674
QRISK male age 2 Fibrillation	NORMAL	14.4518	2.8904	14.4518
QRISK male age 2 renal	NORMAL	28.2702	5.654	28.2702
QRISK male age 2 hypertension	NORMAL	-18.8167	3.7633	-18.8167
QRISK male age 2 diabetes	NORMAL	0.9630	0.1926	0.963
QRISK male age 2 bmi	NORMAL	10.5517	2.1103	10.5517
QRISK male age 2 FXCD	NORMAL	26.6047	5.3209	26.6047
QRISK male age 2 sbp	NORMAL	0.2911	0.0582	0.2911

QRISK male age 2 town	NORMAL	3.007	0.6014	3.007
QRISK2 male 1 year survival	CONSTANT	0.997	NA	NA

The QRISK2 model was modified to allow a linear relationship between HbA1c and the risk of cardiovascular disease for individuals with Impaired Glucose tolerance and type 2 Diabetes (HbA1c>42 mmol/mol). The parameter distributions for these additional inputs are reported in Table 109.

Table 109: Additional parameters for linear relationship between HbA1c and cardiovascular disease

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate	Source
Female RR of MI due to HbA1c in diabetics	LOGNORMAL	0.078	0.030	1.08	(8)
Male RR of MI due to HbA1c in diabetics	LOGNORMAL	0.108	0.023	1.11	(8)
RR of stroke due to HbA1c in diabetics	LOGNORMAL	0.092	0.026	1.096	(8)
Log(RR) of cvd due to IGR	NORMAL	0.223	0.043	1.25	(9)

Congestive Heart Failure

The parameter distributions for congestive heart failure based on the Framingham Heart Study (10) are reported in Table 110.

Table 110: Input parameters for Congestive Heart Failure Risk model for men and women

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate
Male Heart failure baseline hazard	NORMAL	-9.2087	0.9209	-9.2087
Male Heart failure Age	NORMAL	0.0412	0.0278	0.0412
Male Heart failure LVH	NORMAL	0.9026	1.0359	0.9026
Male Heart failure Heart rate	NORMAL	0.0166	0.0174	0.0166

Male Heart failure Systolic blood pressure	NORMAL	0.00804	0.0117	0.00804
Male Heart failure CHD	NORMAL	1.6079	0.5336	1.6079
Male Heart failure Valve disease	NORMAL	0.9714	0.6557	0.9714
Male Heart failure Diabetes	NORMAL	0.2244	0.6682	0.2244
Female Heart failure baseline hazard	NORMAL	-10.7988	1.0799	-10.7988
Female Heart failure Age	NORMAL	0.0503	0.0301	0.0503
Female Heart failure LVH	NORMAL	1.3402	0.8298	1.3402
Female Heart failure Heart rate	NORMAL	0.0105	0.0193	0.0105
Female Heart failure Systolic blood pressure	NORMAL	0.00337	0.0109	0.00337
Female Heart failure CHD	NORMAL	1.5549	0.5973	1.5549
Female Heart failure Valve disease	NORMAL	1.3929	0.6707	1.3929
Female Heart failure Diabetes	NORMAL	1.3857	0.7105	1.3857
Female Heart failure BMI	NORMAL	0.0578	0.0555	0.0578
Female Heart failure Valve disease	NORMAL	-0.986	1.4370	-0.986

Microvascular Complications

The parameter distributions for the risk models for foot ulcer, blindness, renal failure, first amputation and second amputation are reported in Table 111. Parameters for renal failure were based on the UKPDS Outcomes Model 1 (2), whereas parameters for other microvascular complications were based on the UKPDS Outcomes Model 2 (8).

Table 111: Input parameters for microvascular complications

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate
Renal failure baseline hazard	NORMAL	-10.016	0.939	-10.016

Renal failure Weibull shape	NORMAL	1.865	1.4352	1.865
Renal failure systolic blood pressure	NORMAL	0.404	0.106	0.404
Renal failure blindness	NORMAL	2.082	0.551	2.082
Foot ulcer baseline hazard	NORMAL	-11.295	1.13	-11.295
Foot ulcer age at diagnosis	NORMAL	0.043	0.014	0.043
Foot ulcer female	NORMAL	-0.962	0.255	-0.962
Foot ulcer BMI	NORMAL	0.053	0.019	0.053
Foot ulcer HbA1c	NORMAL	0.16	0.056	0.16
Foot ulcer PVD	NORMAL	0.968	0.258	0.968
Amputation baseline hazard	NORMAL	-14.844	1.205	-14.844
Amputation age at diagnosis	NORMAL	0.023	0.011	0.023
Amputation female	NORMAL	-0.445	0.189	-0.445
Amputation atrial fibrillation	NORMAL	1.088	0.398	1.088
Amputation HbA1c	NORMAL	0.248	0.042	0.248
Amputation HDL	NORMAL	-0.059	0.032	-0.059
Amputation heart rate	NORMAL	0.098	0.05	0.098
Amputation MMALB	NORMAL	0.602	0.18	0.602
Amputation peripheral vascular disease	NORMAL	1.01	0.189	1.01
Amputation white blood count	NORMAL	0.04	0.017	0.04
Amputation Stroke	NORMAL	1.299	0.245	1.299
Amputation shape	NORMAL	2.067	0.193	2.067
Amputation with Ulcer lambda	NORMAL	-0.881	0139	-0.881
Amputation with Ulcer age at diagnosis	NORMAL	-0.065	0.027	-0.065
Amputation with Ulcer PVD	NORMAL	1.769	0.449	1.769

Second Amputation baseline hazard	NORMAL	-3.455	0.565	-3.455
Second Amputation HbA1c	NORMAL	0.127	0.06	0.127
Blindness baseline hazard	NORMAL	-10.6774	0.759	-10.6774
Blindness age at diagnosis	NORMAL	0.047	0.009	0.047
Blindness HbA1c	NORMAL	0.171	0.032	0.171
Blindness heart rate	NORMAL	0.08	0.039	0.08
Blindness systolic blood pressure	NORMAL	0.068	0.032	0.068
Blindness white blood cells	NORMAL	0.052	0.019	0.052
Blindness CHF	NORMAL	0.841	0.287	0.841
Blindness IHD	NORMAL	0.61	0.208	0.61

Cancer

The parameter distributions for the incidence and hazard ratios for breast cancer and colorectal cancer are reported in Table 112.

Table 112: Input parameters for breast cancer and colorectal cancer risk models

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate	Source
Colorectal cancer men	NORMAL	0.0011	0.0001	0.0011	(11)
Colorectal cancer women	NORMAL	0.0005	0.0000	0.0005	(11)
Breast cancer pre-menopause	NORMAL	0.0010	0.0001	0.0010	(12)
Breast cancer post-menopause	NORMAL	0.0028	0.0002	0.0028	(12)
Colorectal cancer BMI relative risk for men	LOGNORMAL	0.1906	0.0111	1.21	(13)

Colorectal cancer BMI relative risk for women	LOGNORMAL	0.0392	0.0151	1.04	(13)
Breast cancer BMI relative risk for pre-menopause	LOGNORMAL	-0.1165	0.0251	0.89	(13)
Breast cancer BMI relative risk for post-menopause	LOGNORMAL	0.0862	0.0205	1.09	(13)

The parameter distributions for breast and colorectal cancer mortality are reported in Table 113.

Table 113: Input parameters for breast cancer and colorectal cancer mortality (14)

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate
Breast cancer 5 year survival	BETA	439.69	2354.44	0.157
Colorectal cancer 5 year survival	BETA	1457.56	1806.35	0.447

Osteoarthritis

The parameter distributions for the incidence and hazard ratios for osteoarthritis are reported below.

Table 114: Input parameters for the osteoarthritis risk model (15)

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate
Osteoarthritis incidence	NORMAL	0.0053	0.0000004	0.0053
Osteoarthritis RR of diabetes	LOGNORMAL	0.723	0.317	2.06
Osteoarthritis RR of BMI	LOGNORMAL	0.073	0.026	1.076

Depression

The parameter distributions for the incidence and hazard ratios for depression are reported below.

Table 115: Input parameters for the depression risk model

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate	Source
Odds of depression	BETA	336	8803	0.0397	(16)
Odds ratio for diabetes	LOGNORMAL	0.4187	0.1483	1.52	(16)
Odds ratio for stroke	LOGNORMAL	1.8406	0.5826	6.3	(17)

Mortality

The other cause mortality rates by age were assumed constant in the probabilistic sensitivity analysis (18).

The parameter distribution for the hazard ratio for other cause mortality with diabetes is reported below.

Table 116: Input parameters for mortality hazard ratio for diabetes (19)

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate
Mortality hazard ratio for diabetes	LOGNORMAL	0.588	0.186	1.80

Utilities

The parameter distributions used to estimate health state utilities in the model are reported below.

Table 117: Utility input parameters

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate	Source
Renal/ulcer baseline utility	NORMAL	0.689	0.014	0.689	(20)
Renal dialysis	NORMAL	-0.078	0.026	-0.078	(20)
Foot ulcer	NORMAL	-0.099	0.013	-0.099	(20)
Amputation/heart failure baseline utility	NORMAL	0.807	0.005	0.807	(8)
Heart failure	NORMAL	-0.101	0.032	-0.101	(8)
Amputation	NORMAL	-0.172	0.045	-0.172	(8)

Stable angina multiplicative factor decrement	NORMAL	0.801	0.038	0.801	(5)
Unstable angina multiplicative factor decrement	NORMAL	0.77	0.038	0.77	(5)
MI multiplicative factor decrement	NORMAL	0.76	0.018	0.76	(5)
Stroke multiplicative factor decrement	NORMAL	0.629	0.04	0.629	(5)
Cancer baseline utility	NORMAL	0.8	0.0026	0.8	(21)
Cancer decrement	NORMAL	-0.06	0.008	-0.06	(21)
Osteoarthritis utility	NORMAL	0.69	0.069	0.69	(22)
Depression baseline utility	NORMAL	0.48	0.048	0.48	(23)
Depression remitters	NORMAL	0.31	0.031	0.31	(23)
Depression responders	NORMAL	0.20	0.020	0.20	(23)
Depression non-responders	NORMAL	0.070	0.007	0.070	(23)
Depression drop-outs	NORMAL	0.050	0.005	0.050	(23)
Weight loss utility decrement	NORMAL	-0.0025	0.001	-0.0025	(24;25)
Age utility decrement	NORMAL	-0.004	0.0001	-0.004	(5)

Unit Health Care Costs

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate	Source
Cost of insulin	GAMMA	3.367	408.6	1375.72	(26)
Cost of anti-hypertensives	GAMMA	100	1.96	195.94	(27)
Cost of GP appointment	GAMMA	100	0.47	46.95	(28)

Nurse appointment (Advanced)	GAMMA	100	0.26	25.52	(28)
Health care assistant appointment	GAMMA	100	0.03	3.40	(28)
Eye screening	GAMMA	15.3664	1.58219	24.31	(29)
HbA1c test	GAMMA	100	0.03	3.00	(30)
Lipids test	GAMMA	100	0.01	1.00	(30)
LfT test	GAMMA	100	0.01	1.00	(30)
B12 test	GAMMA	100	0.01	1.00	(30)
Urine test	GAMMA	100	0.01	1.00	(30)
Nicotine replacement therapy	GAMMA	100	1.03	103.00	(28)
HbA1c diagnosis screening	GAMMA	100	0.148147	14.81	(30)
Unstable Angina hospital admission	GAMMA	100	12.75591	1275.59	(3)
Revascularisation in hospital	GAMMA	100	60.36846	6036.85	(3)
MI Hospital admission	GAMMA	100	15.54896	1554.90	(3)
First Outpatient appointment	GAMMA	100	1.653571	165.36	(3)
Subsequent outpatient appointments	GAMMA	100	1.100574	110.06	(3)
Fatal CHD	GAMMA	100	7.125001	712.50	(31)
Fatal Stroke	GAMMA	100	44.42562	4442.56	(32)
First year stroke cost	GAMMA	100	126.77	12,676.60	(33)
Subsequent year stroke cost	GAMMA	100	17.399	1739.91	(33)
Transient Ischemic Attack	GAMMA	100	27.266	2722.65	(33)
Glytrin Spray	CONSTANT	NA	NA	12.61	(3)
Isosorbide mononitrate	CONSTANT	NA	NA	13.54	(3)
Verapamil	CONSTANT	NA	NA	50.57	(3)
Atenolol	CONSTANT	NA	NA	36.42	(3)
Aspirin	CONSTANT	NA	NA	8.01	(3)

Ramipril	CONSTANT	NA	NA	90.45	(3)
ARB	CONSTANT	NA	NA	253.28	(3)
Clopidogrel	CONSTANT	NA	NA	554.41	(3)
Congestive Heart Failure inpatient year 1	GAMMA	17.088	197.61	3376.7	(34)
Congestive Heart Failure non-inpatient year 1	GAMMA	50.135	20.664	1,035.97	(34)
Congestive Heart Failure inpatient subsequent	GAMMA	23.465	66.426	1558.71	(34)
Congestive Heart Failure non-inpatient subsequent	GAMMA	109.8	9.377	1,029.62	(34)
Blindness inpatient year 1	GAMMA	7.98	179.63	1433.85	(34)
Blindness non-inpatient year 1	GAMMA	14.799	127.99	1894.16	(34)
Blindness inpatient subsequent years	GAMMA	41.395	11.58	479.36	(34)
Blindness non-inpatient subsequent years	GAMMA	79.725	9.7955	780.94	(34)
Amputation inpatient year 1	GAMMA	35.733	282.7	1896.28	(34)
Amputation non-inpatient year 1	GAMMA	16.817	169.84	2856.05	(34)
Amputation inpatient subsequent years	GAMMA	23.023	82.364	1792	(34)
Amputation non-inpatient subsequent years	GAMMA	57.062	29.875	1611	(34)
Renal Haemodialysis	GAMMA	100	420.49	42049.00	(35)
Renal Automated Peritoneal dialysis	GAMMA	100	272.1714	27217.14	(35)

Renal Ambulatory peritoneal dialysis	GAMMA	100	197.4225	19742.25	(35)
Renal transplant	GAMMA	100	236.5973	23659.73	(36)
Immunosuppressants	GAMMA	100	69.58745	6958.75	(36)
Foot ulcer not infected	GAMMA	100	1.677526	167.75	(37)
Foot ulcer with cellulitis	GAMMA	100	4.431003	443.10	(37)
Foot ulcer with osteomyelitis	GAMMA	100	8.215817	821.58	(37)
Breast Cancer	GAMMA	100	138.1811	13818.11	(38)
Colorectal cancer Dukes A	GAMMA	100	100.9135	10091.35	(39)
Colorectal cancer Dukes B	GAMMA	100	173.1532	17315.32	(39)
Colorectal cancer Dukes C	GAMMA	100	265.5026	26550.26	(39)
Colorectal cancer Dukes D	GAMMA	100	166.2553	16625.53	(39)
Osteoarthritis	GAMMA	100	9.616886	961.69	(40)
Depression – Practice nurse surgery	GAMMA	100	0.090154	9.02	(41)
Depression – Practice nurse home	GAMMA	100	0.270463	27.05	(41)
Depression – Practice nurse telephone	GAMMA	100	0.090154	9.02	(41)
Depression – Health visitor	GAMMA	100	0.387834	38.78	(41)
Depression – District nurse	GAMMA	100	0.377628	37.76	(41)
Depression – Other nurse	GAMMA	100	0.090154	9.02	(41)
Depression – HCA phlebotomist	GAMMA	100	0.034021	3.40	(41)
Depression – Other primary care	GAMMA	100	0.255154	25.52	(41)
Depression – Out of Hours	GAMMA	100	0.268661	26.87	(41)
Depression – NHS Direct	GAMMA	100	0.25295	25.30	(41)
Depression – Walk-in Centre	GAMMA	100	0.388316	38.83	(41)
Depression – Prescribed medicines	GAMMA	100	0.096144	9.61	(41)

Depression – Secondary Care	GAMMA	100	0.81	81.00	(41)

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