The effect of medium term physical activity interventions on cognitive function and indices of cardiovascular health in overweight and obese adults

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Lessons learnt: don't leave things to the last minute and don't ever give up!

Abstract

The cumulative effect of obesity with a sedentary/low-active lifestyle at mid-life places individuals at elevated risk for obesity-associated comorbidities and accelerated cognitive decline in later life. There is a paucity of research examining the relationship between physical activity (PA) and cognitive function in middle-aged obese adults, further confounded by a lack of objective measurement of PA. Study 1 (n=63) aimed to examine the relationship between objectively measured physical activity with multiple cognitive test outcomes in a sample of low-active, overweight/obese, middle-aged adults. The findings indicated that IQ and age were the greatest predictors of cognitive function, with small contribution from PA and body composition. Increased physical activity and/or cardiorespiratory fitness (CRF) translates to improved cognitive function in non-obese adults, yet this has largely been unexplored in overweight/obese adults. It is not known what aspects of exercise (volume or intensity) yield optimal improvements, or the physiological adaptations that are required to translate to cognitive change. Study 2 (n=28) aimed to compare the impact of 12-weeks high-intensity exercise regimes (interval and continuous) on indices of cardiovascular fitness and cognitive function in middle-aged, overweight/obese females relative to a no-exercise control group. The findings suggest equivalent improvement in CRF between groups, and a favourable effect of training following INT for a limited number of cognitive outcomes (executive function and spatial memory). Study 3 (n=33) aimed to examine the impact of increasing habitual activity through pedometer "step-count" targets over 12-weeks on indices of cardiometabolic health and cognitive function. Findings indicate that post-intervention step count was associated favourably with indices of executive function, verbal and spatial memory. Taken together these studies found a limited number of exercise associated improvements, predominantly in executive function and spatial working memory.

Publications and Presentations

Presentations

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Abbreviations

ADP	air-displacement plethysmography
AIT	aerobic interval training
AVLT	auditory verbal learning test
BDNF	brain-derived neurotrophic factor
BED	binge eating disorder
BMI	body mass index
CBF	cerebral blood flow
CBT	Corsi block tapping task
CP	critical power
CPM	counts per minute
CRF	cardiorespiratory fitness
CV	cardiovascular
CVD	cardiovascular disease
DBP	diastolic blood pressure
HbA1c	glycated haemoglobin
HIIT	high-intensity interval training
HR_{max}	heart rate max
HR_{peak}	heart rate peak
IGF-1	insulin-like growth factor 1
LPA	light-intensity physical activity
LT	lactate threshold
LTPA	leisure time physical activity

MCI	mild cognitive impairment
METs	metabolic equivalents
MICT	moderate intensity continuous training
MINS	minutes
MPA	moderate- intensity physical activity
MRI	magnetic resonance imaging
MVPA	moderate-vigorous intensity physical activity
NAA	N-acetylaspartate
NIRS	near-infrared spectroscopy
PA	physical activity
PCA	principal component analysis
PHR	peak heart rate
PPO	peak power output
RAVLT	Rey's auditory verbal learning test
RI	ramp incremental
RPE	ratings of perceived exertion
SB	sedentary behaviour
SBP	systolic blood pressure
SE	step exercise
SIT	sprint interval training
SOP	standard operating procedure
T2DM	type 2 diabetes mellitus
TLX	task load index
TMT	trail making test
ToH	Tower of Hanoi
VAS	visual analogue scales
VEGF	vascular endothelial growth factor
$\dot{\mathbf{V}}\mathbf{O_2}$	pulmonary oxygen uptake

VPA	vigorous-intensity physical activity
VSLT	visual spatial learning test
VVLT	visual verbal learning test
WC	waist circumference
WHR	waist-hip ratio
WML	white matter lesions
WR_{peak}	work rate peak

Chapter 1:
Literature Review

Chapter 1 Literature Review

1.1 Obesity and cognitive function

The physical consequences of obesity have been well documented indicating increased risk of mortality and morbidity, including (but not limited too) cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, metabolic syndrome and sleep apnoea (Eckel, Kahn, Robertson, & Rizza, 2006; Poirier et al., 2006). In addition to somatic comorbidities, the relationship between obesity and cognitive function is an area of investigation that has grown over the past two decades. It is known that mid-life obesity is a significant risk factor for Alzheimer's disease and vascular dementia in later life (Rosengren, Skoog, Gustafson, & Wilhelmsen, 2005; Whitmer, Gunderson, Barrett-Connor, Quesenberry Jr, & Yaffe, 2005; Xu et al., 2011) and this risk is reported to be independent of comorbidities (Anstey, Cherbuin, Budge, & Young, 2011; Beydoun, Beydoun, & Wang, 2008; Whitmer et al., 2008). The increasing prevalence of obesity at mid-life and an ageing population contribute significantly to increasing prevalence rates (Loef & Walach, 2013). The number of people in the United Kingdom in 2015 estimated to be living with dementia is 850,000 (Prince et al., 2014). Therefore, it is of great importance to examine strategies to preserve or improve cognitive function in a population with elevated risk of impairment. It is known that obesity at mid-life is associated with an accelerated trajectory of cognitive aging, however, research examining the impact of mid-life obesity on mid-life cognitive function is in its infancy.

1.1.1 Defining Obesity

Obesity is characterized by excessive fat accumulation in adipose tissues, the diagnostic criteria for which is when body fat exceeds 35% in women and 25% in men according to the WHO. The gold standard for measuring fat mass and fat-free mass are two variants of the same technique, underwater weighing and air-displacement plethysmography (ADP) (Fields et al., 2002). Both machine-based methods are based on the principle of body density, with water displacement and air displacement as the criterion underlying the underwater weighing and ADP techniques, respectively. Underwater weighing estimates body fat by measuring the volume of

water displaced by the body and the difference in the weight of the body both in water and in normal environment. This estimates body density based on the principle that fat floats in water (or other less dense liquids). ADP uses air displacement to estimate fat mass and fat free mass. Underwater submersion a key requisite for underwater weighing, ADP precludes the inconvenience associated with underwater submersion however both techniques require special (and costly) apparatus. Both methods are accurate but are largely unfeasible for clinical practice and research, and therefore mainly used as a gold standard to which other methods are validated against. Other machine-based techniques use computed tomography (CT), MRI and dual energy X-ray absorptiometry (DEXA) to provide reliable measurements of fat mass. Due to the high cost of these methods they are not routinely applied in research settings and clinical practice. The most widely applied methods include anthropometric measures such as skinfold thickness, waist circumference and WHR or machine based measures such as body impedance analysis (BIA) and near infrared reactance. Body mass index (BMI) >30kg/m^2 is predominantly used as a surrogate marker of obesity, and BMI >40kg/m^2 signalling morbid obesity (Pasco et al., 2014). BMI is a ratio of weight for height and does not take into account body composition, so therefore is not accurate at indicating adiposity (Pasco et al., 2014). BMI typically overestimates obesity prevalence in those with muscular builds (Romero-Corral et al., 2008) and underestimates in those with low lean tissue but excess fat (Romero-Corral et al., 2008).

A report published by The Health and Social Care Information Centre (HSCIC) on 3rd March 2015 indicated that current UK rates on obesity are 26% men and 24% women. Additionally, 41% men and 33% of women are overweight (HSCIC, 2015). Obesity is associated with most major cardiovascular (CV) risk factors, such as plasma lipids, blood pressure, glucose, inflammation, and places additional stress on the heart by unfavourably affecting structure and systolic and diastolic ventricular function (Lung & Institute, 2014; Peeters et al., 2003; Worre-Jensen, Jensen, Heitmann, & Sørensen, 2007). It is a complex condition with multiple causal factors and is associated with many chronic diseases such as cardiovascular diseases (CVDs), stroke, hypertension, T2 DM (Karandish & Shirani, 2015; Lung & Institute, 2014). Furthermore, obesity is also associated with psychosocial issues, such as body esteem and self esteem (Witherspoon, Latta, Wang, & Black, 2013). Of particular concern is the rise in prevalence of severe, or morbid obesity in adults and children (Ells et al., 2015; Lung & Institute, 2014).

1.1.1.1 Obesity paradoxes

The relationship between obesity and health is complicated, and several obesity paradoxes have been identified (McAuley & Blair, 2011). **"Pre-obesity**" is the paradox where being overweight is protective in normal populations, despite "overweight" implying increased risk for health. This was supported by a meta-analysis of 97 studies including 2.88 million individuals examined all-cause mortality for overweight and obesity relative to normal weight (Flegal, Kit, Orpana, & Graubard, 2013). Optimal survival occurred in the overweight BMI category (25-30 kg/m^2), who had a 6% lower mortality rate than normal BMI 25 - 30 kg/m^2). Furthermore, although this did not reach significance, Class 1 obesity (30 - 35kg/m^2) had a 5% lower mortality rate than the normal BMI category. This provided empirical evidence that being overweight was associated with reduced mortality risk when compared to normal weight counterparts in a very large sample. "**Fat but fit**" refers to the paradox where obesity is not a risk factor for mortality in physically fit individuals. It appears that low CRF and inactivity are a greater health threat than obesity (McAuley & Blair, 2011). In a number of studies, once cardiorespiratory fitness has been taken into account, the relationship between obesity and mortality risk is attenuated (Lavie, McAuley, Church, Milani, & Blair, 2014; McAuley & Blair, 2011). Available data indicates that obese individuals who are fit do not have higher risk for CVD and all-cause-mortality when compared to their normal weight and fit counterparts. Another interesting finding that potentially underpins this thesis is that "fat but fit" individuals have substantially lower mortality risk than normal-weight but unfit individuals (McAuley & Blair, 2011). In an earlier study by the same author of 13,155 men with hypertension, McAuley et al., (2009) found that obese, hypertensive men who were fit had no increased CVD or all-cause mortality risk compared with the group of fit, normal-weight men.

This indicates that efforts to increase fitness independent of weight loss may be a more relevant public health agenda, especially given the poor success rates of weight loss maintenance (Jeffrey, Drewnowski, & Epstein et al., 2000). One interesting point is that the likelihood of having high fitness is greatly decreased with increasing BMI. Evidence for this was found by Duncan (2010) who analysed submaximal exercise test data in 4675 adults aged 20–49 years from NHANES (1999–2002). The findings indicated that for normal weight, overweight and obese adults, the percentage of adults in each category that were high in fitness was 30%, 17% and 9%, respectively. "**Healthy obesity**" describes the fact that a sizeable population of obese adults have normal cardiometabolic risk profiles. Healthy obesity is indicated by the absence of

six risk factors (hypertension, insulin resistance, high triglycerides, impaired fasting glucose/diabetes, low HDL, and high C-reactive protein (McAuley & Blair, 2011). There is dispute as to whether metabolically healthy obesity (MHO) is maintainable over time (Bell, Kivimaki, & Hamer, 2014). However, it has been posited that CRF may influence the prognosis of MHO (Ortega et al., 2012).

Although several obesity paradoxes are evident, recent evidence indicates these typically do not apply to morbid obesity (Class III, BMI > 40 kg/m^2) (Lavie et al., 2014). Prognosis for morbidly obese patients is adversely affected for CHD and heart failure (Das et al., 2011; Nagarajan et al., 2013). This level of severe obesity is a major risk factor when considering the development CV diseases and poor prognosis. Efforts to treat and prevent morbid obesity are urgently required (Lavie et al., 2014).

The topic “obesity and cognitive function” fails to acknowledge the complexity of what obesity means for different individuals. When disseminating research findings or public health messages the term ‘obesity’ is often used as one category, yet it is widely known obese individuals are not all the same in terms of amount of excess fat, location of excess fat and most importantly of all, impact on health and/or psychosocial status. This research described in this section collectively shows that relationship between obesity and health is complex. In some individuals obesity does translate to poorer health, however this is not the case for all. In both obese and normal weight counterparts low cardiorespiratory fitness is predictive of mortality. Furthermore, there is increasing evidence to suggest that physically fit obese individuals do not have elevated CVD risk or mortality. This may have theoretical relevance for the relationship between obesity and cognitive function.

1.1.2 Defining cognitive function

Cognitive function is a global term that describes the processing, integration, storage and retrieval of information (Smith, Hay, Campbell, & Trollor, 2011). Cognitive processes may be categorised under distinct domains including attention, executive function, spatial and verbal learning and memory, working memory and psychomotor performance. These cognitive abilities may be assessed through performance on domain specific cognitive function tests. Objective data collected from cognitive function tests can be used to assess baseline performance to compare to normative data for specific populations. Serial testing may also be utilised to track or monitor cognitive change, either indicative of age-related decline, disease progression or

alternatively, a response to an intervention. One major issue for serial testing is that data for normative change is lacking (Attix et al., 2009). Further complicating the assessment of clinical and meaningful change is the influence of sample characteristics such as demographic parameters, motivation, and health, as well as factors such as practice effects, regression to the mean and measurement error (Cysique et al., 2011; Salthouse, 2012). It is known that certain sample characteristics, namely health related outcomes, predispose individuals to an accelerated rate of cognitive decline. However, no single neurological abnormality has been identified that accounts for age-related cognitive decline, meaning functional decrements are the product of an interaction between multiple causative factors (Ash & Rapp, 2014).

Cognitive function has been examined with regard to various health outcomes or psychosocial influences. However, irrespective of the suggested predictor variable under investigation, one issue that is uniformly observed across all areas of research is that there are a huge number of cognitive tests that can be administered for each cognitive domain. Evidence of this is shown in Table 1.1, from a meta-analysis conducted by Smith et al., (2010) of just 29 studies examining cognitive function and exercise.

Table 1.1 Classification of cognitive tests by domain from a meta-analysis of 29 studies taken from Smith et al. (2010).

Neurocognitive Domain			
Attention	Executive Function	Working Memory	Memory
Accuracy Index	Attentional Flexibility	Digit Span	ADAS Word List Recall
Complex/Choice RT	Categorical Fluency (Animal Naming)	N-Back Spatial Task	Auditory Verbal Learning Test
d2 Test of Attention	Cattell's Matrices	N-Back Task	Benton Visual Retention Test
Digit Matching RTe	Cognitive Flexibility	Self-Ordered Pointing	CERAD delayed recall
Digit Symbol Substitution Test	Covert Orienting of Attention Task	Visual Memory span	RAVLT
Mental Speed	Go-No-Go Test	WAIS Letter Number Sequencing	RAVLT Delay
Paced Auditory Serial Attention Test (PASAT)	Mental Control		RAVLT, Temporal Order
Picture Arrangement	Nonverbal Fluency Test		RBMT faces
Premotor Time	Number Copying Speed		RBMT pictures
Response Compatibility RT	RIPA Organization		RIPA Auditory Processing
Ruff 2 and 7 Test (Letters)	RIPA Problem Solving		RIPA Immediate Memory
Simple RT	RIPA Abstract Reasoning		RIPA Recent Memory
Single/Choice Time Sharing	Ruff 2 and 7 Test (Digits)		Sternberg Memory Search Task, Y-intercept
Spatial Attention Task	Selective Reminding Intrusions		Sternberg Memory Search Task, Slope
Speed of Movement	Set Shifting Ability		Visual and Verbal Memory Test
Stopping Task RT	Stopping Task		Visual Reproduction, Immediate
Stroop Color	Stroop Color/Word or Interference		Visual Reproductions
Stroop Word	Trail Making Test Part B		VLMT Delayed Recall
Task Switching RT	Useful Field of View		VLMT Direct Recall
Trail Making Test Part A	Verbal Fluency Test (FAS)		VLMT Recognition
Visuospatial Cognitive Performance Test	WAIS Similarities		WMS Facial Recognition
Word Copying Speed	Wisconsin Card Sorting Task		WMS Figural Memory, Immediate
			WMS Figural Memory, Delayed
			WMS Logical Memory, Immediate
			WMS Logical Memory, Delayed
			WMS Verbal Paired Associates
			WMS Visual Reproduction

ADAS = Alzheimer's Disease Assessment Scale; RT = reaction time; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; RAVLT = Rey Auditory Verbal Learning Task; WAIS = Wechsler Adult Intelligence Scale; PASAT = Paced Auditory Serial Attention Test; RBMT = Rivermead Behavioral Memory Test; RIPA = Ross Information Processing Test; VLMT = Verbal Learning and Memory Test; WMS = Wechsler Memory Scale.

1.1.2.1 Domains of cognitive function

The term “executive function” is frequently cited as an umbrella term for a wide range of cognitive processes that are largely linked to the prefrontal cortex (Miyake & Friedman, 2012; Podell et al., 2012). Distinct executive functions have been identified and include verbal reasoning, problem-solving, planning and organisation, sequencing, the ability to sustain attention, working memory, resistance to interference, impulse control, multitasking, cognitive flexibility and utilisation of feedback (Anderson, Jacobs, & Anderson, 2011; Elliott, 2003; Toplak, West, & Stanovich, 2013). However, the most commonly assessed facets deemed to be indicative of executive function are shifting, inhibition and updating (Miyake & Friedman, 2012; Podell et al., 2012). Despite the identification of multiple distinct executive functions, the assessment of such functions is marred by the “task impurity problem” as most measures of executive function require a non-executive component to perform the task (Miyake & Friedman, 2012).

Verbal memory refers to the acquisition, retention and recall of verbal information (Tulving & Thomson, 1973). Typically, episodic verbal memory is assessed through list-learning over multiple trials, followed by delayed recall approximately 30 minutes later (Delis, Kramer, Kaplan, & Ober, 1987; Rey, 1958). This method helps to distinguish between measures of acquisition and retention, with acquisition corresponding to the total number of words recalled across trials and retention corresponding to the number of words recalled in the delayed trial or during a recognition task (Genon et al., 2013). Verbal learning is assessed through the increase in words recalled across the initial trials. Impairments in the encoding of contextual information and consolidation of new verbal material drive deficits in episodic memory performance (Silva et al., 2012), a cognitive construct that has been identified as highly predictive of future cognitive decline (Blacker et al., 2007) and Alzheimer’s Disease (Genon et al., 2013).

Spatial memory is a process which allows a person to remember locations and also the relationships between objects in a space, either in 2D or 3D format, and is essential for forming and retrieving memories of events (Suthana, Ekstrom, Moshirvaziri, Knowlton, & Bookheimer, 2011). Most neuropsychological studies on spatial memory function use object-location memory tasks (Kessels, Nys, Brands, van den Berg, & Van Zandvoort, 2006). Such tasks typically involve the presentation

of a number of objects in a spatial layout (either on a computer screen or on a board), with the task being to remember the locations and demonstrate this by relocating the objects to their original position from the presentation phase (Kessels et al., 2006). The right hippocampus and bilateral posterior parahippocampal gyrus are cited as the structures supporting object location and the processing of spatial scenes (Burgess, Maguire, & O'Keefe, 2002; Erickson, Miller, Weinstein, Akl, & Banducci, 2012a; Heo et al., 2010). Impairments in spatial memory are often the first symptoms following damage to the medial temporal lobes caused by pathologies such as Alzheimer's Disease (Burgess et al., 2002). Superior spatial memory performance in older adults was positively correlated with hippocampal blood flow in a study conducted by Heo et al. (2010), although it is known that hippocampal blood flow decreases with age.

1.1.3 Obesity and cognitive function in mid-life

Two recent systematic research reviews (Fitzpatrick, Gilbert, & Serpell, 2013; Prickett, Brennan, & Stolwyk, 2015) have concluded that although there is evidence of impaired cognitive function in obese younger adults (aged 18-65 years), there is not enough evidence to support the view that these are independent of obesity-related comorbidities or other variables (education, mood, CVD risk and age). Therefore, the research undertaken in this thesis examined the role of indices of cardiovascular health as potential mechanisms mediating the relationship between obesity and cognitive deficits. Irrespective of whether the contribution is independent or potentiated by comorbidity, impairments are evident in obese samples when compared to healthy weight counterparts. All of the research presented in this thesis was undertaken in adults below the age of 65 years.

1.1.3.1 Executive Function

Concept formation and set-shifting.

The Wisconsin Card Sorting Test (WCST) was used to examine concept formation and set-shifting in four studies. Three studies found decrements in performance in obese samples relative to comparison groups (Fagundo et al., 2012; Lokken, Boeka, Yellumahanthi, Wesley, & Clements, 2010). However, none of these studies controlled for cardiovascular risk, although they did control for age and education. The fourth study did not find any significant decrements in performance in obese but matched for cardiovascular factors and depression, in addition to age and education (Ariza et al., 2012).

Decision making and delay discounting

Performance on the Delay Discounting Task (delay of gratification) and Iowa Gambling task were significantly better in a normal weight group when compared to an obese group and an obese group with binge eating disorder (BED) (Davis, Patte, Curtis, & Reid, 2010). However, in this study the normal weight group had substantially higher education, and the addition of this variable rendered all differences non-significant. Two studies showed significantly worse performance on the Iowa Gambling task, even after controlling for education (Fagundo et al., 2012; Pignatti et al., 2006). No significant differences were found between obese women and normal weight women, using a delay discounting task (Nederkoorn, Smulders, Havermans, Roefs, & Jansen, 2006)

Inhibition

Performance on the Stroop colour-word interference task indicated no difference in interference between an obese and a comparison group (Ariza et al., 2012), however Fagundo et al. (2012) reported that obese had significantly higher Stroop interference compared to healthy controls. The stop signal task also did not detect any difference between obese and healthy weight individuals (Nederkoorn et al., 2006).

1.1.3.2 Working memory

Working memory has been shown to be similarly impaired in overweight and obese young adults (24.9 ± 4.5), relative to healthy weight counterparts (Coppin, Nolan-Poupart, Jones-Gotman, & Small, 2014). This was observed through a greater number of total errors and over-estimation errors on the conditioned cue preference test. In these cases, age and education were matched between groups and did not account for the findings.

Although no significant differences in accuracy and reaction time for performance on a verbal n-back task were observed between obese, overweight and healthy weight groups, the obese demonstrated lower task-related activation in the right parietal cortex (Gonzales et al., 2010). Conversely, performance for a one-back visual memory task (reaction time and accuracy) was shown to be poorer in obese subjects when compared to healthy weight individuals (Stingl et al., 2012). In this case, a negative correlation between BMI and neuronal activity was observed in the occipital area. This was interpreted by the authors as evidence of greater effort during encoding, although as this was correlated with reduced performance these

compensatory mechanisms were unsuccessful. When compared to lean individuals, structural MRI studies have shown lower gray matter density in the medial frontal gyrus of the prefrontal cortex in obese individuals (Pannacciulli et al., 2006). This region is involved in inhibition of inappropriate responses and control of goal-directed behaviour. Additionally, decreased basal metabolism in the prefrontal cortex was associated with increasing BMI and poorer inhibitory control processing (Volkow et al., 2009).

1.1.3.3 Psychomotor performance and speed

In middle aged adults (32-62 years), information processing speed (as measured by WAIS Digit–Symbol Substitution Test (DSST), showed a significant negative relationship with BMI (Cournot et al., 2006). This remained significant after adjustment for age, sex, educational level, diabetes, systolic blood pressure, and perceived health score. However, no differences in processing speed, as measured by a similar test, were found between obese and non-obese adults (Ariza et al., 2012).

1.1.3.4 Complex attention

Selective attention, on a subtest of the Sternberg test, was observed to be significantly poorer in obese individuals (Cournot et al., 2006) when comparing those in the highest quartiles of BMI. Additionally, attentional switching measured by performance on the Trail Making Test (TMT), was shown to be significantly poorer in obese (Fergenbaum et al., 2009) who demonstrated a fourfold increased risk for lowered executive function relative to healthy weight individuals. However, no significant differences were found in TMT performance between obese and healthy weight individuals in three other studies (Ariza et al., 2012; Boeka & Lokken, 2008; Gonzales et al., 2010).

1.1.3.5 Memory

Verbal memory

Two studies reported that verbal memory test performance (immediate learning and delayed recall) was significantly poorer in obese relative to non-obese individuals (Cournot et al., 2006; Gunstad, Paul, Cohen, Tate, & Gordon, 2006). However, Boeka and Lokken (2008) reported that verbal memory (California Verbal Learning Test-II) was not significantly different to normative data in a group of morbidly obese adults

seeking bariatric surgery. Gonzales et al. (2010) also reported no significant difference in verbal memory between normal, overweight and obese groups.

1.1.4 Is the relationship between obesity and cognitive function explained by CVD risk factors?

Obesity is associated with many comorbidities known to adversely impact cognitive function such as T2DM, hypertension, hypercholesterolaemia, and insulin resistance, especially when these are found to co-occur in individuals. (Yaffe et al., 2014). Further complicating the issue is that sub-clinical or pre-disease states including metabolic disturbances (insulin resistance, raised serum lipids, and cholesterol) or vascular function (elevated blood pressure) are cerebrovascular risk factors (Morra, Zade, McGlinchey, & Milberg, 2013). Furthermore, evidence from MRI studies indicates that asymptomatic cerebrovascular brain injury is common, often starting in midlife due to uncontrolled CVD risk factors (DeCarli (2013). Asymptomatic brain infarction, white matter hyperintensities and accelerated brain atrophy accumulate undiagnosed leading to late-life impairment.

The negative association of obesity with cognitive function appears to be potentiated by high blood pressure. Waldstein and Katzel (2006) examined the interactive relationship between indices of obesity (waist circumference and BMI), blood pressure (systolic and diastolic) and cognitive function. Poorest performance in psychomotor skill and response inhibition, as measured by the grooved pegboard and Stroop Colour-Word tasks respectively, was observed in those with higher waist circumference and high blood pressure. The cumulative effects of obesity and hypertension with respect to cognitive deficit were also demonstrated by (Elias, Elias, Sullivan, Wolf, & D'agostino, 2003). Poorest performance in logical memory (immediate and delayed recall) and visual reproduction was observed in those with both obesity and hypertension, compared to those with just one risk factor (either obesity or hypertension).

It is also apparent that interactions between clusters of risk factors may exert conjoint effects upon cerebrovascular health and cognitive function. Cardiovascular risk factors such as diabetes, hypertension and high cholesterol levels, all predispose an individual to cognitive decline through distinct pathways and also by potentiating each other (Imtiaz, Tolppanen, Kivipelto, & Soininen, 2014). The interaction between T2DM

and a subclinical marker of cardiovascular disease, coronary artery calcified plaque (CAC), was reported by Hugenschmidt et al. (2013). Initially T2DM status was associated with poorer performance on DSST, RAVLT, and phonemic fluency, however inclusion of CAC attenuated this relationship and was an important predictor of cognitive performance. This highlights the contribution of subclinical cardiovascular disease to cognitive dysfunction in diabetes, as opposed to diabetes status alone. Given that risk of cognitive decline is highest in individuals managing multiple comorbid conditions, there is a call for the early treatment of hypertension and cardiovascular risk before an individual presents with symptoms. As many cardiovascular risk factors are modifiable, this highlights the opportunity for intervention before comorbidities become clinically apparent (DeCarli, 2013; Hugenschmidt et al., 2013). It has been suggested that it may be more appropriate to focus on interventions that target overall risk, as opposed to reducing individual risk factors (Dregan, Stewart, & Gulliford, 2012). Interventions which drive mechanistic changes upon multiple aspects of cardiovascular health would therefore be most effective.

It is difficult to quantify the contribution of the individual cardiovascular risk factors associated with cognitive function as there may be interaction between risk factors, and this also may be modulated by age (Van Den Berg, Kloppenborg, Kessels, Kappelle, & Biessels, 2009). However, it seems that multiple risk factors at mid-life increase the risk of cognitive decline and dementia in later life (Dregan et al., 2012; Reijmer et al., 2012; Xu et al., 2011). T2DM and hypertension are more robustly associated with decrements in cognitive function although obesity and dyslipidemia are also associated with mild to moderate decrements (Van Den Berg et al., 2009). Interestingly, in a sample of middle-aged women (n=1,448) followed over 34 years it was found that obesity and low leisure time physical activity (LTPA) were only risk factors for dementia when combined with each other (Mehlig et al., 2014). This is despite both being identified as strong risk factors for T2DM in combination and individually. Conversely, optimal cardiovascular health, as measured in accordance with the American Heart Association, was examined alongside cognitive function from young adulthood (18 – 30 years) to midlife (Reis et al., 2013). Overall better cardiovascular health, comprising of seven metrics including avoidance of overweight or obesity, a healthy diet, non-smoking, physical activity, total cholesterol, blood pressure, and fasting glucose within healthy levels, was positively associated with improved DSST performance, reduction in Stroop interference and increased recall of RAVLT in midlife at a 25-year follow-up.

1.1.5 Interim summary

It is apparent from the extant literature that there is not adequate control for CVD risk factors when examining the relationship between obesity and cognitive function. This may in part explain the inconsistent findings. There is currently not enough valid evidence to support an independent contribution of adiposity to cognitive function outcomes. It is known, however, that low CRF is unfavourably associated with multiple CV risk factors irrespective of body size. There is evidence to suggest that improving CRF in obese individuals may off-set the risk of cognitive dysfunction that is associated with mid-life obesity and sedentary behaviour.

1.2 Exercise and cognitive function

A wealth of research provides substantial evidence that exercise and physical activity (PA) have a beneficial impact on cognitive function (section 1.2.2). Irrespective of the plausible mechanisms suggested to mediate this, the relationship is not well understood. Consistency between studies is lacking in the cognitive domains (and tests administered) shown to be responsive to exercise or PA. It is also not possible to ascertain whether particular aspects of exercise (intensity, duration, mode) confer greatest benefit to domain specific cognitive functions and whether this differs between samples with compromised health.

1.2.1 Defining exercise and physical activity

Physical activity can be defined as any voluntary body movement generated by the contraction of skeletal muscles resulting in energy expenditure (Caspersen, Powell, & Christenson, 1985). Light physical activities are distinct from exercise and typically involve sitting, standing and walking or domestic tasks such as light housework (Ainsworth et al., 2000). Exercise is a subset of physical activity that is structured, planned and repetitive, with the aim of improving or maintaining fitness (Caspersen et al., 1985). Understanding these concepts is imperative when attempting to interpret the impact of either physical activity or exercise upon measures of cognitive function. Effects may well be dependent upon intensity, pattern or volume.

1.2.1.1 Intensity

Physical activity can be categorised according to estimated energy expenditure in metabolic equivalents (METs), with light PA (LPA; <3METs), moderate PA (MPA; 3-5.99 METs) and vigorous PA (VPA; >6METs) (Crouter, DellaValle, Haas, Frongillo, & Bassett, 2013). Individuals may be classified in terms of physical activity levels by daily number of steps, according to guidelines set down by Tudor-Locke and Bassett Jr (2004). Step-count determined categories are as follows; sedentary <5000 steps/d, low active 5000 to 7499 steps/d, somewhat active 7500 to 9999, active ≥10,000 to 12,499, and highly active 12,500 steps/d. Due to the use of objective measures of PA, such as accelerometers, PA categories also correspond to counts per minute (CPM) cut-points: sedentary (<99 CPM), LPA (100-1952 CPM), MPA (1952-5999 CPM) and VPA (>6000 CPM) (Freedson, Melanson, & Sirard, 1998). To define these,

cut-points of counts per minute correspond to categories of PA intensity based on calibration studies (Augustin, Mattocks, Cooper, Ness, & Faraway, 2012).

Intensity domains are used to categorise exercise based on the physiological response and metabolic stress induced, and these are moderate, heavy, very heavy and severe (Rossiter, 2011). **Moderate-intensity** exercise corresponds to work-rates below the lactate threshold (LT), whereby blood lactate increases above resting value (~ 1 mM) but does not substantially rise any further and steady state oxygen uptake ($\dot{V}O_2$) is attained within approximately 2 – 3 minutes (Turner et al., 2006; Whipp, Ward, & Rossiter, 2005; Wilkerson, Koppo, Barstow, & Jones, 2004). **Heavy-intensity** exercise corresponds to work-rates that induce a mild but stable increase of blood lactate (between 2–4mM) and $\dot{V}O_2$ steady state is established but delayed, typically by ~15-20 minutes (Katch, Weltman, Sady, & Freedson, 1978; Rossiter, 2011; Wilkerson et al., 2004). This exercise is perceived to be less comfortable than moderate-intensity exercise (Parfitt, Rose, & Burgess, 2006). Exercise in the heavy domain lies between LT and critical power (CP), which is the upper limit for steady state exercise (Rossiter, 2011). **Very heavy-intensity** comprises of exercise above critical power, where both blood lactate (5-10 mM) and $\dot{V}O_2$ fail to reach steady state and increase to the limit of tolerance (Rossiter, 2011; Turner et al., 2006). Exercise in the **severe-intensity** domain is associated with substantial and progressively increasing blood lactate and $\dot{V}O_2$ will continue to rise until exercise is terminated or $\dot{V}O_2$ is reached (Turner et al., 2006; Wilkerson et al., 2004). This supramaximal exercise can only be tolerated for very short periods of time, and exhaustion is reached before $\dot{V}O_2$ max can be attained (Turner et al., 2006; Wilkerson et al., 2004).

1.2.1.2 Interval exercise

Interval (INT) exercise is a mode of exercise, comprising of repeated and relatively short bouts of high-intensity workloads interspersed with periods of rest or low-intensity active recovery (Billat, 2001). The rationale behind INT is that it allows for individuals to spend more time exercising at a higher intensity than would be possible if performed in one continuous session (Tschakert & Hofmann, 2013). It is exercising at the higher intensity that translates to superior adaptive responses and training effects, such as cardiorespiratory fitness or vascular function (Ramos, Dalleck, Tjonna, Beetham, & Coombes, 2015; Weston, Wisløff, & Coombes, 2014). It is evident from the extant literature that the terminology to describe INT regimes is not consistent. Tschakert and Hofmann (2013) reported a large number of

denominations: “intermittent exercise, interval-type exercise, interval training, high-intensity interval training, aerobic high-intensity interval training, repeated-sprint exercise, sprint intervals, and low-volume high-intensity interval training” (p. 601). A prominent research group in this area have used the term ‘aerobic interval training (AIT)’ (Molmen-Hansen et al., 2012; Tjønna et al., 2008; Wisløff et al., 2007), whereas, other prominent groups have described ‘sprint interval training (SIT)’ to describe all-out supramaximal intervals (Burgomaster et al., 2008; Gibala et al., 2006). A recent review has suggested that to standardise the terminology a classification scheme should be adhered to for interval training based on intensity (Weston et al., 2014). AIT is to be removed from the dialogue, and INT falls into two categories as indicated in Figure 1.1:

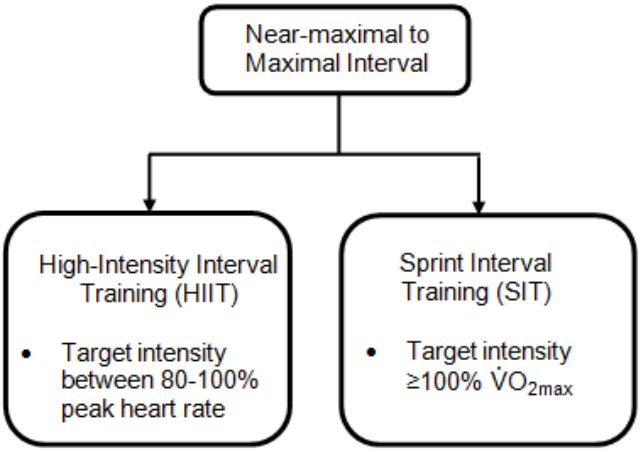

Figure 1.1 Suggested classification scheme for interval training adapted from (Weston et al., 2014)

Furthermore, the HIIT prescription differs between studies in terms of the durations and target intensities of the interval bouts. Additionally, the ratio between the interval bouts and recovery periods is termed the duty cycle. All of these may be manipulated to alter the metabolic demand induced by the exercise. The most widely used HIIT prescription is the four intervals of 4 minutes (4 x 4 HIIT) interspersed with ~3 minutes of active recovery (Moholdt et al., 2009; Molmen-Hansen et al., 2012; Rognmo, Hetland, Helgerud, Hoff, & Slørdahl, 2004; Schjerve et al., 2008; Tjønna et al., 2008; Wisløff et al., 2007). The target intensity of the interval bouts was guided by heart rate (HR) max or peak, and ranged between 85%-95% $HR_{max/peak}$ and active recovery bouts were at a work rate corresponding to 50-70% $HR_{max/peak.}$ Alternatively, protocols using short-interval duration HIIT comprise of 1-minute interval bouts interspersed with 1-minute recovery bouts. Under this 10 x 1 HIIT prescription, exercise intensity

of the interval bouts was set as 89-100% peak power output (PPO) (Currie, Dubberley, McKelvie, & MacDonald, 2013; Klonizakis et al., 2014; Little, Jung, Wright, Wright, & Manders, 2014). Alternatively, intensity was determined using $\dot{V}O_2$ in a protocol using 1-minute interval bouts at 80% $\dot{V}O_{2peak}$ interspersed with 4-minute recovery bouts at 50% $\dot{V}O_{2peak}$ (Mitranun, Deerochanawong, Tanaka, & Suksom, 2014). Another short-interval duration HIIT prescription examined manipulation of the duty cycles, whilst controlling for exercise volume, and the impact of metabolic stress on arterial stiffness (Rakobowchuk, Harris, Taylor, Cubbon, & Birch, 2013). For both conditions, interval bouts were at a work rate (WR) corresponding to 120% $\dot{V}O_{2peak}$ interspersed with active recovery at 20 Watts. However, 30s:60s (work:recovery) duty cycles were undertaken by those in the HIIT condition, whereas the moderate-intensity interval training group performed duty cycles of 10s:20s.

1.2.2 Exercise and cognitive function in mid-life

Controlled trials in younger adult populations are rare and have yielded heterogeneous findings. A review conducted on the impact of exercise interventions on memory in adults (aged 18-65 years) concluded that long-term exercise has small but negligible effects on memory (Roig, Nordbrandt, Geertsen, & Nielsen, 2013). The following studies are in adults samples aged 18-65 years, however this research was not conducted in obese samples.

Improved visual-spatial memory was observed in a running group (n=14) relative to no-exercise controls (n=14) following a six-week intervention in young adults (mean age 19.7 years) (Stroth, Hille, Spitzer, & Reinhardt, 2009). However, although verbal memory and attention were assessed, no significant changes were observed. Conversely, Pereira et al. (2007) demonstrated improvements in short-term verbal memory (Rey Auditory Verbal Learning Test; RAVLT) following 12 weeks of aerobic exercise in 8 young adults (mean age 33 years). Improvement on RAVLT performance was associated with increased cerebral blood flow in the dentate gyrus of the hippocampus. Conflicting findings regarding verbal memory may be attributed to differing exercise regimes. The protocol by Stroth et al. (2009) comprised of three 30-minute running sessions per week over a 6-week intervention and exercise intensity was at 70-100% lactate threshold. The protocol by Pereira et al. (2007) comprised of four 60-minute sessions per week for 12 weeks. Sessions included 40

minute of ‘aerobic activity’ plus warm-up and cool-down. The aerobic activity, selected by the participant, ranged from cycling on a stationary ergometer, running on a treadmill, climbing on a StairMaster, or using an elliptical trainer.

In sedentary middle-aged adults (n=68; mean age 48 years) Hötting et al. (2012a) examined the impact of 6-month intervention on cognitive function and cardiovascular fitness. The study compared a cycling group (endurance training) to a stretching group and a no-exercise control. The cycling protocol comprised of two 60-minute sessions per week at 85% lactate threshold. Relative to controls and stretching group, significant improvements in immediate and delayed verbal recall were observed in the cycling group. However, improvement in attention was significantly greater in the stretching group compared to the cycling group.

A further two studies have reported improvement in memory after training regimes in young adults, however in both cases they failed to account for the acute effect of exercise on cognitive function. Griffin et al. (2011) reported improved hippocampal learning (performance on face-name task) following 5 weeks of exercise training on a stationary cycle (3 sessions per week at 60% VO_{2max}). This occurred alongside increased brain-derived neurotrophic factor (BDNF) response during exercise, obtained from venous samples. Alternatively, four weeks of exercise sessions (4 session/week of 30-minutes jogging or brisk walk) were shown to improve performance on a memory task (novel object recognition) in a sample of young adults (20.6 ± 0.4 years) (Hopkins, Davis, VanTieghem, Whalen, & Bucci, 2012). However, this effect was only observed in the participants who exercised less than 24 hours before the cognitive assessment. The effects of acute exercise are widely reported and known to have greater effect sizes on memory, when compared to long-term interventions (Roig et al., 2013). The acute effects of exercise on cognitive function are known to last up to up to 48 hours from the end of exercise therefore, any studies conducting post-intervention tests within this time frame are measuring acute response as opposed to long-term change.

1.2.3 Interval exercise and cognitive function in mid-life obesity

To date, only one study has investigated the impact of a high-intensity-interval-training (HIIT) intervention on cognitive function in obese adults (Drigny et al., 2014).

Six men (mean age 49 years, mean body fat percentage 31%) underwent assessment for cognitive function, aerobic capacity, cerebral oxygenation, central haemodynamic and cardiometabolic parameters before and after a 4-month intervention. The programme comprised of 2 HIIT sessions per week on an ergocycle, plus an additional 60-minute session of moderate intensity continuous exercise (60% peak power output) and two 20-minute resistance training sessions. This therefore was not a 'pure' assessment of interval exercise. HIIT sessions designed by Drigny et al. (2014) comprised of 10-minute sets made up of repeated 15-30s bouts at 80% maximal aerobic power interspersed with 15-30s passive recovery. Participants performed 2-3 10-minute sets within a session (34-48 minutes) complying with a Borg rating of perceived exertion (RPE) of 15. The sets were also separated by 4-minute recovery bouts. Significant improvements were observed in short-term memory (Forward Digit Span score increase of ~1 point), attention and processing speed (Digit Symbol Substitution Test score increase of ~6.2 points) and verbal memory (RAVLT scores: total List A1-15 score increased by 9 words; delayed recall increase of 3.5 words). Cerebral oxygen extraction significantly improved post-training during both exercise and recovery.

In addition to (Drigny et al., 2014), only one study has examined the impact of exercise on cognitive function in obese middle-aged adults. However, the type of exercise cannot be categorised clearly in terms of work-rate profile (i.e. interval or continuous) as it was based on dance/rhythmic activities. Monleón et al. (2015) examined the effect of an 8-month physical activity intervention on cardiopulmonary fitness, body mass index (BMI), and vigilance performance in 29 obese adults (mean age 48.5 years; mean BMI 38.5). The training consisted of two 60-minute sessions of supervised dance/rhythmic activities per week, with an intensity target of 12-13 on the Borg rating of perceived exertion scale (moderate intensity activity). Following the intervention, performance on a psychomotor vigilance task had improved as indicated by faster responses and fewer lapses (missed responses) relative to baseline. This coincided with a small reduction in BMI (mean reduction ~1kg/m^2), and significant improvement in cardiopulmonary fitness (as indicated by greater distance covered in 6-minute walk test).

Monleón et al. (2015) examined the impact of 8 months PA (based on dance and rhythmic activity) on a psychomotor vigilance task in obese adults (mean age 48.5 years; mean BMI 38.5). Improved performance was observed following the intervention, in addition to increased cardiopulmonary fitness and reduced BMI. Drigny et al. (2014) examined the impact of 4 months of high-intensity interval training (HIIT) on multiple tests of cognitive function in 6 obese men (mean age 49 years, mean body fat percentage 31%). Significant improvements were observed in short-term memory (Forward Digit Span), attention and processing speed (Digit Symbol Substitution Test) and immediate and delayed verbal memory (RAVLT). Cerebral oxygen extraction, as measured by near-infrared spectroscopy (NIRS) significantly improved post-training during both exercise and recovery.

1.2.4 Habitual physical activity and cognitive function

Much of the research investigating the relationship between PA and cognitive function has been conducted in older adults. Self- report of PA is typically used as a variable to predict risk of decline or presence/occurrence of dementia/impairment. One caveat which should be noted is that interpretation of the extant literature is hampered by the differing definitions of PA employed and the lack of objective measurement that characterise research to date. However, this research suggests that PA potentially contributes to the differential preservation of cognitive function that is observed between ageing adults (Bielak, Cherbuin, Bunce, & Anstey, 2014).

Cross-sectional research in younger adults suggests low levels of “free-living” PA are associated with increased risk of poor performance on fluid intelligence (Singh-Manoux, Hillsdon, Brunner, & Marmot, 2005) and response inhibition (Hillman et al., 2006). However, PA was assessed through self-report questionnaire which is subject to bias and provides no detailed or accurate information on the intensity or volume of exercise/PA undertaken. Singh-Manoux et al. (2005) reported that adults (35-55 years) reporting low levels of PA had increased risk of poor performance on a measure of fluid intelligence, as measured by Alice Heim 4-I test, and this was after adjustment for education, employment grade, self-rated health, blood pressure level, cholesterol level, smoking status, mental health status, and social network index score. Initially low PA was associated with risk for poor performance on measures of memory, phonemic fluency and semantic fluency, however adjustment for education and socioeconomic position greatly attenuated these relationships. PA was derived

from self-report, and categories were as follows: “Low active”: <2 hours/week of moderate activity and <1 hour of vigorous; “high active”: >2.5 hours/week of moderate or >1 hour of vigorous activity. “Medium active” was classed for anyone falling between high and low active. Additionally (Hillman et al., 2006), reported low physical activity was associated with slower reaction times on the congruent and incongruent conditions of the Erikson Flanker Task in a young cohort (25.5 ± 4.9 years), although accuracy was not significantly different to those with higher activity level. During a task switching performance in young adults (21.4 ± 0.3 years), a physically active group showed more efficient executive functioning relative to a sedentary group (Kamijo & Takeda, 2010). Event-related brain potential (ERP) was measured (P3 amplitude) through electroencephalograms (EEGs), and results indicated P3 ERP amplitude was larger for the sedentary group during a test that placed greater demand on working memory, indicating a greater amount of attentional resources were required relative to the active group.

1.2.5 Objectively measured physical activity and cognitive function in obesity

There is limited research exploring objectively measured PA and cognitive function in obese, and/or middle-aged adults. The following studies were conducted in pre-bariatric (morbidly obese, including some with comorbidities) adults, across a range of ages (20-80 years). The relationship between cognitive function and objectively measured PA was assessed in 71 pre-bariatric surgery patients using a biaxial accelerometer (SenseWear Pro_2 armband) (Langenberg et al., 2015). The parameters of physical activity were: composite physical activity score based on frequency, intensity and duration of PA periods; mean steps·min^{-1}; step frequency; percent of PA within wear time; and active energy expenditure per minute. Performance on tests of executive function (computerised Iowa Gambling Task, IGT), working memory (computerised Corsi Block Tapping Test, CBT) and verbal memory (Auditory Verbal learning Test, AVLT) were not significantly associated with any measures of PA, when age, BMI, somatic comorbidity and depressive symptoms were controlled for. When interactions were explored, depression score (measured using the Patient Health Questionnaire-Depression Scale) significantly impacted the relationship between PA and working memory. Of the participants with low depression scores, those with low PA had worse performance on CBT than those with high PA. Participants with high depression scores showed poor performance on CBT regardless of high or low PA. This perhaps highlights that PA has limited capacity to

help in samples that have additional burden from comorbidity and psychological factors. The meagre support for an association between PA and cognitive function in a severely obese sample was also observed by Galioto et al. (2014). Self-reported PA was collated in 85 bariatric patients, and objectively measured PA was also collected in a subset (n=31) of these patients. Self-report of weekly PA was weakly correlated with poorer attention and executive function. Self-reported PA (daily minutes) and objectively measured daily minutes of MVPA were negatively correlated with memory. With respect to the number of domains tested, higher minutes of PA were not associated with better cognitive function. This sample were classed as sedentary and light active (steps/day was ~7949; MVPA ~105 min/week). The pre-bariatric samples participating in both studies showed a similar activity pattern as more than half were classed as sedentary or low active (Galioto et al., 2014; Langenberg et al., 2015). It was suggested by the authors of the two separate studies that the low volume of moderate and vigorous PA possibly explained the lack of association between PA and cognitive function, as participants were not attaining a level of PA sufficient to drive cognitive benefit. It could also be that the lack of variance in PA in these studies reduced the potential to detect a relationship between PA and cognitive function.

1.2.5.1 Objectively measured PA and cognitive function in older adults

The use of objective measures, such as accelerometers, when examining the relationship between PA and cognitive function is predominantly restricted to elderly populations. This research indicates that higher accumulated minutes of LPA and MVPA were both associated with improved executive function (inhibition; TMT) (Kerr et al., 2013). Additionally, accumulated minutes of MPA showed favourable associations with increased hippocampal volume and, indirectly with memory (Makizako et al., 2014), and lower accumulated MPA and LPA associated with severe white matter lesions (WML) and brain atrophy (Doi et al., 2015). The limited research in older adults indicates that LPA and MVPA are associated with cognitive function (memory and executive function). Vigorous-intensity PA per se was not reported but was combined with moderate-intensity to form MVPA (Doi et al., 2015; Makizako et al., 2014). It must be noted that vigorous activity is not common in older adults, which may also explain the lack of relationship between accelerometer measured vigorous activity and cognitive outcomes in ageing samples.

1.2.6 How does exercise impact cognitive function?

The benefits of exercise for the brain are becoming increasingly evident but remain poorly understood. This is largely due to the fact that changes within the brain in response to exercise are difficult to measure in humans. Many processes have to be inferred (such as angiogenesis by MRI, or peripheral sampling of BDNF). Regular exercise directly impacts the brain through increased neurogenesis, angiogenesis, metabolism and cerebrovascular function, all of which support synaptic plasticity (Cotman, Berchtold, & Christie, 2007; Voss, Vivar, Kramer, & van Praag, 2013). This ultimately translates to improved cerebral perfusion and metabolism (Colcombe et al., 2006). Review of the cellular/molecular processes through which exercise promotes structural and functional changes within the brain is beyond the scope of this thesis. However, a brief overview is included as the evidence indicates that parameters of exercise may be manipulated to optimise cerebrovascular adaptation (Lucas, Cotter, Brassard, & Bailey, 2015).

1.2.6.1 Exercise and structural brain changes

Figure 1.2, taken from Lucas et al. (2015), highlights the potential mechanisms through which exercise translates to adaptations within the brain. It is thought that the mechanical shear stress resulting from the change in blood flow, and neural activation required to generate movement promote a cascade of cellular processes that promote structural changes (Bolduc, Thorin-Trescases, & Thorin, 2013; Lucas et al., 2015). It is known from studies using transcranial Doppler and MRI techniques that cerebral blood flow increases during exercise up to approximately 70% $\dot{V}O_{2max}$ (Subudhi, Lorenz, Fulco, & Roach, 2008). Exercise requires activation in specific brain areas and this leads to increases in localised cerebral blood flow coupled with metabolic demand. It has been proposed (Bolduc et al., 2013) that shear stress-dependent eNOS activity increases during exercise, due to the increase in cerebral blood flow and neuronal activity. Nitric oxide bioavailability is posited to maintain cerebrovascular function. Additionally, the elevated neuronal activity that is required to drive bodily movement increases metabolic demand, and perfusion increases to meet this demand (Bélanger, Allaman, & Magistretti, 2011). Exercise also activates the expression of key factors that mediate neurogenesis such as brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), insulin-like growth factor 1 (IGF-1) (Cotman et al., 2007; Voss et al., 2013)

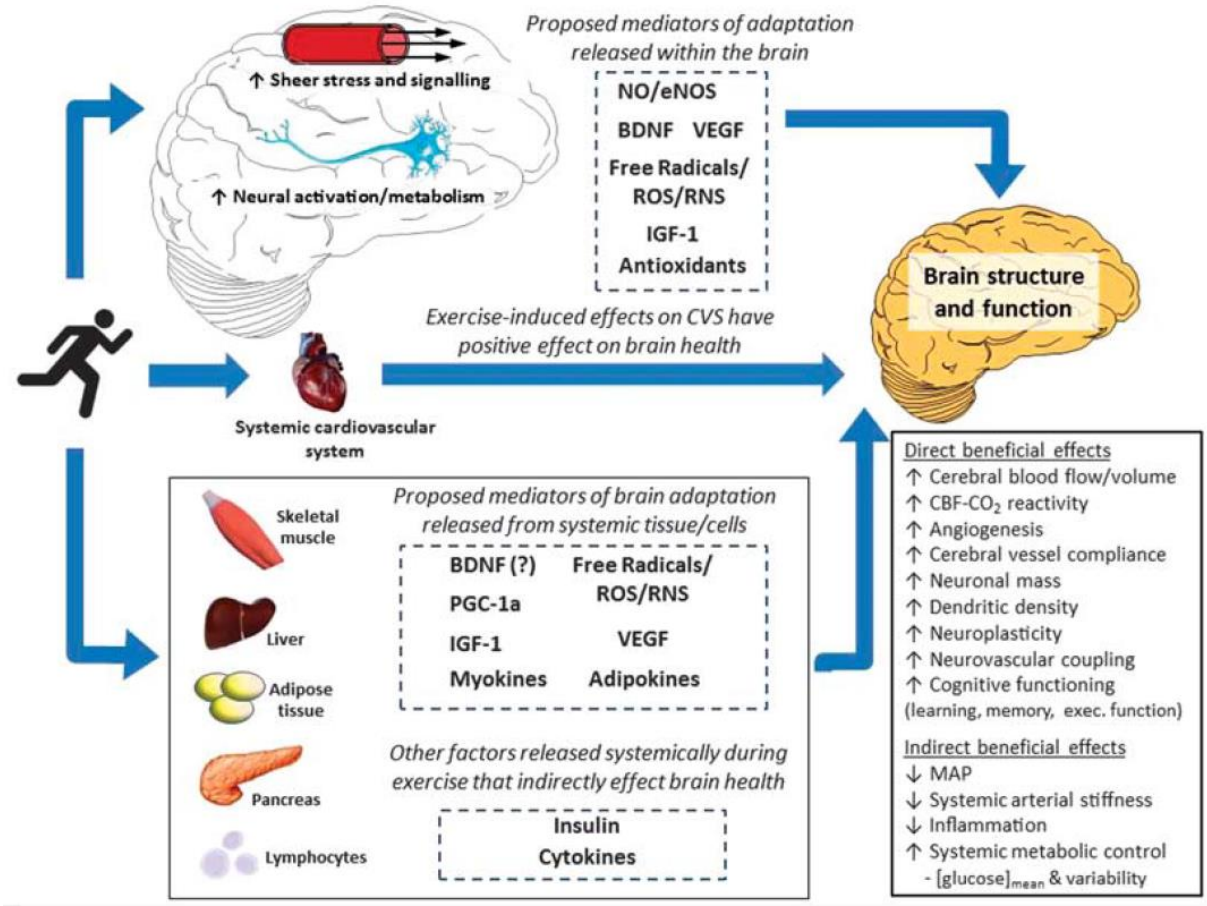

Figure 1.2 Schematic of the mechanisms driven by exercise that are proposed to alter brain structure and function from Lucas et al. (2015)

1.2.6.2 Exercise-related structural change and cognition

Exercise-induced structural brain changes have been associated with improvements in cognitive function. Research conducted in older adults has established an association between cardiovascular fitness and higher brain volume in areas such as the superior frontal cortex volume, hippocampus and medial temporal lobe (Bugg & Head, 2011; Erickson et al., 2009; Erickson et al., 2011). Following 12 months of cardiovascular exercise, anterior hippocampal volume increased by 2%, and interestingly, this was correlated with the increase in BDNF (Erickson et al., 2011). Improved performance on a spatial memory task was directly associated with the increase in hippocampal volume, but not the change in cardiorespiratory fitness or

BDNF levels. Following a 6-month intervention, increase in physical activity correlated with increase in RAVLT score (Ruscheweyh et al., 2011). Higher physical activity levels positively correlated with increased gray matter volume in prefrontal and cingulate regions, and also with changes in BDNF. The neurophysiological adaptations that occurred in response to exercise drove cognitive function changes, indicating the importance of exercise to maintain the structures supporting memory (Roig et al., 2013).

Cerebral blood volume (CBV) in the dentate gyrus, a sub-region of the hippocampus, was shown to increase following 12-weeks of aerobic exercise training in adults (mean aged 21-45 years) (Pereira et al., 2007). This translated to improved performance on recall of Trial 1 of the RAVLT, but not other outcomes such as delayed recall or recognition. Performance on trial 1 correlated with the increase in CBV and VO_{2max}. Cerebral vasculature is not the only explanation for fitness related structural changes and improved cognition. Higher aerobic fitness was associated with higher levels of N-acetylaspartate (NAA), a metabolite found in cell bodies of neurons, which was associated with superior working memory span, but not short term attention or spatial memory (Brugniaux, Marley, Hodson, New, & Bailey, 2014; Erickson et al., 2012b).

1.2.6.3 Reduction of systemic factors

As indicated in Figure 1.3, exercise favourably impacts on multiple systemic cardiovascular risk factors implicated in cognitive decline. The figure elegantly highlights the large number of plausible mechanistic pathways through which exercise may impact upon brain structure and function.

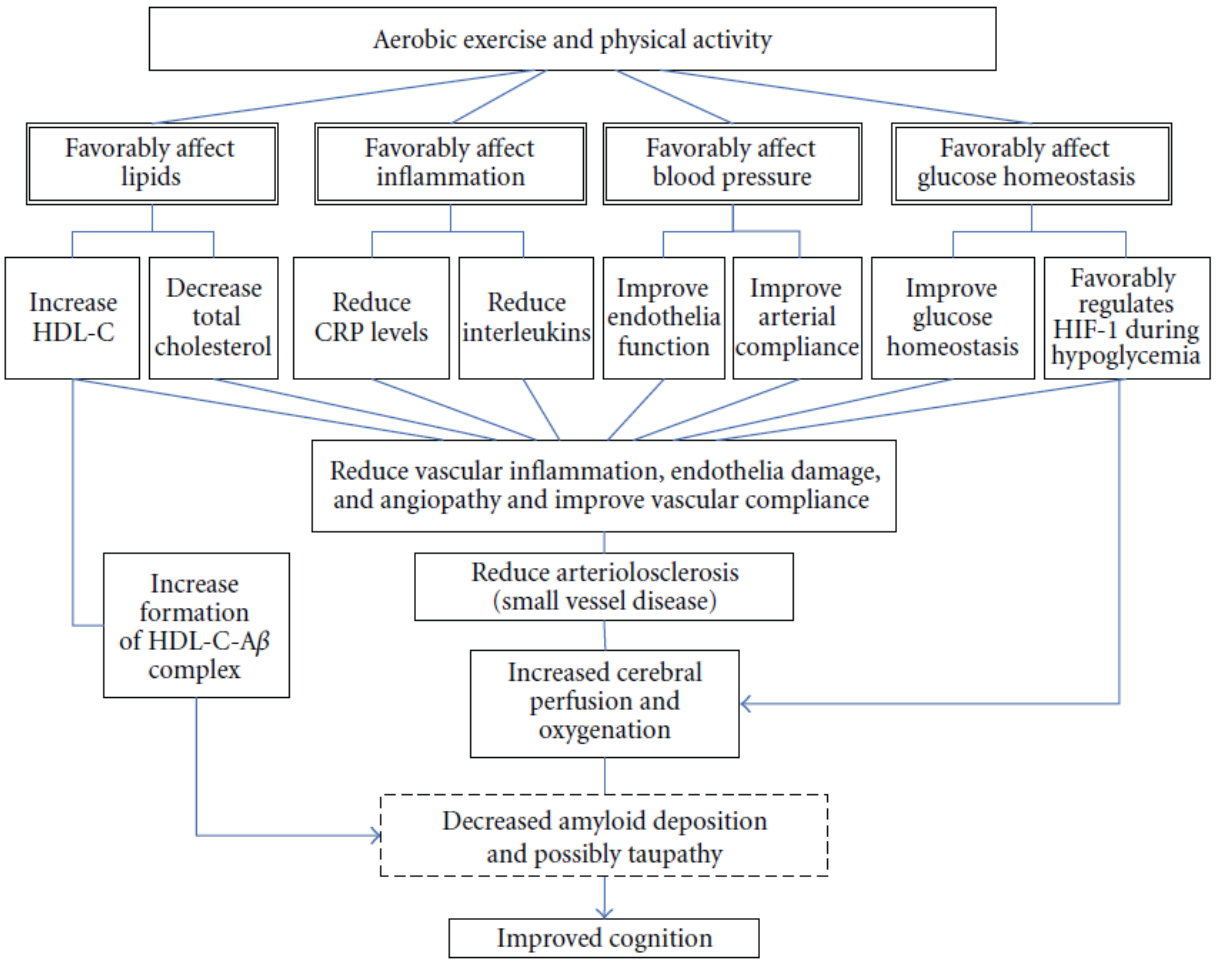

Figure 1.3 Schematic of the mechanisms through which exercise and physical activity favourably impact cognitive function by reducing systemic cardiovascular risk factors from (Obisesan et al., 2012)

Evidence of this relationship is provided by studies that have reported that cognitive change was related to improvement in systemic risk factors following exercise intervention. In women with mild cognitive impairment (aged 55-85 years) improved performance in the Trail Making Test (part B) and Stroop colour/word task were associated with increased fitness following 6-months high intensity (75-85% HRR) aerobic exercise (Baker et al., 2010). This coincided with reduced fasting plasma levels of insulin, increased glucose disposal during a metabolic clamp and reduced cortisol levels.

1.2.7 Manipulation of exercise to target systemic factors

The physiological adaptation to training, and consequent reduction in systemic cardiovascular risk factors, has shown to be responsive to differing exercise intensities, volumes or modalities. It is not known how exercise impacts cognitive function, or how the various aspects/modes of PA can be manipulated to influence cognitive function. In order to harness the benefits of exercise on cognitive function effectively, we need to establish the role of each exercise parameter (intensity, frequency, duration, mode) on the underlying mechanisms supporting brain health and subsequent cognitive performance.

1.2.7.1 Cardiorespiratory fitness

$\dot{V}O_{2max}$ strongly predicts mortality in patients with and without cardiovascular disease, and was a stronger predictor of increased risk of death than was hypertension, smoking, diabetes or other exercise test measures such as ST-segment depression, the peak heart rate, or the development of arrhythmias during exercise (Myers et al., 2002). Additionally, the risk of death doubled for those with an exercise capacity less than 5 MET (17.5 ml/kg/min) compared to those whose capacity was over 8 MET (28 ml/kg/min). Every 1 MET (3.5 ml/kg/min) increase in exercise capacity was associated with a 12% improvement in survival. Kaminsky et al. (2013) have also reported a 10-25% improvement in survival rate for every 1 MET (3.5 ml/kg/min) increase in exercise capacity. A systematic review of studies conducted in those with life-style induced cardiometabolic disease has reported that the gains in cardiorespiratory fitness (CRF) following HIIT (19.4% increase) are nearly double that induced by MICT(10.3%) (Weston et al., 2014). The baseline values for $\dot{V}O_{2max}$ were similar for both conditions among studies (HIIT: 22.5 ml/kg/min; MICT: 22.6 ml/kg/min). Cardiorespiratory fitness is shown to be more responsive to HIIT than MICT, with five studies showing superior improvement following an HIIT regime (Mitranun et al., 2014; Molmen-Hansen et al., 2012; Schjerve et al., 2008; Tjønna et al., 2008; Wisløff et al., 2007).

1.2.7.2 Exercise and Glycaemic control in T2 DM

Traditionally, high intensity exercise has not been recommended for individuals with T2DM (Albright et al., 2000), favouring instead low-moderate intensity (50% $\dot{V}O_2$) over a higher volume (~3-5 days/week, session duration 30-60 mins). The reasoning behind this was to promote self-efficacy and adherence, and to reduce fear of

hypoglycaemia or physical discomfort. High-intensity exercise results in substantial muscle glycogen depletion, which elevates risk of post-exercise hypoglycaemia (Colberg et al., 2010). However, it is known that high-intensity exercise improves glycaemic control to a greater extent than low-intensity (Boulé, Kenny, Haddad, Wells, & Sigal, 2003) and even moderate-intensity exercise (Terada et al., 2013). However, high-intensity exercise (in a continuous fashion) cannot be sustained for long periods due to a reduced tolerance for exercise caused by low $\dot{V}O_{2max}$ and muscle fibre composition abnormalities (increased number of type IIb muscle fibres, low percentage of type I fibres, and a low capillary density) (Albright et al., 2000). The evidence suggests that high-intensity interval training (HIIT) induces superior improvements in glycaemic control relative to moderate-intensity continuous training (MICT). Terada et al. (2013) examined predictors of the heterogeneous glycaemic responses to training, which are often observed, and found that the greatest reduction in capillary blood glucose was in HIIT group relative to MICT, and in those with higher baseline capillary blood glucose. Additionally, session duration also predicted greater reduction in blood glucose. MICT protocol comprised of 40% oxygen consumption reserve ($\dot{V}O_R$) and HIIT sessions comprised 1-minute bouts at 100% $\dot{V}O_R$ interspersed with 3 min recovery bouts at 20% $\dot{V}O_R$. Additionally, Karstoft et al. (2014) reported glycaemic control only improved following an interval walking training (IWT) regime, but did not in the continual walking training (CWT) comparison group. Groups were matched on energy expenditure, training volume and mean training intensity, suggesting it is the spikes and/or variation in exercise intensity that drives favourable metabolic outcome (Karstoft et al., 2014; Mitranun et al., 2014). It has been observed that those with highest baseline values of capillary glucose showed the greatest reduction post-exercise (Terada et al., 2013).

1.2.7.3 Vascular function

Flow mediated dilation was shown to improve to a greater extent following HIIT relative to MICT (Molmen-Hansen et al., 2012; Schjerve et al., 2008; Tjønna et al., 2008; Wisløff et al., 2007). These studies are from the same research group using the 4 x 4 HIIT protocol described in section 1.2.1.2. Wisløff et al. (2007) reported no change in SBP or DBP following both HIIT and MICT. SBP was shown to significantly decrease following HIIT, but not MICT (Mitranun et al., 2014; Molmen-Hansen et al., 2012), and no change was observed in DBP. Reductions in both SBP and DBP were reported following HIIT and MICT (Tjønna et al., 2008).

1.2.7.4 Body fat

It seems that body weight (and body fat) are more responsive to MPA or LPA over a higher volume, when compared to HIIT (Pattyn, Coeckelberghs, Buys, Cornelissen, & Vanhees, 2014). Greater exercise volume is recommended for fat loss (Vanhees et al., 2012), with no additional benefit from higher intensity exercise. Waist circumference and body weight were reduced by 4.5cm and 5-6% respectively in participants undertaking 150 minutes/week of LPA over a 24-week intervention (Ross, Hudson, Stotz, & Lam, 2015). Participants who performed the same amount of exercise, but at a higher intensity, did not show any further reductions. Lower exercise intensity and longer duration activate fat metabolism to provide energy for movement, whereas carbohydrates are used at higher intensities (Hansen, Dendale, van Loon, & Meeusen, 2010)

1.2.7.5 Enjoyment/quality of life

HIIT was reported to be more enjoyable than MICT, based on informal comments by participants (Tjønna et al., 2008), with the variation of the interval protocols deemed as motivating whereas the continual exercise was described as boring. Also, superior improvements in participant quality of life were reported following AIT relative to MICT (Fu et al., 2013; Molmen-Hansen et al., 2012; Wisløff et al., 2007) as measured by Short-Form 36-item Health Survey and MacNew global score.

1.2.8 Work-matched interval and continuous exercise: health

There are multiple studies suggesting HIIT confers superior benefits for health, when compared to moderate-intensity continuous exercise (Chapter 1, 1.2.7). In terms of comparing work-matched HIIT and CON training regimes upon indices of health, only one intervention study was found. This study examined the effect on INT and on glycaemic control and endothelium-dependent vasodilatation in 43 participants with type 2 diabetes (Mitranun et al., 2014). The training regimes were matched for exercise session duration and energy expenditure. The protocol comprised of three 30- or 40-minute sessions (CON and INT respectively) per week for 12 weeks. The intervention increased training intensity over 12 weeks for both groups, with the CON group exercising at 65% $\dot{V}O_{2peak}$ for sessions. The INT sessions comprised of repeated 1–minute bouts at 85% VO_2 peak interspersed with 4-minute recovery at 60% VO_2 peak. Relative to a sedentary control, both INT and CON improved glycaemic control, aerobic fitness, and endothelium-dependent vasodilation.

However, the magnitude of improvement was greater in INT for these measures. An additional benefit was observed in INT only for blood markers (HbA1c, erythrocyte malondialdehyde, serum von Willebrand factor, plasma glutathione peroxidase and nitric oxide). This suggests that when matched for total work, undertaking exercise in intervals of higher intensity provides superficial benefits for health related indices. Additionally, and of relevance to exercise adherence, obese women (with and without diabetes) perceived interval training to be easier when compared to continuous exercise (Coquart et al., 2008). Whilst the continuous and interval exercise sessions were matched for relative workload (100% power at ventilatory threshold) and session duration (32-minutes), ratings of perceived exertion (RPE) were significantly lower for the INT sessions.

1.2.9 Habitual PA and systemic risk factors

Accelerometer-measured indicators of PA volume have shown association with BMI categories in a large U.S sample (n=3,522), with steps per day, daily minutes of moderate and vigorous activity decreasing as BMI category increased from healthy weight to obese (Tudor-Locke, Brashear, Johnson, & Katzmarzyk, 2010). These findings were supported in a Norwegian sample (Hansen, Holme, Anderssen, & Kolle, 2013), with daily minutes of overall PA, moderate and vigorous intensity activity being lower in the overweight/obese BMI categories than in those with a healthy weight. A linear decrease in BMI and the probability of being overweight was observed as daily MVPA increased from 0 to 40-50 minutes in the International Physical activity and the Environment Network (IPEN) adult study (n=5712) (Van Dyck et al., 2014). This study found no associations between sedentary time and weight status after controlling for MVPA. In a highly sedentary and abdominally-obese sample, daily sedentary time, light-intensity time and mean activity were associated with waist-circumference and clustered metabolic risk score, independent of MVPA (Healy et al., 2008b). Waist circumference was predicted by sedentary time when controlling for MVPA, but the reciprocal relationship was not significant (MVPA controlling for sedentary time). This indicates that sedentary time had more influence on waist circumference than MVPA in this abdominally obese sample. Daily time spent in sedentary, light-activity and MVPA were 57%, 39%, and 4% respectively.

In a sample (n=878) of obese adults with high risk of T2DM, sedentary time was a greater predictor of poor health than MVPA (Henson et al., 2013). Sedentary time

was negatively associated with 2-hour plasma glucose and metabolic markers (triacylglycerol and HDL-cholesterol), whereas MVPA and total physical activity were associated with adiposity but not with cardiometabolic markers. It must be noted that of the accelerometer (Actigraph GT3X) wear time, 71% was spent sedentary, 24.3% was spent in light activity and only 3.9% of time was spent in MVPA. It may be possible that the sedentary nature of the sample accounted for the lack of relationship between MVPA (3.9% of wear time) and cardiometabolic variables. These findings are in contrast to those of Ekelund, Griffin, and Wareham (2007) who found clustered metabolic risk factor in an obese sample (n=258) was predicted by total time spent in MVPA, but not time spent sedentary, time spent at light-intensity activity or aerobic fitness. Additionally, total accumulated MVPA predicted variance in clustered metabolic risk, whereas MVPA accumulated in bouts (5- or 10-minute bouts) failed to reach significance. This research highlights that it is important to consider how PA is fractionated (i.e. in bouts or non-bouts) and the issues of entering PA summaries concomitantly into a statistical model.

Both MVPA bout minutes (>10 min) and MVPA non-bout minutes (<10 min) have been independently associated with BMI and waist circumference (Strath, Holleman, Richardson, Ronis, & Swartz, 2008). However, the strength of the relationship between lower BMI and MVPA bout minutes was 4-fold that of MVPA non-bout minutes. The strength of the relationship between lower WC and MVPA bout minutes was 3-fold that of MVPA non-bout minutes. The authors highlighted that MVPA accumulated in bouts were at a higher intensity (average 2,370 counts·min^{-1}) compared to non-bout MVPA minutes (average 1,472 counts·min^{-1}). In an overweight/obese T2DM sample, waist circumference and BMI were positively associated with prolonged sedentary time (>30 minutes) and negatively with light-intensity activity (Healy, Winkler, Brakenridge, Reeves, & Eakin, 2015). An equal (beneficial) impact on BMI was observed when prolonged sedentary time was displaced with either non-prolonged sedentary time or light activity. This indicates that merely breaking up prolonged sedentary time, with increasing number of sedentary breaks, is an effective intervention strategy for abdominally-obese and T2DM samples. The fractionation of sedentary time and its impact on health, must be explored as a separate concept to the fractionation of PA/exercise

There is conflicting evidence regarding whether accruing PA through longer continuous bouts (≥10 minutes) is superior for health benefits than a PA volume accrued through non-bouts (~3 minutes, ~5 minutes). Glazer et al. (2013) compared

the association of objectively measured MVPA, when the same volume was accumulated by either bouts (>10 mins) or non-bouts (<10 mins), with CVD risk factors such as measures of adiposity and blood lipid and glucose levels. MVPA accumulated through non-bouts was associated with lower prevalence of obesity, smaller waist circumferences and lower triglyceride levels, BMI and Framingham risk score. Interestingly, the magnitude of these relationships was similar to those accrued through bouts of MVPA >10 mins. In this sample, compliance with national PA guidelines (150 minutes of total MVPA per week) was associated with lower CVD risk and lower prevalence of obesity and IGT, regardless of how MVPA was accrued (>10 mins or shorter bouts). It is important to look at summaries of PA (i.e. moderate-intensity) in both bouts (>10 minutes) and intermittent regimes (<10 minutes), however this results in two variables with a large amount of shared variance although both are clinically important. The same issue arises for sedentary behaviours as both total accumulated minutes of sedentary behaviour (SB), and prolonged SB (>30 minutes, > 60 minutes) have been shown to be implicated in health. The fractionation of a PA summary creates variables that are a function of each other, but also distinct and of clinical relevance to a research question (i.e. bouts versus non-bouts).

1.2.10 Is adoption of “exercise” manageable and effective for highly sedentary adults?

Contemporary exercise recommendations state that at least 150 minutes per week of moderate-intensity aerobic exercise, or 75 minutes per week of vigorous-intensity (ACSM and AHA) are required to confer substantial benefit to health (Haskell et al., 2007). However, this presents two issues: firstly, some individuals are not physically capable of attaining the prescribed amount of exercise; secondly, even those meeting the recommended moderate to vigorous physical activity (MVPA) levels may still be spending the majority of their time sedentary (Craft et al., 2012; Hamilton, Healy, Dunstan, Zderic, & Owen, 2008). The attainment of the recommended daily MVPA is not sufficient to nullify the negative influence of inactivity upon health when the majority of time is spent sedentary (Helmerhorst, Wijndaele, Brage, Wareham, & Ekelund, 2009; Lahjibi et al., 2013). Therefore, it is important to examine the impact of light activity and sedentary time upon on the very same cardiovascular and cardiometabolic risk factors implicated in cognitive decline.

It is widely accepted that being physically active reduces the risk of all-cause mortality (Löllgen et al., 2009; Samitz et al., 2011; Woodcock, Franco, Orsini, & Roberts, 2011). However, the greatest benefit is observed in moving those at the lowest end of the physical activity spectrum into light activities. Two large scale meta-analyses observed the largest reductions in all-cause mortality risk in those moving from no activity to low activity, with minor additional benefit from further increases in PA (Löllgen et al., 2009; Woodcock et al., 2011). From a public health perspective, interventions aimed at increasing activity from the lowest category of physical activity would confer greatest impact on cardiovascular health outcomes (Franklin & McCullough, 2009).

1.2.10.1 Change in habitual PA and health

1.3 Step count and cardiovascular health

Research linking cognitive function outcomes and objective measures of physical activity, particularly at the lower end of the spectrum, is lacking. However, there is mounting evidence linking step count to cardiovascular and cardiometabolic parameters implicated in change in cognitive function. For those falling within the sedentary category (≤5000 steps/day) exercise prescription recommendations from ACSM (Garber et al., 2011) state that an increase of just ≥2000 steps per day to make a total daily target of ≥7000 would be beneficial for health, whereas alternative guidelines (Tudor-Locke & Bassett Jr, 2004) suggest a target of 10,000 steps per day to reduce disease risk and maintain health.

The use of steps per day to define sedentary behaviour is based on the rationale that a low step-count indicates more time spent in sedentary behaviours. The 2005–2006 National Health and Nutrition Examination Survey (NHANES) accelerometer data showed that participants accumulating <5000 steps per day spent an extra 2.75 – 2.95 hours in sedentary behaviours compared to those who accumulated ≥10 000 steps/day (Tudor-Locke, Johnson, & Katzmarzyk, 2011). Changes in daily number of steps were shown to reduce accelerometer measured sedentary time in individuals with T2DM, with an increase of 2500 steps translating to a reduction of sedentary time by >1 hour (De Greef, Deforche, Tudor-Locke, & De Bourdeaudhuij, 2010). Reducing sedentary time and increasing activity levels are important for particular populations whose sedentary behaviour exacerbates the risk of developing preventable chronic diseases (Owen, Bauman, & Brown, 2009).

Many studies have used a target of 10,000 steps per day in interventions. Achieving this target has reduced SBP in sedentary, obese subjects by approximately 3 mmHg (Hultquist, Albright, & Thompson, 2005; Iwane et al., 2000) or up to 8 mmHg (Swartz et al., 2003b). Swartz and colleagues also observed improved glucose tolerance post intervention, as glucose levels 2-hours post glucose ingestion had decreased by 11% from baseline tests. Furthermore, in an overweight cohort (average BMI 29.5 kg/m2) with a baseline of approximately 7000 steps per day, increasing by an average of 3,500 steps to just over 10,000 for 12 weeks was associated with reductions in BMI, WC and resting heart rate (Chan, Ryan, & Tudor-Locke, 2004). The improvements in waist circumference and heart rate were related to the increase in steps per day. Conversely, in a sample of healthy but non-exercising young men reducing ambulatory activity from approximately 10,000 steps to approximately 1,400 steps per day reduced insulin sensitivity (Krogh-Madsen et al., 2010) in just two weeks.

Despite the associated health benefits of accumulating 10,000 steps per day, this may not be attainable for some individuals. This has been confirmed by Sidman, Corbin, and Masurier (2004) who observed that women with lower baseline steps were significantly less likely to meet a 10,000 daily step goal when compared to those with higher baseline steps. Alternatively, lower and more attainable targets of step increases have proven to be beneficial for some cardiovascular and cardiometabolic outcomes. A systematic review conducted by Bravata et al. (2007) of pedometer based RCTs found that an increase of approximately 2500 steps per day led to reductions in systolic blood pressure (approximately 3.8 mmHg) but had no impact on plasma glucose. Also, Van Dyck et al. (2013) identified a threshold of increasing steps per day by ≥4000 in order to improve HbA1c in individuals with T2DM.

1.4 Interim summary

The relationship between cognitive function and exercise in obese, middle-aged adults is still in its infancy. When designing the studies for this thesis, information had to be gathered from two separate (but overlapping) areas of research: cognitive function regarding impact of exercise and also cognitive function and obesity. The research was further complicated by a large number of physiological health parameters reported to predict change in cognitive function. Those same

physiological parameters (cardiovascular risk factors) that are shown to be increased in obesity are also reduced by increasing fitness and exercise levels.

The literature described in section 1.1, suggests that overweight/obese individuals may suffer decrements in cognitive function relative to healthy weight counterparts at mid-life. However, reviewers have questioned the validity of the evidence for an independent contribution of obesity to cognitive function, due to limitations regarding control for CVD risk factors and education. This effect is likely not independent of obesity-associated comorbidities as systematic research reviews have highlighted methodological limitations leading to inadequate control for, or measurement of, cardiovascular risk factors. It is possible that any differences in cognitive function observed at mid-life are driven by unmeasured subclinical or undiagnosed CVD risk factors. Additionally, based on the overall hypothesis that impairments in cognitive function are driven by presence of cardiovascular risk factors it may be postulated that we may not see change in cognitive function in obese individuals who do not change in these health parameters. This section also indicated a large number of cognitive tests that were sensitive to detect differences between obese and non-obese samples, predominantly under the domains of executive function and memory.

Section 1.2 describes that research examining the impact of exercise and physical activity on cognitive function. There is currently no data providing information on objectively measured free-living physical activity and cognitive function outcomes in obese middle-aged adults. Additionally, a very limited number of studies have examined the impact of exercise regimes on cognitive function in obese, middle-aged, adults. However, the findings do indicate improved short-term memory, attention and processing speed and verbal memory, and these were associated with improvements in cerebral oxygenation (Drigny et al., 2014) and cardiovascular fitness (Monleón et al., 2015). Once again, this section indicated a large number of cognitive tests that were sensitive to detect change following an exercise intervention or change in CRF.

There is no consensus on the components of exercise necessary for optimal cognitive benefit. It is known from section 1.2.7 that altering the intensity, duration or mode of exercise will have a different impact on physiological adaptation. The literature suggests some specific types of exercise may yield superior adaptation for specific cardiovascular measures (e.g. high-intensity-interval-training and fitness). Based on the hypothesis that cognitive benefit is the result of reduction in systemic cardiovascular risk factors, there is compelling evidence that high-intensity exercise has superior impact on systemic factors (insulin sensitivity, blood pressure, etc).

However, this is not uniform for all health outcomes (e.g. high volume, low intensity exercise and fat loss).

There is vast opportunity for exploratory work examining the impact of specific facets of exercise on cognitive function in obese adults. However, it is not known which physiological parameters should be the primary target of an intervention in order to yield greatest benefit for cognitive function outcomes. Given the demographic of the sample under investigation, exercise prescription in sedentary, obese/overweight middle-aged samples must consider the feasibility and affect induced (enjoyment) by an exercise regime to ensure successful adoption and adherence. Irrespective of the possibilities health benefits of varying exercise regimes (in terms of duration, volume, intensity), they must be desirable and manageable to the target population for successful adoption and continued adherence.

In terms of shaping a thesis from the information gathered, there were several issues that had to be addressed when designing my studies. The first concerned cognitive test selection given that a vast number of tests were sensitive to measures of adiposity or changes following exercise. Secondly, in terms of designing exercise or PA interventions there were a vast number of factors that could be manipulated (intensity, duration, mode). Finally, a large number of physiological parameters are suggested as mechanistic links between cognitive function and exercise or obesity.

1.5 Thesis Aims

Section 1.2.9 highlighted a paucity of research using objective measurements of PA when examining the relationship between habitual PA and cognitive function. It is known that the cumulative effects of obesity with low activity place individuals at greater risk for cardiometabolic complications of obesity and cognitive decline. In non-obese and older adults, habitual PA is favourably associated with cognitive function, indicating that even LPA may have a neuroprotective effect. The relationship between objectively measured PA and cognitive function in obese individuals has not been studied. The accurate assessment of PA may help identify particular facets of PA (volume, bouts, intensity) that confer benefits to both health and cognitive function. In those performing the lowest amounts of PA, it is not known if increasing LPA is sufficient to elicit health benefits, or whether higher-intensity exercise is required. Consideration must be taken of what is manageable when moving those from the lowest end of the PA spectrum upwards, in order to promote exercise adoption and adherence.

Exercise and/or increasing CRF has translated to improvements in cognitive function following intervention in non-obese adults. It is thought this is through direct effects of brain structure and function, and also through the longer-term reduction in CVD risk factors. In healthcare research, interval exercise has shown to be a potent stimulus for increased CRF and reduced CVD risk. However, the use of HIIT prescription for cognitive function outcomes in obesity is new, and to date has only been investigated by one research group. The findings indicate HIIT is useful as a strategy for improving cognitive function, however, the sample included 6 men with no comparison group.

i. *To explore the relationship between objectively measured physical activity and cognitive function in a sample of overweight/obese and middle-aged adults.*

ii. *To compare the impact of medium-term heavy-intensity exercise regimes (interval and continuous) on indices of cognitive function and cardiovascular health. Change over time was examined relative to baseline cognitive performance, IQ and age*

iii. *To examine the impact of a medium-term light-intensity "free-living" pedometer programme on indices of cognitive function and cardiometabolic health. Change over time was examined relative to baseline cognitive performance, IQ and age.*

Chapter 2:
General Methodologies

Chapter 2 General Methodologies

2.1 Introduction

This chapter includes the methodologies that are common to multiple studies presented in this thesis. If any measure or procedure was subject to adjustment between studies, the details of this are listed in the methodology section of the respective study chapter.

2.2 Screening Procedure

The purpose of the screening procedures was twofold; to identify eligible participants for study inclusion, and to quantify within each included sample any confounding variables known to impact upon cognitive function. The screening procedure followed the same protocol for all experimental studies included in this thesis. Individuals expressing an interest in participation were screened over the telephone using an Initial Contact Questionnaire (ICQ, Appendix 6.1). The purpose of telephone screening was to confirm the inclusion/exclusion criteria prior to invitation to the laboratory. Screening took place seven days after an individual had received and read the study specific participant information sheet (PIS, section 2.3. First, screening questions were asked in accordance with the ICQ. Ineligible volunteers were informed during the screening call and consent to keep contact details for future studies was requested. For eligible participants, the researcher verbally outlined the study and explained the procedures in accordance with the PIS. Eligible individuals still expressing willingness to participate were then invited to the laboratory for their first study visit. Once enrolled onto a study, some secondary screening measures were collected and included as covariates in statistical models in the analysis of the data. The screening items obtained were factors known to have a confounding impact on cognitive function, or modulate the responsiveness of cognitive function to the specific interventions undertaken.

2.2.1 Screening measures

The screening measures common across multiple studies are detailed in the following section:

2.2.1.1 Study Eligibility: Cardiovascular Risk

2.2.1.2 AHA/ACSM Health/Fitness Facility Preparticipation Screening Questionnaire

The American Heart Association (AHA)/American College of Sports Medicine (ACSM) Preparticipation Questionnaire (AAPQ) is a widely used screening tool used to identify individuals at elevated risk of adverse exercise-induced events (Balady et al., 1998). The combination of vigorous intensity exercise and symptomatic or subclinical CVD is a major cause of exertion-induced cardiovascular events (Franklin & McCullough, 2009). The incidence of exercise-associated events, such as acute myocardial infarction or sudden death is highest in habitually sedentary individuals (Thompson et al., 2007). The AAPQ is a valid, cost-effective and time-efficient screening tool that allows for the identification of individuals with medical contraindications to exercise. Participants completed the AAPQ by ticking all statements that applied to them regarding health questions within the following categories: “history”, “symptoms”, “other health issues”, and “cardiovascular risk factors” (Appendix 6.2).

Stratified risk was based on the number of symptoms or risk factors for a variety of cardiovascular, pulmonary and metabolic diseases. The risk stratification process assigns an individual to one of the following three categories: ‘low risk’, ‘moderate risk’ and ‘high risk’ as shown in Table 2.1. Exercise testing and physical activity/exercise prescription for participants adhered to the ACSM guidelines according to risk stratification (Heath, 2005).

Table 2.1 ACSM Risk Stratification Categories for Atherosclerotic Cardiovascular Disease

Low Risk	Asymptomatic Individuals (<45 yrs men; <55 yrs women) with ≤ 1 CVD risk factor from Table 2.2
Moderate Risk	Asymptomatic Individuals (<45 yrs men; <55 yrs women) with ≥ 2 CVD risk factors from Table 2.2
High Risk	Individuals with known cardiovascular, pulmonary or metabolic disease or ≥ 1 symptom listed in Table 2.3

ACSM, American College of Sports Medicine; CDV, cardiovascular disease

As shown in Table 2.1 low risk individuals do not have a diagnosis or symptoms of cardiovascular, pulmonary or metabolic diseases, and a maximum of one CVD risk factor listed in Table 2.2. In accordance with the ACSM guidelines, participants identified as low risk were not asked to consult a physician before initiating any physical activity/exercise interventions. Moderate risk individuals do not have a diagnosis or signs/symptoms of cardiovascular, pulmonary or metabolic disease, but have two or more CVD risk factors listed in Table 2.2. Moderate risk classification confers increased risk of an acute cardiovascular event. Therefore in accordance with ACSM guidelines participants classed as moderate risk were supervised by a physician when completing a maximal exercise test. Participation in low-moderate intensity physical activity is considered safe for this group.

Table 2.2 Atherosclerotic Cardiovascular Disease (CVD) Risk Factor Thresholds for use with ACSM Risk Stratification (Heath, 2005)

Positive Risk Factors	**Defining Criteria**
Age	Men ≥ 45 yrs; Women ≥ 55 yrs
Family history	Myocardial infarction, coronary revascularization, or sudden death before 55 yr of age in father or other male first-degree relative, or before 65 yr of age in mother or other female first-degree relative
Cigarette Smoking	Current cigarette smoker or those who quit within the previous 6 months or exposure to environmental tobacco smoke
Sedentary Lifestyle	Not participating in at least 30 min of moderate intensity (40%–60% VO_2R) physical activity on at least three days of the week for at least three months
Obesity	Body mass index ≥30 $kg \cdot m^2$ or waist girth ≥102 cm (40 inches) for men and ≥88 cm (35 inches) for women
Hypertension	Systolic blood pressure ≥140 mm Hg and/or diastolic ≥90 mm Hg, confirmed by measurements on at least two separate occasions, or on antihypertensive medication
Dyslipidemia	Low-density lipoprotein (LDL-C) cholesterol ≥130 $mg \cdot dL^{-1}$ (3.37 $mmol \cdot L^{-1}$) or high-density lipoprotein (HDL-C) cholesterol <40 $mg \cdot dL^{-1}$ (1.04$mmol \cdot L^{-1}$) or on lipid-lowering medication. If total serum cholesterol is all that is available use ≥200 $mg \cdot dL^{-1}$ (5.18 $mmol \cdot L^{-1}$)
Prediabetes	Impaired fasting glucose (IFG) = fasting plasma glucose ≥100 $mg \cdot dL^{-1}$ (5.50 $mmol \cdot L^{-1}$) but <126 $mg \cdot dL^{-1}$ (6.93 $mmol \cdot L^{-1}$) or impaired glucose tolerance (IGT) = 2-hour values in oral glucose tolerance test (OGTT) _140 $mg \cdot dL^{-1}$ (7.70 $mmol \cdot L^{-1}$) but <200 $mg \cdot dL^{-1}$ (11.00 $mmol \cdot L^{-1}$) confirmed by measurements on at least two separate occasions
Negative Risk Factor	**Defining Criteria**
High-serum HDL cholesterol	≥60 $mg \cdot dL^{-1}$ (1.55 $mmol \cdot L^{-1}$)

High risk individuals would exhibit symptoms/signs (as shown in Table 2.3) or have a diagnosis of, cardiovascular, pulmonary or metabolic disease. For these individuals, a medical examination prior to the initiation of physical activity or exercise at any

intensity was required and any maximal exercise test performed was supervised by a physician.

Table 2.3 Major Signs or Symptoms Suggestive of Cardiovascular, Pulmonary, or Metabolic Disease

- Pain, discomfort (or other anginal equivalent) in the chest, neck, jaw, arms, or other areas that many be due to ischemia
- Shortness of breath at rest or with mild exertion
- Dizziness or syncope
- Orthopnea or paroxysmal nocturnal dyspnea
- Ankle Oedema
- Palpitations or tachycardia
- Intermittent claudication
- Known heart murmur
- Unusual fatigue or shortness of breath with usual activities

2.2.2 Intelligence

2.2.2.1 Wechsler Abbreviated Scale of Intelligence (two-subtest form).

Short forms of the Wechsler Scales are suitable for estimation of IQ for research screening purposes (Franklin & McCullough, 2009), as opposed to the full scales which assess particular intellectual capabilities. The administration of the full Wechsler scales is a lengthy procedure lasting between 60-90mins (Löllgen, Böckenhoff, & Knapp, 2009) and IQ per se was not a research outcome in this thesis but collected to use as a covariate in analysis since many cognitive test outcomes are correlated with IQ. Therefore, to meet the research needs and reduce time for participants, the WASI two-subtest form was selected. Both the construct validity of WASI scales, and also convergent validity with an alternative short-form scale, the Wide Range Intelligence Test (Samitz, Egger, & Zwahlen, 2011), have been supported by Canivez, Konold, Collins, and Wilson (2009).

The vocabulary and matrix reasoning subtests were administered and scored adhering to the standardised procedures listed in the WASI (Wechsler, 1997). The Vocabulary subtest is a 42-item scale assessing expressive vocabulary and verbal knowledge. Words were visually presented from the stimulus booklet and participants were asked to orally define each word. The vocabulary scale was recorded with a

dictaphone and transcribed following the testing session. The Matrix Reasoning subtest is a 35-item scale that assesses general intellectual ability and nonverbal fluid reasoning. The task consists of an incomplete grid of patterns presented in a stimulus booklet, with five numbered choices of response presented beneath each grid. Participants answered by stating the number of the response that would complete the pattern. Administration time took 15 minutes.

Raw scores from the Vocabulary and the Matrix Reasoning sub-tests were converted to T scores in accordance with the WASI manual. The T scores were summed and converted to IQ scores using the age-appropriate “IQ Equivalents of Sums of T Scores: Full Scale-2 Subtests” table, which generated an FSIQ-2 score.

2.2.3 Study Exclusion Criteria

The following exclusion criteria were common across the studies presented in this thesis (Table 2.4). Further exclusion criteria specific to each study are listed in the methods section of the respective study chapters.

Table 2.4 Inclusion and Exclusion Criteria common across multiple studies

Inclusion Criteria	Exclusion Criteria
BMI ≥25 kg/m^2	BMI < 25 kg/m^2
Sedentary, low-active.	Moderate-active lifestyle
Visual and verbal ability to provide written informed consent and complete cognitive function tests.	Musculoskeletal impairment or injury affecting ability to complete experimental intervention. Clinical diagnosis of: Uncontrolled Hypertension (and medication) Type 1 diabetes Uncontrolled cardiac dysrhythmias or pacemaker fitted Neurological disorder Depression (and medication) Hypothyroidism (and medication) Previous stroke or Transient Ischaemic Attack Use of any medication known to impact on cognitive functions. Use of antidepressant, anxiolytic, or thyroid medication. Visual impairment preventing the completion of the cognitive tests (e.g. colour-blindness). Unable to provide written informed consent.

2.3 Ethical considerations

Prior to commencement of the studies, ethical approval was obtained from Biological Sciences Faculty Research Ethics Committee (Study 2) and Institute of Psychological Sciences Research Ethics Committee (Study 3) at the University of Leeds. Study 1 was covered by the ethical approval sought for Study 2 and Study 3. For all studies, the same procedure was followed regarding obtaining written informed consent. Participants were provided with a study specific participant information sheet and

given 7 days to read prior to being contacted by the researcher. Participants were then invited to the School of Psychology to a familiarisation visit for a full debrief of the study requirements and procedures and the opportunity to ask any questions. Emphasis was given to the participants' right to withdraw from the study at any time before or during study participation. All participants provided written informed consent prior to study inclusion.

2.3.1 Study 2

Study 2 (Chapter 4) was approved by the Biological Sciences Faculty Research Ethics Committee at the University of Leeds (Reference: BIOSCI 10-021, Date: 10/05/2012). The following amendments were approved:

Amendment 1: (Reference: BIOSCI 10-021, Date: 07/08/12)

Amendment 2: (Reference: BIOSCI 10-021, Date: 19/08/13)

Amendment 3: (Reference: BIOSCI 10-021, Date: 07/10/13)

The final versions of approved documents for Study 2, such participant information sheet (PIs) and consent forms can be seen in Appendix 6.3 and Appendix 6.4, respectively.

2.3.2 Study 3

Study 3 (Chapter 5) was approved by Institute of Psychological Sciences Research Ethics Committee at the University of Leeds (Reference: 13-0141 (Version 1), Date: 26/08/13). The following amendments were approved:

Amendment 1: (Reference: 13-0184, Date: 20/10/13)

Amendment 2: (Reference: 14-0070, Date: 28/03/14)

The final versions of approved documents for Study 3, participant information sheet (PIs) and consent forms can be seen in Appendix 6.5 and Appendix 6.6, respectively.

2.4 Baseline testing

Following screening, eligible participants enrolled on either study 2 or study 3 first attended the School of Psychology for a familiarisation visit prior to attending the baseline testing visits.

2.4.1 Familiarisation visit 1

Written informed consent was obtained after prior reading of the PIS (Appendix 6.3 and Appendix 6.5 for Studies 2 and 3 respectively) and a verbal explanation of all study procedures. Participants completed a Recruitment Information Questionnaire (RIQ, Appendix 6.7), the Wechsler Abbreviated Intelligence Scale (WAIS-III, Appendix 6.8), and a Physical Activity Readiness Questionnaire (PAR-Q, section 2.2.1.2) Participants completed a practise version of the cognitive test battery to familiarise them with the tests, ensure participants understood how to perform the tests correctly and assess compliance (effort). At the end of visit 1, participants were provided with an ActiGraph accelerometer to wear for a period of seven days and a log sheet (Appendix 6.9) to complete during their week wearing the accelerometer. Laboratory Visit 1 took 90 minutes to complete.

2.4.2 Baseline visit 2

Participants attended baseline visit 2 in a 12-hour fasted state. The cognitive test battery was completed (see respective study chapters for study specific tests). Systolic and diastolic blood pressure were taken (see section 2.7). Anthropometric indices were measured (see section 2.8).

2.5 Measurement of cognitive function

The selection of cognitive tests included in this thesis were based upon the following two criteria. Firstly, tests were considered if they had previously detected differences between obese and healthy weight adults, or between those with or without obesity associated comorbidities. Secondly, tests sensitive to longitudinal change in cognition following weight loss and/or physical activity interventions or a reduction in comorbidity symptoms were also considered. The domains vulnerable to deficits in obesity are frequently cited as executive function, memory and attention (Sellbom & Gunstad, 2012). These domains are also known to be amenable to improvement following aerobic exercise intervention or reductions in cardiovascular risk (Erickson et al., 2012a; Obisesan et al., 2012; Smith et al., 2010).

Divergent cognitive tests batteries were employed to meet study specific requirements and address the corresponding research questions. However, many cognitive tests were utilised in more than one study, the details of which are included in this chapter for brevity. The batteries for each study were designed to test specific

constructs within the global fields of executive function, memory and attention. Additional study specific tests are reported in the methodology section of the appropriate experimental chapters (Chapters 3, 4 and 5), along with any adapted versions of tests. The tests described in this chapter are grouped according to domain tested. The rationale for specific tests used is included in each corresponding section.

2.5.1 Memory

2.5.1.1 Visual Verbal Learning Test (immediate and delayed)

The Visual Verbal Learning Test (VVLT) is a visual analogue of the Rey Auditory-Verbal Learning Test (RAVLT, Rey, 1964) that measures immediate and delayed verbal memory via word list recall. The test administered in the studies in this thesis has been shown to be sensitive to detect impairments in both immediate and delayed verbal memory in individuals with T2DM when compared to adults with normal glucose tolerance (Lamport, Dye, Mansfield, & Lawton, 2013).

In the VVLT, the test stimuli were presented visually as opposed to aurally. Aurally presented information is known to be recalled better than visually presented information (Penney, 1989; Van Der Elst, Van Boxtel, Van Breukelen, & Jolles, 2005). Some of the participant samples accessed for this thesis had above average IQ and many years of education. Given the relationship between estimates of IQ and verbal memory (Steinberg, Bieliauskas, Smith, Ivnik, & Malec, 2005), the visual presentation of stimuli was chosen to prevent ceiling effects and increase the sensitivity of the test to detect differences in a highly educated and high IQ sample.

Participants were presented with 16 words from word list A, in a randomised order controlled by E-prime at a rate of one word every 2 seconds. Participants were then given 60 seconds to recall as many of the words they had just seen using a dictaphone. This procedure was followed for another two trials, to make a total of three initial learning trials (Trials A1 – A3). Trial A3 was followed by a presentation of a 16-word interference list (List B) and a subsequent free recall of these words (Trial B1). A free recall of List A immediately succeeded this (Trial A4). After a 20-minute delay period, wherein other cognitive tests were performed, participants were once again instructed to recall List A (Trial A5). Word stimuli were presented centrally on the screen in capitals, font size 28, and in yellow text on a black background. The word lists were created using the SOP for creating 16 word VVLT lists (Appendix 6.10) and words selected from the MRC Psycholinguistic database (Wilson, 1988).

Parallel versions of the test, which were administered in a counterbalanced fashion, can be seen in (Appendix 6.11). Counterbalanced versions were matched on the following properties: concreteness, imageability, familiarity, age of acquisition and word length.

In accordance with Lezak (2004) and Lamport et al. (2013) the following direct and derived scores were used to calculate indices of verbal learning: Immediate word span (Trial A1), final acquisition level (Trial A3), total acquisition (∑ A1, A2 & A3), proactive interference (Trial A1 minus Trial B1) and retroactive interference (Trial A3 minus A4, delayed recall (Trial A5). Additionally, rate of learning over trials (LOT) was derived from total acquisition corrected for immediate learning span LOT= ((∑ A1-A3) - (3*Trial A1 Score)) in accordance with Ivnik et al. (1992).

Norms presented for men and women aged 40-49 years by Savage and Gouvier (1992) for RAVLT indicate approximately 7.6 words for delayed recall and a total acquisition of 22.4 words over the first 3 trials for immediate learning.

2.5.1.2 Rey Recognition Test

Recognition tasks allow for the assessment of memory storage that is distinct from retrieval (Harris, Ivnik, & Smith, 2002a). Comparison of the recognition (VVLT List A) and the delayed recall score from the previously administered VVLT (Trial A5) can be used as a proxy of the efficiency of spontaneous retrieval (Lezak, 2004). The recognition task administered for this thesis has demonstrated sensitivity to detect impairments in recognition in adults with T2DM and impaired glucose tolerance when compared to adults with normal glucose tolerance (Lamport et al., 2013). The stimuli consisted of a total of 48 words: 32 words (16 from List A and 16 from List B) from the initial VVLT presentation (2.5.1.1 and Appendix 6.11), and a further 16 new distracter words (List C). The words were presented in a random order visually in the middle of a computer screen at the rate of one word every 2 seconds. Participants were required to respond to the stimuli by pressing keys labelled 1, 2, or 3, corresponding to word lists A, B, or C. Words presented visually remained on the screen for 3 seconds. Outcome variables are number correct and reaction time for correct responses only.

Raw scores were collected for correctly recognised hits and also false positives for all 48 recognition trials. A recognition score below 12 (out of possible 15 from original RAVLT) would be rare according to norms published by Ivnik et al. (1992). More

recently Lezak (2004) suggested that one or two errors per recognition trial would be normal but further deviation from this would be indicative of dysfunction.

In accordance with Harris et al. (2002a), recognition percent correct (RPC) was calculated. This is the total proportion of 48 recognition items correctly identified as belonging to their respective lists (Lists A, B and C). The comparison between a score from the original VVLT List A or B performance, to their respective recognition trial score can be used to identify specific problems in verbal memory (Harris et al., 2002a). A deficit in delayed recall (Trial A5 from VVLT) but a normal RPC score highlight retrieval problems but not storage capacity. A deficit in delayed recall, coupled with a poor RPC score would be indicative of problems in encoding and/or storage.

2.5.1.3 Visual Spatial Learning Test (immediate and delayed)

The Visual Spatial Learning Test (VSLT;(Malec, Ivnik, & Hinkeldey, 1991)) is a test of visuospatial memory and learning. The test administered for this thesis has demonstrated sensitivity to impairments in immediate spatial memory in individuals with T2DM when compared to adults with normal glucose tolerance (Lamport et al., 2013).

The VSLT apparatus consisted of a 6 x 4 grid and fifteen nonsense geometric designs in black and white. Participants were initially presented with a blank grid and the 15 designs placed next to the grid as shown in Figure 2.1. Participants were then shown the grid with seven of the designs placed on specific squares within the grid. The positions were pre-determined according to parallel versions of the test, which were administered in a counterbalanced fashion (Appendix 6.12) Participants were given ten seconds to view the positioning of the seven designs placed on the grid, and instructed to look away whilst the examiner removed all designs from the grid.

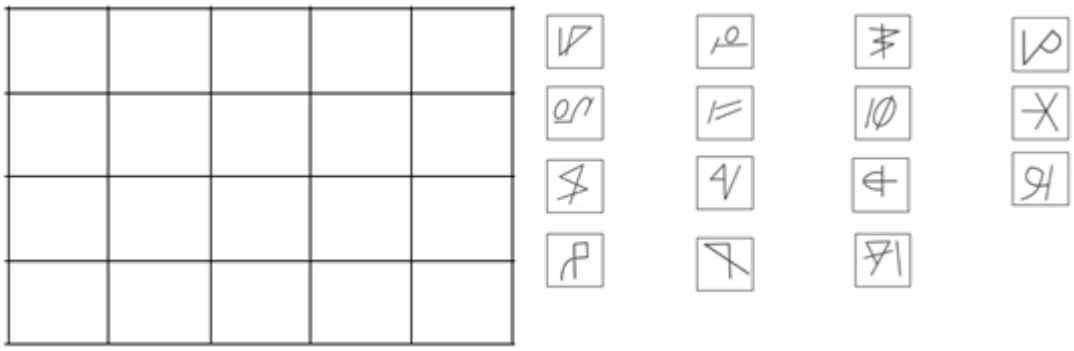

Figure 2.1 VSLT grid and the 15 possible target designs

Participants were then presented with the empty grid and fifteen designs and given the task to select the target seven designs and place them back in the correct grid spaces. This procedure was repeated for a further two trials, to make a total of three initial learning trials (Trials 1-3). Three initial learning trials were followed by a 30-minute delayed recall. Other cognitive tests from the battery were performed during this 30 minute interval. For the delayed component of the VSLT, participants were presented with the empty grid and the fifteen designs placed beside it and instructed to select the seven designs seen previously and place them in the correct grid squares. For each trial, scores were obtained for the number of correct designs only, correct locations only and correct designs in the correct locations.

2.5.1.4 Corsi Block Tapping Task

The Corsi Block-Tapping Task (CBT) (Corsi, 1973) is a widely used spatial working memory task that requires the simultaneous storage and manipulation of spatial and temporal information under conditions where the information is changing (Shah, Prados, Gamble, De Lillo, & Gibson, 2013; Toepper et al., 2010b).

Completion of the CBT under fMRI has shown increased prefrontal cortex activity in both the ventrolateral and dorsolateral prefrontal brain regions during the task (Toepper et al., 2010a). A further experiment, isolating the encoding phase of CBT showed increased activity in the right hippocampus during the encoding phase, in addition to activity within the parietal, frontal and occipital regions (Toepper et al., 2010b). The CBT detected differences in performance within an obese sample between those with somatic comorbidities (hypertension, diabetes, etc) and those without (Kiunke et al., 2013). Additionally, the version of CBT administered in this thesis has been shown to be sensitive to differences in performance according to

diabetes status (T2DM or normal glucose tolerance) in middle aged adults (Lamport et al., 2013).

A computerised version was selected for this thesis as, in addition to the Corsi span score traditionally obtained, automatic scoring allows for accurate recording of overall duration of response as well as latencies between responses (Berch, Krikorian, & Huha, 1998). The CBT was administered using E-prime software on a DELL PC with a 17" screen. The display showed a black screen, with nine 1.5cm white blocks arranged in the positions shown in Figure 2.2. These were the same block configurations as the original Corsi apparatus (Berch et al., 1998; Corsi, 1973). The numbers were not displayed to participants but are indicated in Figure 2.2 for clarity for the reader.

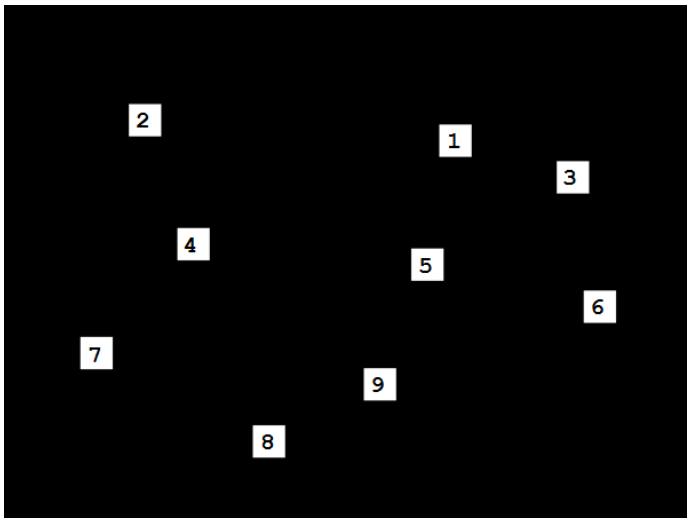

Figure 2.2 On-screen block configuration for CBT

The stimulus material consisted of target blocks that were displayed filled in red. Participants were presented with sequences, where the red target blocks would appear one at a time to replace one of the white blocks in the configuration shown above in Figure 2.2. The path sequences ranged from two to nine blocks, and were presented in a randomised order controlled by E-Prime. The duration of the target blocks was 500ms with a 500ms inter-stimulus interval. The encoding phase (stimulus presentation) therefore increased with each sequence level. Participants were instructed to reproduce each sequence after each presentation, and used a mouse to click on the white boxes in a forward recall order. Four trials per level were presented. The path sequences at each level (levels 2-9) from CBT version 1 are

listed in Table 2.5 as an example. Three parallel versions of CBT were administered in this thesis.

Table 2.5 Path sequence per level of difficulty presented as a digit sequence for CBT version 1

Level 2	**Level 3**	**Level 4**
1,2	2,7,8	1,2,7,6
2,7	5,6,9	4,2,6,8
4,9	3,5,6	6,2,9,8
5,8	2,1,3	5,1,7,3
Level 5	**Level 6**	**Level 7**
6,7,1,5,2	6,7,5,4,1,2	2,6,5,4,7,9,8
2,3,4,8,5[a]	4,1,6,7,8,2 [a]	5,4,1,6,3,9,7 [a]
1,3,8,2,5	2,3,4,6,9,8	2,7,4,3,9,8,5
2,1,8,7,3 [a]	5,6,7,1,4,8 [a]	9,5,3,6,1,8,2 [a]
Level 8	**Level 9**	
2,3,4,5,6,9,8,7	2,7,8,4,9,1,3,5,6	
8,1,4,2,7,3,5,9 [a]	3,1,2,4,7,6,5,8,9 [a]	
7,8,6,5,4,3,1,2	5,1,3,6,8,7,9,2,4	
3,8,2,1,4,7,9,5 [a]	3,1,2,4,8,5,6,9,7 [a]	

Each digit corresponds to the numbered blocks shown in Figure 3.1
[a]Crossing trials in which the path taken from block to block crosses a previous path within the same trial

A further methodological consideration that the computerised version accounted for was path configuration. Traditionally, sequences of the same length had been grouped at the same level and considered to be of similar difficulty (Berch et al., 1998). The highest number of blocks in a sequence remembered would determine the Corsi span score (Corsi, 1973). More recent work has highlighted the impact of path configuration within each level, as the number of times a path crosses itself determines path complexity and therefore, item difficulty (Busch, Farrell, Lisdahl-Medina, & Krikorian, 2005). Within sequences of the same length, individuals remember fewer crossing trials than non-crossing trials (Shah et al., 2013). To control for the intra-level item inconsistency generated through path complexity, each level (4 trials) was split further into 2 non-crossing trials and 2 crossing trials. It has also been shown that as the number of crossings within a trial increases, accuracy decreases and response times increase (Parmentier, Elford, & Maybery, 2005). Therefore, one path crossing per path configuration was standardised for all crossing trials at every level of sequencing.

Accuracy was derived from the sum of correct responses across all levels. Mean reaction times (ms) per target were analysed for correct responses only. Additionally,

span limit for both crossing and non-crossing trials was determined as the highest level at which at least one trial was correctly reproduced. Normative data for the CBT support a Corsi span of approximately 6 in healthy adults (Kessels, van Zandvoort, Postma, Kappelle, & de Haan, 2000).

2.5.2 Attention

2.5.2.1 Rapid Visual Information Processing (RVIP)

A Rapid Visual Information Processing (RVIP) task based on the Bakan Vigilance Task (Bakan, 1959) was administered to assess sustained attention. Vigilance is the ability to maintain attention and focus during unchallenging and monotonous tasks over time (Langner & Eickhoff, 2013). The cognitive effort required to maintain attention in simple, repetitive tasks has been shown to elicit higher stress response and ratings of subjective effort than more stimulating tasks (Warm, Parasuraman, & Matthews, 2008). Imaging studies have shown that sustained vigilance tasks require activation of the frontal and parietal cortical areas (Sarter, Givens, & Bruno, 2001), particularly within the right cerebral cortex (Petersen & Posner, 2012). The original Bakan task demonstrated sensitivity to the impact of differing weight-loss treatment arms in overweight women on correct hits (Green, Elliman, & Kretsch, 2005). Measures of sustained attention have also been shown to be sensitive to differences between obese and normal weight counterparts (Cserjesi, Luminet, Poncelet, & Lenard, 2009). They are also sensitive to impairments in adults with sleep apnoea (Beebe & Gozal, 2002; Dorrian, Rogers, & Dinges, 2005; Engleman & Douglas, 2004; Lal, Strange, & Bachman, 2012) and improvements following aerobic exercise interventions (Smith et al., 2010)

The RVIP task used in this thesis adheres to the experimental paradigm of continuous stimulus detection (non cued) (Langner & Eickhoff, 2013). A series of single digits (numbers 1-9) were presented centrally on the screen at a rate of 600 milliseconds with a 600 millisecond inter-stimulus interval. Number stimuli were presented in yellow (font size 36 Courier New) and on a black background. The task usually lasts for 6 minutes as this has been previously demonstrated to induce fatigue (Auburn et al., 1987) but can be shortened or extended as required. There were 100 stimuli per 1 minute block. Participants were required to correctly identify sequences of either three consecutive odd (e.g. 3, 9, 1) or three consecutive even (e.g. 8, 2, 6) targets in a row.

Participants were reminded that targets within a sequence did not have to be in an ascending or descending order. The number of correctly identified sequences and number of errors (false positives, and misses) was measured as well as the reaction time for these.

2.6 Subjective ratings of cognitive test performance

2.6.1 Cognitive Test Evaluation Questionnaire (CTEQ)

Ratings of subjective performance and mental effort in relation to the cognitive tests were be made after the test battery using visual analog rating scales (VAS) adapted from the NASA TLX (Task Load Index) mental workload measure (Hart & Staveland, 1988). The CTEQ was a pencil and paper task where items were presented as a 100mm line, with descriptors at each end that represented extremes of each item in question. The items assessed were time pressure, concentration, difficulty, performance and frustration. For example, in the case of the question 'How much did you concentrate during these tests?' the descriptors were 'a small amount' (on the left) and 'a large amount' (on the right). Additionally, participants were asked to identify the tests which they found to be the most and least difficult in the test battery (Appendix 6.13). The CTEQ took 3 minutes to complete.

2.7 Assessment of blood pressure

Systolic and diastolic blood pressure were taken at the left arm using an automated Omron M7 BP cuff after participants had been seated for forty minutes with an appropriately sized cuff. Three measures were taken with a minimum of one minute between measurement trials, and the average recorded. The IPSEC approved standard operating procedure (SOP) details the procedure (Appendix 6.14).

2.8 Anthropometric Measures

2.8.1 Body mass index (BMI)

The body mass index (BMI) of participants was calculated from their height (Ht) and body mass (BM) using a stadiometer and scales to the nearest 0.5 cm and 0.1 kg respectively. BMI was determined using the following formula:

$$BMI = BM\ (kg)/\ Ht^2\ (m)$$

where BM = body mass and Ht = height.

2.8.2 Waist circumference (WC)

Waist circumference (WC) was measured with participants stood straight with arms at sides, feet together and abdomen relaxed. Using a standard tape measure placed around the waist in a horizontal plane above the level of the highest point of the iliac crest, located using the fingertips, WC was measured to the nearest 0.5 cm.

2.8.3 Hip Circumference (HC)

Hip circumference (HC) was measured while participants were standing straight with arms at their sides, feet together, abdomen relaxed and not tensing the gluteal muscles. Using a standard tape measure placed around the greatest protrusion of the gluteal (buttock) muscles, HC was measured to the nearest 0.5 cm.

2.8.4 Body composition

Total body fat free mass (FFM) and percentage body fat (% BF) were measured by bioelectrical impedance analysis (BIA) using the TANITA body composition analyser. Resistance to a low safe electrical current as it travels through the body was measured, giving an estimate of total body water (TBW) using the following formula (Lukaski & Bolonchuk, 1988):

$$TBW = 0.372(Ht^2 \div R) + 3.05(Sex) + 0.142(BM) - 0.069(age)$$

Where Ht = height, R = resistance, BM = body mass.

Based on the fact that approximately 73 % of FFM consists of water, total body FFM can then be determine. Finally, FFM was deducted from BM giving the fat mass (kg), the percentage of which can be calculated.

2.9 Measurement of physical activity

2.9.1 Actigraph accelerometer

Physical activity was objectively measured using Actigraph GT3X monitors and all data collected by the devices was downloaded and analysed using ActiLIfe 5 software. The Actigraph devices are one of the most widely used monitors in physical activity research (Bassett Jr, Rowlands, & Trost, 2012; Kelly et al., 2013). The GT3X monitor uses a triaxial accelerometer that measures acceleration of the body in three planes (vertical, medio-lateral and anterior-posterior) (Kelly et al., 2013; Warren et al., 2010).

In terms of movement frequencies, the majority of daily physical activity lies between 0.3-3.5 Hz, with approximately 0.75 Hz indicating slow walking and ≥4 Hz indicative of fast running (Santos-Lozano et al., 2012). The inter and intra-instrument reliability of the GT3X accelerometers was assessed using mechanical oscillations (Santos-Lozano et al., 2012). Their results support the accuracy of this device to estimate free-living physical activity with an intra-instrument coefficient of variation of ≤2.5% (between frequencies of 2.1-4.1 Hz) and an intra-class correlation coefficient for activity counts of 0.97. Additionally, the GT3X counts per minute demonstrated a strong positive correlation with oxygen consumption (VO_2) in a lab setting for healthy weight adults for treadmill paced slow walking (4.8 $km \cdot h^{-1}$), fast walking (6.4 $km \cdot h^{-1}$) and running (9.7 $km \cdot h^{-1}$) (Kelly et al., 2013).

The monitors estimate human movement by converting the raw accelerations to a digital signal, this is then filtered according to the appropriate cut-points and converted to “counts” (Bassett Jr et al., 2012). The counts are derived from the amplitude and frequency of the acceleration measured from a specific device, and therefore vary between monitor brands (Warren et al., 2010). The application of cut-offs or intensity thresholds impacts on how movement counts are classified in terms of intensity. Therefore, to reduce misclassification error, it is essential that the cut-points are appropriate for the user characteristics (e.g. obese/overweight) and movement characteristics (e.g. sedentary, low-active, high intensity) to be assessed (Warren et al., 2010).

The Actigraph monitors, secured to elastic waist bands provided, were worn vertically on the hip to allow for use of the inclinometer function. The following sections describe the specific frequency, cut-points and filters applied to the devices.

2.9.1.1 Frequency

The normal frequency filter was applied. An alternative filter, the low frequency extension (LFE), has increased sensitivity to detect movement at the low end of the intensity spectrum (Cain, Sallis, Conway, Van Dyck, & Calhoon, 2013) so could potentially have been applied given that all participants researched in this thesis were sedentary. However, even though the LFE was found to reduce the misclassification of sedentary behaviours to non-wear time, the sensitivity also overestimated step counts (Cain et al., 2013; Wanner, Martin, Meier, Probst-Hensch, & Kriemler, 2013). Step count was an essential outcome variable for Study 3 (pedometer study) so the application of LFE would have made this outcome unusable.

2.9.1.2 Epoch length

Epochs are the time intervals into which the measured information is summarised, and are traditionally set as 60s in adults (Heil, Brage, & Rothney, 2012). The devices administered were set to store data in epochs of 60 seconds. Before being stored to memory, within each 60s epoch the data samples were collected at a rate of 30Hz, filtered and stored to memory. The devices stored 30 x 60 = 1800 data points for every enabled axis every 60 seconds.

2.9.1.3 Cut points

The Freedson adult (1998) cut points were selected as these are widely used and also validated in obese samples(Freedson et al., 1998). The cut-points categorise PA as follows; sedentary (<99 CPM), LPA (100-1952 CPM), MPA (1952-5999 CPM) and VPA (>6000 CPM). A review of 12 different cut-points for adults on ActiGraph accelerometer data failed to find clear evidence to support one cut-point being superior to the others (Loprinzi et al., 2012). This review highlighted that it is unlikely that any cut-point will have perfect sensitivity or specificity. This is potentially due to the fact that once a cut point is validated against one criterion (i.e. obesity/weight category) it assumes that all people in that category behave in the same way. By applying absolute cut-points to determine PA level, there is an assumption that a specific number of raw activity counts means the same thing in terms of PA level to each individual (i.e. 7000 counts·min^{-1} is vigorous-intensity activity). When comparing

3 sets of ActiGraph accelerometer cutpoints (Freedson, Swartz and Hendelmen) against HRR, it was found that the majority of time identified as moderate intensity by (78.3%), Swartz (88.0%), and Hendelman (94.7%) corresponded with a HRR indicative of light intensities (less than 45% HRR) (Ham, Reis, Strath, Dubose, & Ainsworth, 2007). This not only demonstrates the variability in PA classifications between the 3 cut points selected (Freedson, Swartz and Hendelmen) but also a high rate of misclassification between light and moderate intensity as the moderate cut-points did not correspond with changes in heart rate indicative of moderate-intensity. Vigorous-intensity PA demonstrated less variability amongst cut-point methods in terms of frequency and duration, the majority of counts above 7000 counts·min^{-1} corresponded with >60% HRR.

However, if the focus of research is sedentary behaviour then cut-points may be altered to increase sensitivity to detect movement at the lowest end of the activity spectrum. In the GT3X models, research has shown that 150 counts per minute (CPM) may be the most appropriate to measure sedentary behaviour (SB). A validation study comparing 100 cpm or 150 cpm in GT3X against direct observation found 150 cpm to be more accurate when sedentary time was higher and 100 cpm to be more accurate when sedentary time was lower (Kozey-Keadle, Libertine, Lyden, Staudenmayer, & Freedson, 2011).

2.9.1.4 Wear-time

For daily wear time compliance, 10 wearing hours during week days and 8 wearing hours during weekends were required. Periods of 60 or more consecutive minutes of 0 counts were excluded as non-wear time (Bassett Jr et al., 2012). An alternative window for non-wear time of 20 minutes was suggested by Berendsen et al. (2014). The optimal time frame was based on 10 participants wearing CAM accelerometers worn at the thigh, and validated in 6 participants. These findings cannot be applied to the hip-worn Actigraph models that were used for this study. Conclusive evidence regarding optimal non-wear time is lacking, however, allowing for limited movement (1-2 minutes of <50 counts·min^{-1}) can improve accuracy (Winkler et al., 2012).

2.9.1.5 Wear days for compliance

It is recommended that the devices be worn for 7 consecutive days, consisting of 5 week days and two weekend days. Acceptable wear days for compliance were a minimum of 5 days, including 1 weekend day. If the device was not worn for the

adequate number of wear days, then participants were asked to rewear the device for the number of days that were missing.

2.9.1.6 Instructions and wear time log

All participants were asked to complete a wear time log (Appendix 6.9) noting the times the device was put on and taken off on each of the seven wear days. This not only aided data processing, but also served as a reminder for participants to wear the device each day. This also helped to reduce burden on participants who reported they had missed wear days. In this case, they were instructed to continue to wear the device for the missed days as opposed to returning to the lab multiple times to drop off an accelerometer with an incomplete data set and collect a new device.

2.10 Statistical approaches common across studies

In the analysis of the empirical investigations presented within this thesis, cognitive test performance was the primary outcome variable, physiological parameters were collected as secondary outcome variables and IQ and age were included as covariates. The analytical approach for each thesis study was reviewed by an independent statistician, study 1 was reviewed by (Dr Arief Gusnanto, Department of Statistics, School of Mathematics, University of Leeds), and studies 2 and 3 were reviewed by (Frits Quadt, Quadt Consultancy BV). All data were entered and checked in Excel and then analysed using SAS (Statistical Analysis System, Version 9.2; SAS Institute, Inc., Cary, NC) or PASW (Version 20.0, SPSS Inc. Chicago).

All data were summarised and screened for outliers. Residual plots were inspected for deviations from normality, and any data exceeding the 99% confidence interval, corresponding to 2.58 standard deviations, were removed (Tabachnick & Fidell, 2007). Skewed data were normalised using appropriate transformations. Untransformed data are presented in figures for clarity throughout the thesis. For all analyses, the significance level was set at $\alpha = 5\%$.

For the analysis of between-and within-subjects effects upon primary outcomes, SAS-mixed models procedure (PROC MIXED) was employed. This procedure uses a likelihood-based estimation method to estimate unknown variance-covariance parameters (Jennrich & Schluchter, 1986). This model allows for variance in covariates within a subject, which is not permitted in PROC GLM procedures. Additionally, PROC MIXED can accommodate data that are missing at random.

All main effects and interactions were requested in the first model and the model fit, F values and significance of main effects and interactions examined. Non-significant interactions were removed, starting with highest order interactions, and the resulting model was compared to the previous model using the McQuarrie Tsai AICc criterion ((McQuarrie & Tsai, 1998). The AICc criterion gives an indication of the amount of remaining unexplained variance after the model has been fitted, where a smaller AICc value indicates a better model. This was used in preference to the Akaike's information criterion (AIC) because the AICc protects against overfitting (Quadt Consultancy BV, personal communication). If an improvement in model fit was found, other non-significant effects were removed and again the AICc criterion used to evaluate the model fit. Models were chosen on the basis of 'best fit', and interaction terms that improved the fit were retained. F values and corresponding significance values for the main effects and interactions in the final selected model for each cognitive outcome variable are given in the respective chapters or corresponding appendices. Where outliers were indicated by boxplots or regression plots, the analysis was re-run with the outlying data points excluded. Only where the exclusion led to a difference in inferences that could be drawn from the findings, were the data permanently removed and the corresponding values are reported.

Main effects of condition (e.g. exercise or control) were explored using the least squares (LS) means procedure. This employed the Tukey-Kramer (Tukey, 1951) test to compare the LS mean outcome score from each test of cognitive performance in response to each condition at the average level of the corresponding baseline rating. In the event of heterogeneity of regression slopes, indicated by a significant baseline*condition interaction, LS means comparisons were also used to compare the effects of each condition on LS mean cognitive performance score at different levels of the corresponding baseline rating using the Tukey-Kramer test.

Chapter 3:
Study 1

Chapter 3 Study 1 - Relationship between objectively measured physical activity and cognitive function in overweight/obese middle-aged adults.

3.1 Introduction

3.1.1 Physical Activity and cognitive function

Chapter 1 examined the evidence showing compromised cognitive function in overweight/obese samples. This is thought to be driven by obesity-associated comorbidities. The evidence reviewed suggested that self-reported physical activity (PA) has a potentially mechanistic role in the relationship between obesity and cognitive function. Nevertheless, there is a paucity of research and therefore considerable gaps in our knowledge about the relationship between objectively measured PA and cognitive function in obese/overweight samples. It is not known whether particular aspects of PA (e.g. intensity, duration, etc) play a critical role in this relationship. It is also not known whether any specific cognitive domains are more responsive to PA, or lack of it, than others. Little research has been undertaken in middle aged adults and although these findings cannot be directly applied to the middle-aged obese sample studied in this thesis, they suggest cognitive domains which might merit exploration as part of the research presented in this thesis. Lessons and recommendations from the research discussed below were carried forward to shape the research objectives for the study presented in this chapter.

There is very limited evidence available on the association between objectively measured PA and cognitive function in overweight/obese middle-aged adults. As described in Chapter 1, section 1.2.5, only a limited number of studies examining the relationship between PA and cognitive function have used objective measures of PA in non-elderly adults. These studies were conducted in pre-bariatric (morbidly) obese adults with comorbidities, limiting the application of the findings to patient samples of this demographic. Two studies in this area (Galioto et al., 2014; Langenberg et al., 2015) found limited support for an association between memory and MVPA, and also an interaction between low accumulated minutes of total PA, depression and working memory. Both samples examined were low active and it was suggested by the authors that there may not have been enough variability in the physical activity data

to detect effects on cognitive function outcomes. A further suggestion was that participants were not attaining sufficient PA to drive cognitive benefits.

Research in older adults indicates higher accumulated minutes of moderate-intensity and light-intensity predict variation in executive function and memory (Kerr et al., 2013; Makizako et al., 2014). In terms of cognitive preservation, in order to identify suitable PA behaviours for intervention, we must elucidate what specific components of PA are associated with variation in domain-specific cognitive outcomes. There is not enough data to make inferences regarding the type of PA (i.e. intensity) that confers the greatest benefit. The objective measurement of PA is essential to this investigation.

3.1.2 PA outcomes and implications for research

In order to explore or clarify the relationships between PA and other parameters (such as cognitive function or health) it is essential that PA is assessed accurately. Typically, accelerometer counts are summarised into individual summary statistics (daily MVPA, sedentary minutes, light-activity, etc). Collinearity between PA outcomes has been reported (Augustin et al., 2012) as the summaries of PA behaviour (sedentary, light, moderate, vigorous, total counts, etc) are not mutually exclusive. If only one summary (i.e. MVPA) is entered as a predictor in a model, adjustment for all other activity summaries (sedentary, light, etc) is required. However, this is problematic when the variables are not independent of one another as it results in parameter estimates with large variances that are unreliable. Additionally, because these variables are not independent of one another it is not appropriate to enter the summaries of PA levels simultaneously as predictors in a model. An approach is required that addresses the collinearity issue.

3.1.3 Inter- and intra-correlation of PA and health variables

The research described above highlights a potential relationship between PA and cognitive function, but it is apparent from chapter 1 that a variety of health markers also mediate this relationship. Body composition and fat distribution can vary greatly within overweight/obese samples. The sample for this study were all categorised as overweight/obese based on a BMI of at least 25 kg/m^2, however, variation in adiposity measures (WC, WHR, BF% and BMI) must be taken into consideration. This is particularly important as some characteristics, such as waist circumference

(indicative of abdominal obesity), are shown to exert a greater influence on health and also cognitive function when compared to more general measures of obesity (BF %, BMI). As described in (1.1.4), indices of body composition are also highly correlated indices of cardiometabolic health. Therefore, in addition to the overlapping variance of PA outcomes described in section 3.1.2, it is known that PA, body composition and markers of cardiometabolic health are correlated with each other also (Chapter 1). The issues highlighted in this short review helped to shape the statistical approach adopted for the study presented in this thesis chapter.

3.1.4 Summary

Habitual PA is known to have a positive relationship with cognitive function outcomes, however objective measures of PA are rarely used in research. It is not known whether specific facets of PA (i.e. time spent in intensity domains) are associated with domain-specific cognitive function outcomes. This area of research has largely been conducted in older adults, with only two studies examining this relationship in obese, non-elderly samples. The research by Galioto et al. (2014) and Langenberg et al. (2015) found very limited support for a relationship between PA and cognitive function outcomes. However, the samples were fairly homogenous in activity levels in that they were highly sedentary, perhaps making it difficult to detect cognitive function in relation to variance in PA. One thing to consider in this area of research is that PA has the capacity to moderate many of the health markers associated with cognitive decline (blood pressure, fasting glucose, adiposity). However, many of these show high degrees of correlation with each other and with PA outcome variables. Therefore, they should not be considered as distinct variables, rather the overall pattern they show should be explored.

3.2 Objectives and Hypotheses

The primary aim of the work in this chapter was to explore the relationship between cognitive function outcomes and markers of PA including sedentariness, body composition and health in overweight/obese middle-aged adults. Insufficient literature was available to make an a priori hypothesis regarding the relationship between objectively measured activity and domain-specific cognitive performance. Based on the empirical evidence reviewed in Chapter 1 and section 3.1, it was hypothesised that higher scores on tasks of executive function and verbal memory would be predicted by higher accumulated minutes of MVPA and LPA. A secondary objective

was to conduct exploratory analyses of the relationship between health/activity and additional cognitive domains (attention, working memory and spatial memory).

Objectives:

I. To explore the relationship between cognitive outcomes and PA in a sample of overweight/obese middle-aged adults, whilst controlling for age and IQ.

II. To identify the variables (individual or composite) which predict cognitive function within each cognitive domain.

3.3 Methods

3.3.1 Participants

The study sample consisted of males and females aged 30-60 years from the Leeds area who were recruited to take part in Studies 2 (Chapter 4) and 3 (Chapter 5). All participants were classed as overweight/obese (BMI of ≥25 kg/m^2) and low-active according to their average step count (~7235.8 steps/day) recorded over 7 days. As part of the exclusion criteria, all participants reported <2 30-minute sessions of moderate-intensity activity per week. Eligibility was assessed by the researcher (see screening procedure and inclusion/exclusion criteria described in Chapter 2 (section 2.2.3). Seventy three participants (11 males; 62 females) provided both accelerometer and cognitive function data. Of these, 6 returned accelerometers that had failed to record step count. Additionally, data for systolic blood pressure was missing for 1 participant and data for IQ was not recorded for 3 participants. Hence, the final sample consisted of 63 participants. Additional measures of fasting glucose and executive function (TMT and Stroop colour/word interference task) were obtained from those participants (n=51) who took part in study 2.

3.4 Experimental Design

The study conformed to a cross-sectional design. Measures of cognitive function, body composition, cardiometabolic health and physical activity were collected within

a 2-week time frame for each participant. These data were then utilised for all analyses presented in this chapter.

3.5 Experimental protocol

All testing took place in the School of Psychology, and each testing visit was completed within 90 minutes. Individuals meeting the study inclusion criteria for studies 2 and 3 were invited to the laboratory for a study familiarisation visit and administration of the practice cognitive test battery (Visit 1; see section 2.3.1). Between Visit 1 and Visit 2 all participants wore an accelerometer for a 7-day assessment of baseline PA level. Upon completion of the 7-day PA assessment, participants attended the lab for baseline testing visit (Visit 2, see Chapter 2, section 2.2.3) for assessment of cognitive function, body composition and, blood pressure. Fingertip capillary blood samples were collected for assessment of fasting glucose and insulin in a subsample (n=46) for study 3 (pedometer chapter). Figure 3.1 shows the study flow from study familiarisation to completion.

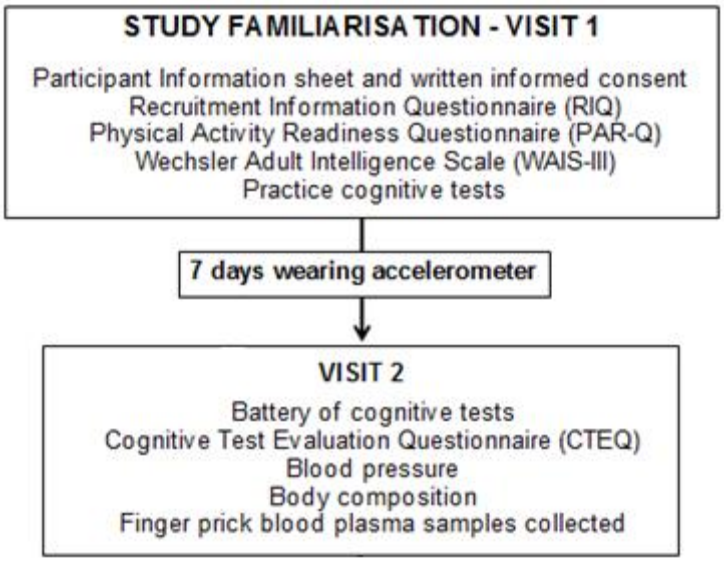

Figure 3.1 Study flow diagram

3.6 Study Procedures

3.6.1 Assessment of physical activity

Physical activity was assessed using a GT3X Actigraph accelerometer as previously described in section (Chapter 2, section 2.9). The PA outcomes that were generated were; daily accumulated minutes of sedentary (<99 CPM), LPA (100-1952 CPM), MPA (1952-5999 CPM) and VPA (>6000 CPM), and daily step count. In addition to these, fractionation of PA was explored by including the following variables: moderate/vigorous-intensity PA (MVPA) bout minutes (>10minutes), MVPA total counts (bouts>10 minutes), and sedentary bouts (SB) (>60 minutes).

3.6.2 Assessment of anthropometric indices

The measures of anthropometric indices were assessed as previously described in section (Chapter 2, section 2.8). The outcomes measured for this study were body fat percentage, body mass index (BMI), waist circumference (WC) and waist-hip ratio (WHR).

3.6.3 Assessment of blood pressure

Systolic and diastolic blood pressure were taken at the left arm using an automated Omron M7 BP with an appropriately sized cuff after participants had been seated for forty minutes. Three measures were taken with a minimum of one minute between measurement trials, and the average recorded. The IPSEC approved standard operating procedure (SOP) shows the procedure (IPSEC ref 00-0204, see Appendix 6.14.

3.6.4 Assessment of cognitive function

All participants attended the cognitive test sessions in a 12 hour fasted state. The tests and order of administration are shown in Table 3.1. All tests were administered for studies 2 and 3, and are therefore described in Chapter 2, section 2.4.

Table 3.1 Order of cognitive test presentation within the cognitive test battery

Cognitive test	Test duration (minutes)	Cognitive domain
1. Visual Spatial Learning Test▲	6	Spatial memory
2. Visual Verbal Learning Test*	12	Verbal memory
3. Corsi Block Tapping Test* (Computerised version)	4	Spatial working memory
4.Bakan Test*	6	Attention
5. Stroop (colour/word) *	3	Executive function
6. Trail Making Test (A&B) ▲	2	Executive function

* Test administered on computer (experimenter not present)

▲Test administered by hand by the experimenter

3.7 Ethical approval

Ethical approval for Study 1 was covered by ethical approval obtained for Studies 2 and 3 (see Chapter 2, section 2.3).

3.8 Analysis of data

All data were analysed using SPSS 21.0 (SPSS, Inc. Chicago, USA) and the significance (α-levels) were set as $p < 0.05$. All data were summarised, plotted as means (± SE) with boxplots produced to check for outliers.

To examine the relationship between anthropometric and physical activity outcomes, Pearson's correlation coefficients were performed. Because of the ratio of cases to variables, and the presence of multicollinearity, principal component analysis (PCA see section 3.8.1) was used to extract factors from the measures of anthropometry and physical activity. Multicollinearity among the predictor variables results in unstable parameter estimates, which greatly impacts on the prediction of the dependent variable in the regression model (Tabachnick & Fidell, 2007).The relationships apparent between the body composition and PA variables rendered them unsuitable for concomitant use in multiple regression models (MR) to predict cognitive function. Systolic blood pressure and fasting glucose were not correlated

with the PA/body composition measures so were retained as individual predictor variables. Hierarchical multiple linear regression analyses (see section 3.8.2) were performed for each individual cognitive outcome variable. This was to establish the extent to which the anthropometric and physical activity principal components (PCs) explained the variance in cognitive function outcomes, whilst controlling for IQ and age, which are known to be important predictors of cognitive function (Diaz-Asper, Schretlen, & Pearlson, 2004; Fjell et al., 2013).

3.8.1 Principal component analysis (PCA)

PCA is a data reduction technique which works by first examining the structure of a high-dimensional data set and then projecting the observations onto principal components (Croux & Haesbroeck, 2000). After mapping the original data, it is transformed (by rotating the axes along which the variables included are plotted) in a linear fashion to a new co-ordinate system, in a lower dimensional space (Gharibnezhad, Mujica, & Rodellar, 2015). Put simply, it extracts the most relevant information from an often intercorrelated data set by reducing it to a lower dimension and revealing the collection of structures which underpin the original high-dimensional data set (Shlens, 2014).

PCA produces eigenvalues, ordered in magnitude from largest to smallest, which represent variance explained along unobserved dimensions (Dinno, 2014). Each eigenvalue represents a portion of the total standardised variance, therefore, to account for all the variance in the data set PCA generates the same number of PCs as there are observed variables (Tabachnick & Fidell, 2007). In this case, a maximum of 12 PCs would explain 100% of the variance in the 12 body composition and physical activity variables. Orthogonal PCs maximise the variance explained (from the 12 original body composition and PA variables), the largest portion of data variability is explained by the first PC, and the subsequently extracted PCs describe the remaining portions of data variability in descending order (Stanimirova, Daszykowski, & Walczak, 2007).

The Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy and Bartlett's test of sphericity were performed to confirm the appropriateness of PCA on this dataset. Varimax rotation was used to extract orthogonal principal components (PCs) (Tabachnick & Fidell, 2007). Twelve variables (4 body composition and 8 PA variables) were compressed, via dimension reduction, to 4 principal components (PCs). The components are distinct from each other, but collectively represent all of

the variance in the 12 body composition and PA variables. Twelve components would explain all (100%) of the variance in the 12 body composition and PA variables, however, this defeats the objective of dimension reduction where the aim is to represent the variables which explain maximum variance in the most parsimonious manner. The number of components to retain was decided using empirical guidelines described below and confirmed by scree plots and parallel analysis.

Selection of the number of factors to be retained for analysis was initially guided by the size of the eigenvalues and the Scree test following varimax rotation (Cattell, 1966), which shows eigenvalues plotted against the components. Eigenvalues represent the variance contributed to the PC after extraction (Tabachnick & Fidell, 2007). Any component with an eigenvalue lower than 1 is deemed as less important since it accounts for only a small proportion of the variance in the sample. Factor loadings indicate the contribution of each original variable to the variance accounted for by a principal component. For inclusion into a principal component, loading values > 0.5 are required, and a higher loading score indicates a higher contribution. Factor loadings above .71 are considered excellent (Comrey & Lee, 2013).

3.8.1.1 Parallel analysis

The widely used Scree test and eigenvalues-greater-than-one rule which are used to determine the number of PCs to extract, are both simplistic, vulnerable to overestimation of components and less adequate in small sample sizes (O'Connor, 2000; Tabachnick & Fidell, 2007). A recommended procedure to decide upon the number of components to retain is Parallel Analysis (Horn, 1965). This three-step procedure involves randomly generating data sets that parallel the original data set (in terms of number of cases and variables). PCA is then repeatedly performed on the randomly generated data sets whilst noting the eigenvalues for each analysis (O'Connor, 2000). Finally, the average eigenvalues for each component from the Parallel Analysis are then compared to the results from the original analysis (Tabachnick & Fidell, 2007). Only eigenvalues from the original data set that exceed the values from the Parallel Analysis are retained, this is usually set as the 95th percentile (Cota, Longman, Holden, Fekken, & Xinaris, 1993; Glorfeld, 1995).

3.8.2 Hierarchical multiple linear regression

A series of hierarchical multiple linear regression analyses were performed to establish the extent to which anthropometric and PA PCs explained the variance in

cognitive function outcomes, whilst controlling for IQ and age. For each cognitive outcome, variables were entered into the regression model in blocks. In every multiple regression model, age and IQ were entered in the first block since these were considered causally prior. The 4 PCs and SBP (which did not show multicollinearity with other outcomes and therefore, was not included in the PCA) were added in the second block. Standardised residual plots were inspected for deviations from normality and MR repeated on the Box Cox transformed variables as appropriate, with Lambda reported where used. Untransformed data are presented in figures for clarity. Variance inflation factor (VIF) values were inspected to confirm that collinearity had been resolved. In every MR output, VIF for all predictor variables was low (1 ± 0.5), and therefore is not reported in tables of results.

For clarity, the whole analytical approach adopted for this study is summarised in the schematic below (Figure 3.2).

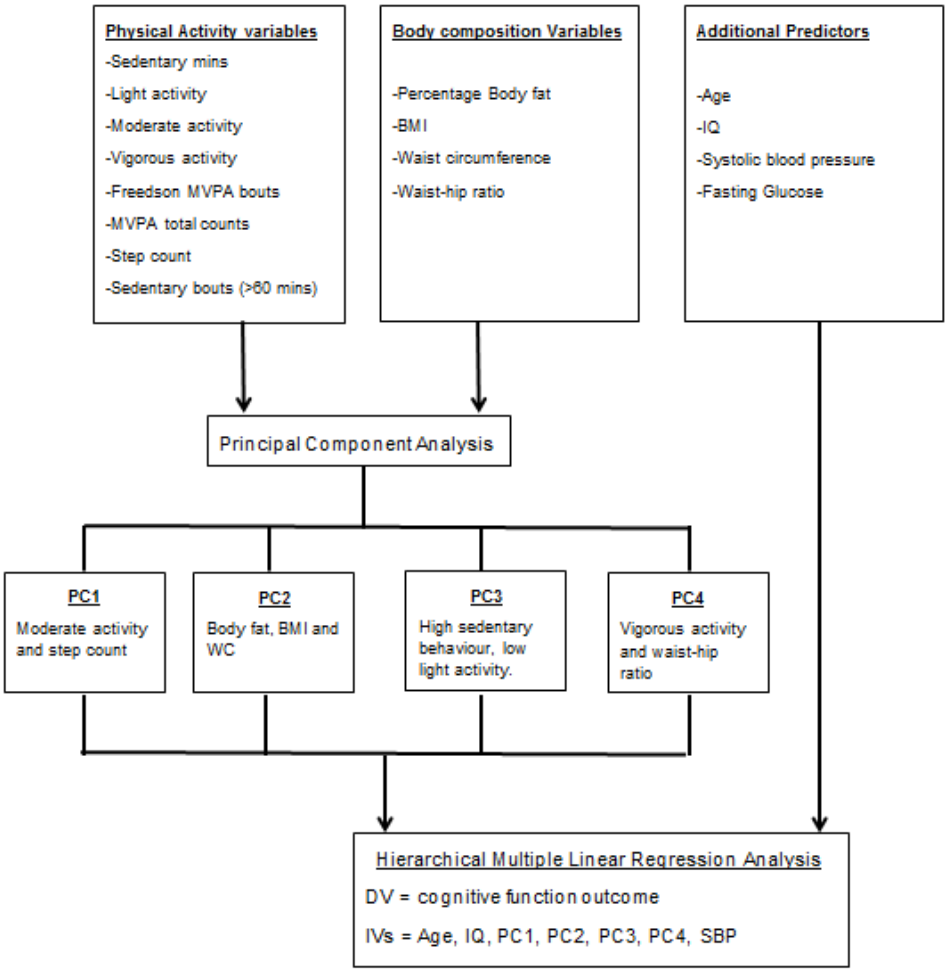

Figure 3.2 Schematic of statistical analysis

3.9 Results

3.9.1 Participant characteristics

Participant characteristics for those participants included in the analysis are shown in Table 3.2. The sample consisted of 63 participants (males = 10; females = 53) aged 30-60 years (mean age: 46.1 ± 7.0 years). All participants included in the analysis were overweight/obese (BMI 32.7 ± 4.4 kg/m^2; body fat percentage 41.6 ± 6.6 %). Systolic (SBP) blood pressure values ranged from healthy (80-120 mmHg) to hypertensive (140+mmHg). Of the sample with glucose data available (n=46), 72.7%

had values in the healthy range (3.6-5.5mmol/L) and 27.3% had values that exceeded the upper limit of the healthy range.

Table 3.2 Participant Characteristics

	Males (n=10)	**Females (n=53)**		**Total sample**			
Characteristic	Mean ± SD	Mean ± SD	p	**n**	**Mean ± SD**	**min**	**max**
Age (yrs)	48.4 ± 6.9	45.6 ± 7.0	.242	**63**	**46.1 ± 7.0**	**30**	**57**
BMI (kg/m^2)	31.8 ± 4.1	32.9± 4.4	.500	**63**	**32.7 ± 4.4**	**25.5**	**44.5**
Body fat percentage (%)	30.5 ± 3.2	43.7 ± 4.7	.000	**63**	**41.6 ± 6.6**	**24.3**	**54.5**
WC (cm)	114.4 ± 8.1	108.8 ± 11.3	.143	**63**	**109.7 ± 11.0**	**86**	**133**
WHR	1.01 ± 0.1	0.94 ± 0.1	.006	**63**	**0.95 ± 0.1**	**.77**	**1.11**
SBP (mmHg)	130.9 ± 14.3	125.0 ± 14.3	.240	**63**	**126.0 ± 14.3**	**99**	**162**
DBP (mmHg)	92.2 ± 10.6	84.6 ± 8.9	.019	**63**	**86.18 ± 10.1**	**68**	**109**
Fasting Glucose[1] (mmol/L)	5.5 ± 0.8	5.5 ± 1.6	.992	**46**	**5.43 ± 1.5**	**4.15**	**10.50**
IQ (score)	122.0 ± 9.6	113.1 ± 12.8	.042	**63**	**114.52 ± 12.7**	**69**	**135**

[1]NB Fasting glucose available in sub-sample only (n=46). DBP=diastolic blood pressure, SBP=systolic blood pressure, min=minimum, max=maximum, WC=waist circumference, WHR=waist-hip ratio

Significant gender differences are apparent from Table 3.2 which shows that percentage body fat was significantly higher in females (43.7 ± 4.7 %) than in males (30.5 ± 3.2 %; $t(61)=-8.54$, $p<.001$). Waist hip ratio was significantly lower in females (0.94 ± 0.1) than in males (1.01 ± 0.1; $t(61)=2.83$, $p<.01$). Diastolic blood pressure was significantly lower in females (84.6 ± 8.9 mmHg) than in males (92.2 ± 10.6 mmHg; $t(61)=2.41$, $p<.05$). IQ was significantly higher in males (122.0 ± 9.6) than females (113.1 ± 12.8; $t(61)=2.07$, $p<.05$). However, the difference in sample size between genders should be noted.

Table 3.3 shows the Wechsler Adult Intelligence Scale (Wechsler, 1997) classifications and the percentage of the study sample that fell within each category. Of the sample, 41.2% were classed as above average (superior or very superior), 54.0% achieved average scores (average or high average). Only 4.8% obtained

scores below average (low average or extremely low). The majority of the sample (67.1%) were categorised as high average to very superior.

Table 3.3 Participant IQ classifications[1]

WASI IQ score	classification	% of sample in category
130 and above	very superior	7.9
120-129	superior	33.3
110-119	high average	28.6
90-109	average	25.4
80-89	low average	3.2
70-79	borderline	0.0
69 and below	extremely low	1.6

[1] Classification based on the Wechsler Adult Intelligence Scale (Wechsler, 1997)

3.9.2 Objectively measured physical activity (7 days)

Table 3.4 shows the objectively measured physical activity behaviours of the sample (n=63) over a 7-day period. Accelerometers were worn for an average of 6.3 ± 1.0 days. Average daily wear time was 807.3 ± 90.4 minutes, this equates to approximately 13.5 hours. The table shows daily total accumulated minutes (irrespective of bout durations) of sedentary, light, moderate and vigorous activity. Sixty-six percent of waking hours were spent sedentary, 29.6 % spent in LPA, 4.2% spent in MPA and 0.1% of daily time was spent in VPA. In terms of vigorous activity 75.3% were accumulating 0 minutes, only 2% were accumulating >5 minutes daily, the maximum was 9.3 minutes daily. When moderate and vigorous activity were combined into one class of behaviour (MVPA) and observed in bouts (≥10 minutes), average daily bouts were ≤1 bout. Only 3 participants (4.8%) achieved the recommended 30 minutes of daily MVPA (accumulated through three 10-minute bouts). Thirty three percent were achieving 1-3 bouts daily. Sixty-two percent (n=39) were doing less than one bout. Sedentary behaviour (SB) was also looked at in bouts (>60 minutes) to look at impact of prolonged sedentary time. The sample had a daily average of 1.6 bouts (>60 mins) per participant, with 14.3% participants accumulating nearly 4 hour-long bouts each day. In terms of step count, 60.3% of the sample were classed as sedentary or low active (below 7500 steps). However, some were highly sedentary (under 2300 steps) and 14.3% were active/highly active (10,000+ steps).

Table 3.4 Objectively measured physical activity characteristics of participants (n=63)[1]

	Males (n=10)	**Females (n=53)**		**Total sample (n=63)**		
Characteristic	Mean ± SD	Mean ± SD	p	**Mean ± SD**	**min**	**max**
Time sedentary (mins/day)	584.3 ± 73.2	524.8± 84.7	.042	**534.2 ± 85.3**	**303.9**	**722.0**
LPA (mins/day)	183.7 ± 61.7	249.3 ± 75.9	.013	**238.9 ± 77.3**	**124.2**	**433.7**
MPA (mins/day)	39.5 ± 18.0	32.6 ± 18.5	.278	**33.7 ± 18.5**	**1.8**	**84.0**
VPA (mins/day)	1.4 ± 3.0	0.2 ± 0.8	.019	**0.5 ± 1.4**	**0.0**	**9.3**
MVPA daily (bouts>10 mins)	1.1 ± 0.8	0.8 ± 0.8	.251	**0.9 ± 0.8**	**0.0**	**3.17**
MVPA total counts (bouts > 10 mins)	443487.6 ± 410762.5	286719.0 ± 309889.3	.169	**311602.9 ± 329195.4**	**0.0**	**1349301**
Daily steps	6832 ± 2193.1	7439.5 ± 3216.3	.571	**7343.2 ± 3069.8**	**2285.7**	**17062.4**
Sedentary bouts (> 60 mins)	2.21 ± 1.2	1.52 ± 0.9	.042	**1.6 ± 1.0**	**0.0**	**3.86**
Wear days	6.3 ± 1.0	6.3 ± 0.9	.860	**6.3 ± 1.0**	**4.0**	**8.0**
Wear time (mins)	809.1 ± 81.9	807.0 ± 92.6	.947	**807.3 ± 90.4**	**631.3**	**1005.0**

[1] Sample size for all variables was as shown, except for daily step count. Total sample size for this variable was n=67 (n = 10 for males; n=57 for females). LPA-light-intensity PA, min=minimum, max=maximum, MPA=moderate-intensity PA, VPA=vigorous-intensity PA

The pattern of activity in this sample is similar to that found in a large U.S sample (Tudor-Locke et al., 2010), where the daily percentage of time spent in sedentary, low/light (combined), moderate and vigorous activities was 56.8%, 40.4%, 2.6% and 0.2% respectively. Only 3.2% of U.S adults achieved the public guidelines. Within the overweight category, average steps per day was ~6,900, with 25.3 minutes of moderate activity and 5.3 minutes of vigorous activity accumulated daily. Within the obese category, average steps per day were ~5,800, and 17.3 minutes of moderate activity and 3.2 minutes of vigorous activity were accumulated daily.

Significant gender differences in some of the PA outcomes are apparent from Table 3.4. Total accumulated sedentary time was higher in males (584.3 ± 73.2 mins/day) than in females (524.8± 84.7 mins/day; $t(61)=2.08$, $p<.05$). Total LPA was higher in females (249.3 ± 75.9) than in males (183.7 ± 61.7; $t(61)=-2.57$, $p<.05$). Total VPA

was significantly higher in males (1.4 ± 3.0 mins/day) than females (0.2 ± 0.8 mins/day; $t(61)=2.40$, $p<.05$). Prolonged sedentary bouts (>60 minutes) were significantly higher in males (2.21 ± 1.2 bouts) than females (1.52 ± 0.9 bouts; $t(61)=2.07$, $p<.05$. Once again, it must be noted that there are more females than males in the sample.

3.9.3 Inter- and intra-correlation of health and physical activity predictor variables

Table 3.5 shows correlation within and between subclasses of predictor variables prior to principal component extraction. As expected, PA variables were related to other PA variables. The strongest relationships were observed between step count, moderate-intensity activity (all three measures) and sedentary behaviour. The table also shows body composition variables were related to step count, and moderate-intensity and vigorous-intensity activity. Systolic blood pressure and fasting glucose did not significantly correlate with any body composition or physical activity variables, and were therefore not incorporated into PCA. Age and IQ showed limited weak correlations with the body composition or physical activity variables.

Table 3.5 Inter- and intra-correlations of relevant participant characteristics

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. BMI	-															
2. percentage body fat	**.654****	-														
3. Waist circumference	**.813****	**.437****	-													
4. Waist-hip ratio	.129	-.093	**.558****	-												
5. Time sedentary (mins/day)	-.183	**-.327****	-.074	.094	-											
6. LPA (mins/day)	.018	.202	-.050	.011	**-.382****	-										
7. MPA (mins/day)	-.024	-.172	-.078	-.207	-.138	-.102	-									
8. VPA (min/day)	-.162	**-.241***	-.022	.052	.018	-.150	**.231***	-								
9. MVPA >10 bout (mins/day)	-.137	-.223	-.150	-.146	-.040	-.197	**.840****	**.289***	-							
10. MVPA total counts	-.222	**-.281***	-.194	-.131	.014	-.160	**.781****	**.379****	**.918****	-						
11. Daily step count	**-.357****	-.214	**-.358****	-.155	**-.242***	**.351****	**.518****	-.039	**.408****	**.458****	-					
12. Sedentary bouts (> 60 mins)	-.167	**-.312****	-.060	.055	**.714****	**-.620****	-.066	.111	.129	.174	**-.307***	-				
13. Age	-.193	-.238	-.092	.206	.224	.119	-.174	**-.311****	-.078	-.136	-.026	.076	-			
14. IQ	-.131	**-.332****	.035	.075	**.400****	.045	-.005	.031	.059	.172	.045	**.241***	.054	-		
15. SBP	.148	-.066	.199	.199	-.191	.125	.052	-.016	-.023	-.003	.140	-.139	.225	.072	-	
16. Fasting glucose	-.095	-.102	-.022	.225	.126	.148	-.163	-.104	-.090	-.131	.050	-.022	.194	-.011	.220	-

p<0.05,p<0.01;*** p<0.001,* [1]*Numbers in the title row correspond to the numbered predictor variables in the first column. BMI=body mass index,* LPA-light-intensity PA, MPA=moderate-intensity PA, *SBP=systolic blood pressure,* VPA=vigorous-intensity PA,

The pattern of correlation coefficients in Table 3.5 suggests multicollinearity amongst the variables that are hypothesised to predict cognitive function. Thus these predictors are not suitable to be included as individual predictors in multiple regression analysis.

3.9.4 Principal component analysis

Principal component analysis (PCA) removes the multicollinearity problem by simplifying the complexity of the relationship between predictor variables and reducing these correlated variables to principal components (PCs) to allow the variables to be used as composite predictors. The KMO measure of sampling adequacy was > 0.6, confirming that the sample size was adequate to apply PCA. Four principal components were retained for subsequent analysis since these had eigenvalues >1 and the Scree plot in Figure 3.3 showed a change in the slope of the line after the fourth factor. Parallel analysis (represented in Figure 3.3 by the red dotted line) was also performed to assess adequacy of extraction.

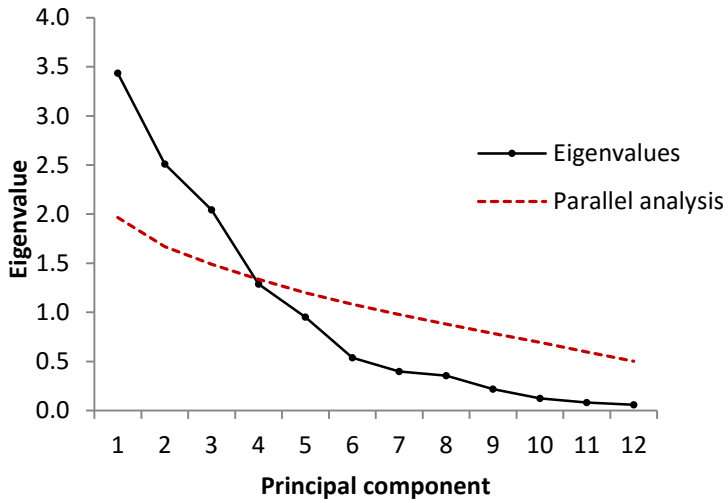

Figure 3.3 Scree plot and parallel analysis of eigenvalues for all physical activity and body composition factors.

The parallel analysis indicated that the fourth component fell below the 95th percentile criterion, and hence technically only 3 components should have been retained. However, this would have meant that one of the principal components theoretically important to this thesis which reflected central adiposity and VPA would have been

lost. The decision was therefore, made to retain four components and interpret these with caution.

Table 3.6 shows the results of the PCA. Four components (PC1-PC4) were retained, each explaining more than 10% of the variance. The cumulative variance explained by the 4 principal components was 77.3%. Table 3.6 shows the eigenvalues and variance explained by each PC, and the factor loadings of the variables within each principal component. The four components were labelled as follows (see Table 3.6 for variable loadings on each PC):

- PC1 (MPA + steps) comprised of 'MPA', 'MVPA bouts' and 'MVPA total counts' which all loaded very highly on this component (>.90), and step count which showed a moderate loading (.50).
- PC2 (adiposity) comprised of 'BMI', 'WC' and 'body fat' which all loaded highly on this component (>.70). Step count, in addition to loading on PC1, also makes a contribution to PC2 (-.43).
- PC3 (SB) comprised of 'sedentary bouts' and 'time sedentary' which had high positive loadings (>.80) on this component, and also 'LPA' which had a high negative loading (-.77) on this component. Step count also makes a contribution to PC3 (-.48).
- PC4 (WHR + VPA) comprised of 'WHR' which had a high positive loading on this component (.82), and also 'VPA' which loaded to a lesser extent on this component (.58). 'WC' and 'body fat' in addition to loading on PC2, also make smaller contributions PC4 (.46 and -.37 respectively).

Table 3.6 Rotated factor loadings for each PC

Variable	Loadings after Varimax rotation[1]			
	PC1 "MPA+steps"	PC2 "Adiposity"	PC3 "SB"	PC4 "WHR+VPA
MPA (mins/day)	**.94**	.03	-.10	-.01
MVPA >10 bout (mins/day)	**.95**	-.05	.04	-.01
MVPA total counts (bouts > 10 mins)	**.93**	-.15	.04	.04
Step count	**.50**	-.43	-.48	-.05
BMI	-.01	**.94**	-.02	-.01
WC	-.08	**.84**	.03	.46
Body fat (%)	-.14	**.75**	-.24	-.37
Sedentary bouts (>60min)	-.02	-.12	**.90**	.03
LPA (min/day)	-.16	-.12	**-.80**	.01
Time sedentary (mins/day)	-.17	-.19	**.77**	.06
WHR	-.24	.20	-.03	**.82**
VPA (mins/day)	.19	-.13	.06	**.58**
Eigenvalues of PC	3.44	2.51	2.04	1.29
% of variance explained by PC	28.62	20.92	17.02	10.72
Cumulative % variance	28.62	49.54	66.56	77.28

[1] Values represent loadings on each principal component.[2.] Loadings printed in green are intended to highlight substantial/meaningful loadings on more than one PC

3.9.5 Predictors of cognitive function

Multiple linear regression analyses were performed for each cognitive test outcome. For each two models were produced. Model 1 included only the covariates, IQ and age added in the first block as these are known to be causally prior to cognitive function. In the second model SBP and the 4 PCs were added in a second block. For brevity, model 2 is reported unless this failed to reach significance, in which case the results from model 1 are reported in tables in the appendices. Data on fasting glucose was available in 46 participants. However, when entered into model 2, the accumulated missing data from the 5 entered variables reduced the sample size for analysis to 38 (with 8 predictors). Therefore, fasting glucose was also omitted from the analysis.

3.9.5.1 Verbal memory

Five outcomes were generated by the visual verbal learning test (VVLT); total acquisition, delayed recall, recognition, proactive interference and retroactive interference. See section 2.4.1.1 for details on how the scores are derived for the VVLT outcomes.

3.9.5.1.1 Total acquisition (total words recalled)

Model 1 was significant, $F(2,61)=5.08$, $p < .01$, and explained 12% of the variance in total words recalled (adjusted $R^2 = .12$). The β coefficients (Table 3.7) indicated that IQ was a significant predictor of words recalled ($\beta = .36$, $t= 3.01$, $p< .01$). Translated in terms of number of words recalled, for every 1.0 point increase in IQ score, there is a change of 0.17 words, $B = 0.17$, $p<.001$, so 10 points difference in IQ (one standard deviation) is likely to produce almost 2 more words recalled. Age did not significantly predict total words recalled.

Model 2 just failed to reach statistical significance, $F(7, 61)=2.13$, $p = .056$, and accounted for 12% of the variance in total words recalled (adjusted $R^2 =.12$). The beta coefficients for the PCs and SBP were non-significant. The relationship between IQ and total words recalled remained significant following inclusion of the PCs and systolic blood pressure, $\beta= 0.32$, $p < 0.05$.

Table 3.7 Multiple linear regression analyses of relationship between immediate verbal memory (total acquisition) and health parameters

		Immediate verbal memory: total acquisition				
Model		**B**	**SE B**	**β**	**t**	**Sig**
1						
	Constant	19.39	7.65		2.54	.01
	Age	-0.14	0.10	-0.16	-1.34	.19
	IQ	**0.17**	**0.06**	**0.36**	**3.01**	**.00**
2						
	Constant	32.31	9.89		3.27	.00
	Age	-0.13	0.11	-0.15	-1.16	.25
	IQ	**0.15**	**0.06**	**0.32**	**2.43**	**.02**
	SBP	-0.09	0.05	-0.21	-1.59	.12
	PC1	0.13	0.73	0.02	.182	.86
	PC2	-0.92	0.84	-0.14	-1.09	.28
	PC3	0.42	0.73	0.07	.578	.57
	PC4	0.27	0.73	0.05	.371	.71

Model 1: adjusted R^2 = .12; F(2,61)=5.08, p< .01
Model 2: adjusted R^2 = .12; F(7, 61)=2.13, p= .056

3.9.5.1.2 Delayed recall

For VVLT delayed recall neither model was significant, F(2,61)=2.33, ns and F(7,61)=1.06, ns, respectively (see Appendix 6.15).

3.9.5.1.3 Recognition List A

The standardised residuals deviated from normality, and were transformed using Box Cox transformation (λ = 1.2). Model 1 was significant, F(2,61)=6.90, p < .01, and explained 16% of the variance in recognition of List A (adjusted R^2 =.16).

In model 2, the inclusion of the PCs and blood pressure resulted in a model that approached significance, F(7,61) = 2.08, p = .062 and explained 10% of the variance (adjusted R^2 =.10). Table 3.8 shows that recognition score was predicted by IQ (β = .29, t= 2.27, p< .05) and age (β = -.324, t= -2.60, p< .01). This translates to an increase of 0.11 words recognised for every 1.0 point increase in IQ score (B=0.12, p<.01), and a decrease of 0.23 words for every 1.0 year increase in age (B=-0.23, p<.01). The coefficients for the PCs and SBP were not significant.

Table 3.8 Multiple linear regression analyses of relationship between verbal recognition and health parameters

		Recognition List A (n=62)				
Model		**B**	**SE B**	**B**	**t**	**Sig**
1						
	Constant	12.61	5.94		2.12	.04
	Age	**-0.22**	**0.08**	**-0.32**	**-2.74**	**.01**
	IQ	**0.12**	**0.04**	**0.32**	**2.75**	**.01**
2						
	Constant	10.31	7.88		1.31	.20
	Age	**-0.23**	**0.09**	**-0.34**	**-2.60**	**.01**
	IQ	**0.11**	**0.05**	**0.29**	**2.27**	**.03**
	SBP	0.03	0.04	0.10	0.78	.44
	PC1	0.05	0.58	0.01	0.09	.93
	PC2	0.03	0.67	0.01	0.04	.97
	PC3	0.47	0.59	0.10	0.81	.42
	PC4	0.25	0.59	0.05	0.43	.67

Model 1: adjusted R^2 = .16; F(2,61)= 6.90, p< .01
Model 2: adjusted R^2 = .10; F(7,61)= 2.08, p= .06

3.9.5.1.4 Proactive Interference

The scoring of proactive interference is described in Chapter 2, section 2.5.1.1, but a high score is not desirable (indicates greater proactive interference experienced). Neither model 1 nor model 2 were significant, F(2,61)= 1.32, ns, and F(7,61)= .50, ns, respectively (see Appendix 6.16).

3.9.5.1.5 Retroactive Interference

The scoring of retroactive interference is described in Chapter 2, section 2.5.1.1, but a high score is not desirable (indicates greater retroactive interference experienced). Model 1 was significant, F(2,60) = 3.67, p = .03, and explained 08% of the variance in retroactive interference(adjusted R^2 =.08). Age significantly predicted retroactive interference score (β=.32, t=2.67, p<.01). This translated to a .10 increase in retroactive interference score for every 1.0 year increase in age (B = .10, p< .01). IQ did not significantly predict retroactive interference. Model 2 was not significant, F(7,60) = 1.27, ns, see Appendix 6.17.

3.9.5.2 Spatial Memory

Four outcomes were generated by the visual spatial learning test; designs recalled, locations recalled, combined designs and locations recalled, delayed recall (designs and locations).

3.9.5.2.1 Designs

For VSLT designs, model 1 was significant, F(2,54) = 4.85, p< .01, and explained 13% of the variance in spatial memory (designs) (adjusted R^2 =.13). Designs recalled were predicted by age (β = -.27, t= -2.10, p< .05) and IQ (β = .32, t= 2.48, p< .05). This translates to a .10 decrease in designs score for each 1.0 year increase in age (B=-.11, p<.05) and a 0.07 increase in design for every 1.0 point increase in IQ score (B=0.07, p<.05). Model 2 was not significant, F(7,54) = 1.77, ns, see Appendix 6.18.

3.9.5.2.2 Locations

For VSLT locations, model 1 approached significance, F(2,54)= 2.94, p= .06, and explained 7% of the variance in spatial memory (locations) (adjusted R^2 =.07). Locations recalled were predicted by age (β = -.29, t= -2.17, p< .05). This translates to a decrease in 0.18 locations score for every 1.0 year increase in age (B=-0.18, p<.05). IQ was not a significant predictor in model 1. Model 2 was not significant, F(7,54) = 1.10, ns, see Appendix 6.19.

3.9.5.2.3 Designs and locations

For VSLT designs/locations model 1 approached significance, F(2,54)= 5.12, p<.01, and explained 13% of the variance in spatial memory (designs/locations), adjusted R^2 =.13. Designs/locations score was predicted by age (β = -.33, t= -2.61, p< .01) and IQ (β = -.26, t= -2.08, p< .05). This translates to a 0.26 decrease in designs/locations score for every 1.0 year increase in age (B=-0.26, p<.05) and a 0.11 increase in designs/location score for every 1.0 point increase in IQ score (B=0.11, p<.05). Model 2 was not significant, F(7,54) = 1.71, ns, see Appendix 6.20.

3.9.5.2.4 Delayed designs and locations

Model 1 approached significance, F(2,54)= 3.01, p=.06, and explained 7% of the variance in VSLT delayed (designs/locations) (adjusted R^2 =.07). Model 2 approached significance, F(7,54) = 2.13, p= .06 and explained 13% of the variance (adjusted R^2 =.13). Delayed recall of designs/locations was predicted by PC3 “SB” (β= .31, t= -2.37, p< .05 and age (β= -.34, t= -2.49, p< .05), as indicated in Table 3.9. In terms of delayed designs/locations score this translates to a 0.79 increase for every 1.0 point increase in PC3 factor score (B=0.79, p<.05) and a 0.12 decrease for every 1.0 year increase in age (B=-.012, p<.05).

Table 3.9 Multiple linear regression analyses of relationship between VSLT designs and locations (delayed) and health parameters

		VSLT delayed (designs/locations) (n=58)				
Model		**B**	**SE B**	**β**	**t**	**Sig**
1	Constant	3.50	3.50		1.00	.32
	Age	**-0.09**	**0.05**	**-0.26**	**-1.99**	**.05**
	IQ	0.04	0.03	0.21	1.61	.11
2	Constant	6.24	4.24		1.47	.15
	Age	**-0.12**	**0.05**	**-0.34**	**-2.49**	**.02**
	IQ	0.02	0.03	0.10	0.76	.45
	SBP	0.01	0.02	0.05	0.34	.73
	PC1	-0.35	0.32	-0.14	-1.09	.28
	PC2	-0.57	0.38	-0.21	-1.50	.14
	PC3	**0.79**	**0.33**	**0.31**	**2.37**	**.02**
	PC4	0.30	0.31	0.13	0.96	.34

Model 1: adjusted R^2 = .07; F(2,54) = 3.01, p= .058
Model 2: adjusted R^2 = .13; F(7,54) = 2.13, p = .058

3.9.5.3 Attention

Four outcomes were generated by the rapid visual information processing (RVIP) task; total correct, reaction time of correct, missed targets and false positive responses.

3.9.5.3.1 Total correct

Model 1 approached significance, F(2,61)= 2.60, p=.08, and explained 5% of the variance in Bakan total correct (adjusted R^2 =.05). Model 2 was significant, F(7,61) = 2.41, p< .05 and explained 14% of the variance (adjusted R^2 =.14). Total correct score was predicted by PC2 “Adiposity” (β= -.30, t= -2.31, p< .05) and PC4 “WHR + VPA” (β= .27, t= 2.22, p< .05) as indicated in Table 3.10. This translates to a 2.72 increase in total correct score for every 1.0 point increase in PC4 factor score (B=2.72, p<.05) and a 3.21 decrease in total correct score for every 1.0 point increase in PC2 score (B=-3.31, p<.05).

Table 3.10 Multiple linear regression analyses of relationship between Bakan total correct and health parameters

		Bakan total correct (n=62)				
Model		**B**	**SE B**	**β**	**t**	**Sig**
1	Constant	0.20	14.32		0.01	.99
	Age	-0.11	0.18	-0.07	-0.59	.55
	IQ	**0.25**	**0.11**	**0.28**	**2.26**	**.03**
2	Constant	25.68	17.23		1.49	.14
	Age	-0.21	0.19	-0.15	-1.12	.27
	IQ	0.17	0.11	0.20	1.56	.12
	SBP	-0.10	0.09	-0.14	-1.08	.28
	PC1	-0.84	1.21	-0.08	-0.69	.49
	PC2	**-3.21**	**1.39**	**-0.30**	**-2.31**	**.03**
	PC3	0.60	1.22	0.06	0.49	.62
	PC4	**2.72**	**1.22**	**0.27**	**2.22**	**.03**

Model 1: adjusted R^2 = .05; F(2,61) = 2.60, p= .08
Model 2: adjusted R^2 = .14; F(7,61) = 2.41, p< .05

3.9.5.3.2 Reaction time for total correct

Model 1 approached significance, F(2,61)= 3.03, p= .056 and explained 6% of the variance, adjusted R^2= .06. Model 2 was significant, F(7,61) = 2.32, p< .05 and explained 13% of the variance (adjusted R^2 =.13). Reaction time (for total correct) was predicted by PC3 (Sedentary behaviour) (β= .29, t= 2.29, p< .05), as indicated by Table 3.11. This translates to 14.59 ms increase in reaction time for every 1.0 point increase in PC3 factor score (B=14.59, p<.05).

Table 3.11 Multiple linear regression analyses of relationship between Bakan reaction time (correct) and health parameters

		Reaction time of hits (n=62)				
Model		**B**	**SE B**	**β**	**t**	**Sig**
1	Constant	402.18	73.74		5.45	.00
	Age	**2.20**	**0.93**	**0.30**	**2.37**	**.02**
	IQ	-0.56	0.57	-0.12	-0.99	.33
2	Constant	326.24	89.75		3.64	.00
	Age	**2.31**	**0.98**	**0.31**	**2.36**	**.02**
	IQ	-0.70	0.58	-0.15	-1.21	.23
	SBP	0.70	0.47	0.19	1.48	.14
	PC1	3.23	6.32	0.06	0.51	.61
	PC2	9.17	7.26	0.16	1.26	.21
	PC3	**14.59**	**6.37**	**0.29**	**2.29**	**.03**
	PC4	-5.93	6.36	-0.12	-0.93	.36

Model 1: adjusted R^2 = .06; F(2,61) = 3.03, p= .056
Model 2: adjusted R^2 = .13; F(7,61) = 2.32, p< .05

3.9.5.3.3 Misses

Model 1 approached significance, F(2,61)= 2.64, p=.08, and explained 5% of the variance in Bakan misses (adjusted R^2 =.05). Model 2 was significant, F(7,61) = 2.41, p< .05 and explained 14% of the variance (adjusted R^2 =.14). The number of missed responses was predicted by PC2 "Adiposity" (β= -.29, t= -2.30, p< .05) and PC4 "WHR + VPA" (β= -.27, t= -2.22, p< .05), as indicated by Table 3.12. This translates to a 3.2 increase in misses for every 1.0 point increase in PC2 factor score (B= 3.2, p<.05) and a 2.7 decrease in misses for every point 1.0 increase in PC4 factor score (B=-2.7, p<.05).

Table 3.12 Multiple linear regression analyses of relationship between Bakan misses and health parameters

		Bakan misses (n=62)				
Model		**B**	**SE B**	**β**	**t**	**Sig**
1	Constant	59.87	14.29		4.19	.00
	Age	0.11	0.18	0.08	0.61	.55
	IQ	**-0.25**	**0.11**	**-0.29**	**-2.28**	**.03**
2	Constant	34.45	17.21		2.00	.05
	Age	0.21	0.19	0.15	1.13	.27
	IQ	-0.18	0.11	-0.20	-1.58	.12
	SBP	0.10	0.09	0.14	1.09	.28
	PC1	0.82	1.21	0.08	0.68	.50
	PC2	**3.20**	**1.39**	**0.29**	**2.30**	**.03**
	PC3	-0.60	1.22	-0.06	-0.49	.62
	PC4	**-2.70**	**1.22**	**-0.27**	**-2.22**	**.03**

Model 1: adjusted R^2 = .05; F(2,61 = 2.64), p= .08
Model 2: adjusted R^2 = .14; F7,61)= 2.41, p< .05

3.9.5.3.4 False Positives

The standardised residuals deviated from normality, and were transformed using Box Cox transformation (λ = 0.6). Neither model 1 nor model 2 were significant, F(2,62)= 1.12, ns, and F(7,62) = 1.23, ns, respectively (see Appendix 6.21).

3.9.5.4 Spatial working memory (Corsi)

Four outcomes were generated by the computerised Corsi block tapping task; accuracy, reaction (correct responses), correct responses (crossing trials), correct responses (uncrossing trials).

3.9.5.4.1 Accuracy

Model 1 was significant, F(2,62)= 12.03, p< .001 and explained 26% of the variance (adjusted R^2= .26). Model 2 was significant, F(7,62) = 4.03, p< .01 and explained 26% of the variance (adjusted R^2 =.26). As indicated in Table 3.13 accuracy score was significantly predicted by age (β = -.42, t= -3.53, p< .001) and by IQ (β = .35, t= 2.95, p< .001). PC3 "SB" approached significance (β = .21, t= 1.82, p= .07). This translates to a 0.76 decrease in accuracy for every 1.0 year increase in age (B=-0.76, p<.001), a 0.34 increase in accuracy with every 1.0 point increase in IQ, and a 2.59 increase in accuracy for every 1.0 increase in PC3 factor score (B=2.59, p=.07).

Table 3.13 Multiple linear regression analyses of relationship between Corsi correct responses and health parameters

		Number correct (n=63)				
Model		**B**	**SE B**	**β**	**t**	**Sig**
1	Constant	44.86	14.83		3.02	.00
	Age	**-0.72**	**0.20**	**- 0.40**	**-3.62**	**.00**
	IQ	**0.39**	**0.11**	**0.39**	**3.60**	**.00**
2	Constant	38.77	19.20		2.02	.05
	Age	**-0.76**	**0.22**	**-0.42**	**-3.53**	**.00**
	IQ	**0.34**	**0.12**	**0.35**	**2.95**	**.00**
	SBP	0.11	0.11	0.12	1.03	.31
	PC1	0.56	1.40	0.04	0.40	.69
	PC2	0.00	1.62	0.00	0.00	1.00
	PC3	**2.59**	**1.42**	**0.21**	**1.82**	**.07**
	PC4	0.28	1.43	0.02	0.20	.84

Model 1: adjusted R^2 = .26; F(2,62)= 12.03, p< .001
Model 2: adjusted R^2 = .26; F(7,62 = 4.03, p<.001

3.9.5.4.2 Reaction time for correct responses

Model 1 was significant, F(2,62)= 4.97, p< .01 and explained 11% of the variance (adjusted R^2= .11). Model 2 was significant, F(7,62)= 2.77, p< .05 and explained 17% of the variance (adjusted R^2 =.17). As indicated in Table 3.14, reaction time (correct responses) was significantly predicted by IQ (β = -.25, t= -2.00, p<.05) and SBP (β = .33, t= 2.64, p< .01). Age (β = .32, t= 1.88, p< .01) and PC4 "WHR + VPA" (β = -.23, t= -1.86, p= .07) showed a trend towards significance. This translates to a 3.57 ms increase in RT for every 1.0 mmHg increase in SBP (B=3.57, p<.001), and a 2.99 ms decrease in RT for every 1.0 point increase in IQ score (B=-2.99, p<.05). For every 1.0 point increase in PC4 "WHR + VPA" score there was a decrease in reaction time 34.1 ms (B=-34.1, p=.07). For every 1.0 point increase in PC4 "WHR and VPA" score there was a 34.1 ms decrease in reaction time (B=-34.1, p<.05).

Table 3.14 Multiple linear regression analyses of relationship between Corsi reaction times (correct) and health parameters

		Reaction time of correct (n=63)				
Model		**B**	**SE B**	**β**	**t**	**Sig**
1	Constant	1046.16	197.38		5.30	.00
	Age	**6.93**	**2.63**	**0.32**	**2.63**	**.01**
	IQ	**-2.82**	**1.44**	**-0.23**	**-1.96**	**.06**
2	Constant	695.87	246.47		2.82	.01
	Age	**5.21**	**2.77**	**0.24**	**1.88**	**.07**
	IQ	**-2.99**	**1.49**	**-0.25**	**-2.00**	**.05**
	SBP	**3.57**	**1.35**	**0.33**	**2.64**	**.01**
	PC1	-3.36	17.97	-0.02	-0.19	.85
	PC2	-7.46	20.86	-0.05	-0.36	.72
	PC3	17.23	18.30	0.11	0.94	.35
	PC4	**-34.06**	**18.30**	**-0.23**	**-1.86**	**.07**

Model 1: adjusted R^2 = .11; F(2,62) = 4.97, p< .01
Model 2: adjusted R^2 = .17; F(7,62) = 2.77, p< .05

3.9.5.4.3 Accuracy: crossing trials

Model 1 was significant, F(2,62)= 5.28, p< .01 and explained 12% of the variance (adjusted R^2= .12). Model 2 was significant, F(7,62) = 2.32, p< .05 and explained 13% of the variance (adjusted R^2 =.13). As indicated in Table 3.15, accuracy (crossing-trials) was predicted by age (β = -.32, t= -2.51, p< .01), PC3 "SB" (β = .26, t= 2.13, p< .05), and IQ (β = .24, t= 1.90, p= .06). This translates to a 0.30 decrease in accuracy score for every 1.0 year increase in age (B=-.30, p<.01), and a 1.68 increase in

accuracy score for every 1.0 point increase in PC3 “SB” factor score (B=1.68, p<.05). Accuracy score increases by 0.12 for every 1.0 point increase in IQ (B=.12, p=.06)

Table 3.15 Multiple linear regression analyses of relationship between Corsi correct responses (crossing trials) and health parameters

		Crossing trials: number correct (n=63)				
Model		**B**	**SE B**	**β**	**t**	**Sig**
1	Constant	13.62	8.30		1.64	.11
	Age	**-0.26**	**0.11**	**-0.28**	**-2.34**	**.02**
	IQ	**0.15**	**0.06**	**0.29**	**2.44**	**.02**
2						
	Constant	9.00	10.64		0.85	.40
	Age	**-0.30**	**0.12**	**-0.32**	**-2.51**	**.01**
	IQ	**0.12**	**0.06**	**0.24**	**1.90**	**.06**
	SBP	0.08	0.06	0.17	1.29	.20
	PC1	-0.47	0.78	-0.07	-0.61	.55
	PC2	0.05	0.90	0.01	0.06	.95
	PC3	**1.68**	**0.79**	**0.26**	**2.13**	**.04**
	PC4	-0.34	0.79	-0.05	-0.42	.67

Model 1: adjusted R^2 = .12; F(2,62) = 5.28, p< .01
Model 2: adjusted R^2 = .13; F(7,62) = 2.32, p< .05

3.9.5.4.4 Accuracy: non-crossing trials

Model 1 was significant, F(2,62)= 12.15, p< .001 and explained 27% of the variance (adjusted R^2= .27). Model 2 was significant, F(7,62) = 3.90, p< .05 and explained 25% of the variance (adjusted R^2 =.25). As indicated in Table 3.16, accuracy (non-crossing trials) was significantly predicted by age (β = -.41, t= -3.43, p< .001) and IQ (β = .35, t= 2.97, p<.001). This translates to a 0.46 decrease in accuracy score for every 1.0 year increase in age (B=-.46, and a 0.21 increase in score for every 1.0 point increase in IQ (B=.21, p<.001). The coefficients for the PCs and SBP were not significant.

Table 3.16 Multiple linear regression analyses of relationship between Corsi correct responses (non-crossing trials) and health parameters

		Non-crossing trials: number correct (n=63)				
Model		**B**	**SE B**	**β**	**t**	**Sig**
1	Constant	31.17	9.10		3.42	.00
	Age	**-0.45**	**0.12**	**-0.40**	**-3.68**	**.00**
	IQ	**0.24**	**0.07**	**0.39**	**3.58**	**.00**
2	Constant	29.95	11.87		2.52	.01
	Age	**-0.46**	**0.13**	**-0.41**	**-3.43**	**.00**
	IQ	**0.21**	**0.07**	**0.35**	**2.97**	**.00**
	SBP	0.04	0.07	0.07	0.54	.59
	PC1	1.00	0.87	0.13	1.15	.25
	PC2	-0.18	1.00	-0.02	-0.18	.86
	PC3	0.89	0.88	0.12	1.01	.32
	PC4	0.65	0.88	0.08	0.73	.47

Model 1: adjusted R^2 = .27; F(2,62)= 12.15, p<.001
Model 2: adjusted R^2 = .25; F(7,62)= 3.90, p< .01

3.10 Summary of findings

The principal component analysis reduced the twelve body composition and physical activity variables into four principal components (PC1 “MPA + steps”; PC2 “adiposity”; PC3 “SB”; PC4 “WHR + VPA” as described in section 3.9.4. The PCs were entered with SBP, age, and IQ (model 2) in multiple regression analyses for each cognitive outcome. Model 1 contained age and IQ only. A summary of the relationships between the cognitive function outcomes and PC predictors is presented in Table 3.17.

Table 3.17 Tabulated summary of findings

Cognitive Outcome		Significant		Predictors of cognitive function						
		Model 1	Model 2	Age[2]	IQ[2]	SBP	PC1 MPA+steps	PC2 Adiposity	PC3 SB	PC4 WHR+VPA
Verbal memory	Total Acquisition	sig	marginal	O	+	O	O	O	O	O
	Delayed recall	ns	ns	O	O	O	O	O	O	O
	Proactive Interference	ns	ns	O	O	O	O	O	O	O
	Retroactive interference	sig	ns	+	O	O	O	O	O	O
	Recognition List A	sig	trend	-	+	O	O	O	O	O
Spatial memory	Designs	sig	ns	-	+	O	O	O	O	O
	Locations	trend	ns	-	O	O	O	O	O	O
	Designs/locations	sig	ns	-	+	O	O	O	O	O
	Delayed designs/locations	trend	trend	-	O	O	O	O	+	O
Spatial working memory	Accuracy	sig	sig	-	+	O	O	O	+	O
	Reaction time (correct)	sig	sig	+	-	+	O	O	O	-
	Accuracy: crossing	sig	sig	-	+	O	O	O	+	O
	Accuracy: non-crossing	sig	sig	-	+	O	O	O	O	O
Attention	Total correct	trend	sig	O	O	O	O	-	O	+
	RT for total correct	trend	sig	+	O	O	O	O	+	O
	False positives	ns	ns	O	O	O	O	O	O	O
	Misses	trend	sig	O	O	O	O	+	O	-
Summary total[1]		9/17	7/17	11/17	9/17	1/17	0/17	2/17	3/17	3/17

[1]Number of significant associations (+ve and –ve) with cognitive function outcomes for each predictor variable; Key: **+** indicates positive association, **-** indicates negative association and O indicates no association, cates significant predictors. [2]associations are shown for model 2 if significant, otherwise for model 1

Table 3.17 shows that age and/or IQ were significantly associated with most of the cognitive function outcomes. In every model (with the exception of attention outcomes), age and IQ made the greatest contribution to explained variance. All associations between age/IQ and the cognitive function outcomes were in the expected direction, i.e. cognitive performance decreased with increases in age and increased with increases in IQ. Systolic blood pressure made little contribution to any cognitive outcome, significantly predicting only one measure of spatial working memory, but not attention, verbal memory or spatial memory.

For verbal memory, model 1 (age and IQ) was significant for 3 out of 5 VVLT outcomes (excluding delayed recall and proactive interference). The inclusion of the PCs and SBP (model 2) resulted in non-significant models for delayed recall, retroactive interference and proactive interference. Model 2 just failed to reach significance for total acquisition and recognition, however, within this model IQ predicted both total acquisition and recognition, and age predicted recognition. None of the verbal memory outcomes were predicted by the PCs or SBP.

For the spatial memory outcomes, model 1 was significant (or showed a trend) for all VSLT outcomes. The inclusion of the PCs and SBP (model 2) resulted in non-significant models for designs, locations and designs and locations. Model 2 just failed to reach significance for delayed designs/locations, and in this both PC3 “SB” and SBP were predictors.

For spatial working memory, models 1 and 2 were significant for all Corsi outcomes. For attention, model 1 showed a trend towards significance for hits, reaction time of hits, and missed responses, but was non-significant for false-positive responses. The inclusion of the PCs and SBP (model 2) resulted in significant models for total correct responses, reaction time for correct responses and number of missed responses.

PC1, labelled “MPA + steps,” was positively loaded on time moderate (mins/day), MVPA bouts (>10 mins), MVPA total counts and step count. PC1 did not make any significant contribution to explained variance for any verbal memory, spatial memory, working memory, attention or executive function outcomes.

PC2, labelled “adiposity,” was positively loaded on BMI, waist circumference and body fat percentage. PC2 significantly predicted 2 measures of attention, with an increased score associated with a decrease in total correct and increase in missed

responses. PC2 (Adiposity) did not make any significant contribution to explained variance for memory (verbal, spatial or working memory).

PC3, labelled “SB,” was loaded positively on total time sedentary (mins·day^{-1}) and number of prolonged sedentary bouts (bouts >60 mins), and negatively on time light-activity (mins·day^{-1}). Increase in PC3 score significantly predicted slower reaction times in an attention task. Associations were also observed with spatial memory and spatial working memory but the direction of these relationships indicated that performance increased as PC3 score increased, which was an unexpected finding. Spatial memory measure (designs/locations) showed a positive association with PC3 score. PC3 did not make any significant contribution to explained variance for verbal memory outcomes.

PC4, labelled “WHR + VPA,” loaded positively on waist-hip ratio and vigorous-intensity activity. Increasing PC4 WHR + VPA score was associated with better performance on 2 attention measures (total correct and fewer missed responses). Faster (i.e. reduced) reaction times for the spatial working memory measure (reaction time for correct responses) were associated (trend) with increased PC4 score. PC4 did not make any significant contribution to explained variance for verbal memory and spatial memory outcomes.

3.11 Discussion

The aim of this cross-sectional study was to explore the relationships between cognitive function and PA in an obese/overweight sample. This was achieved by utilising principal component analysis to reduce a large number of correlated PA and body composition predictor variables to a small number of components. These were then suitable for concomitant use in multiple regression analysis. The study extends previous work by using an objective measure of PA, and exploring the relationship of PA outcomes with multiple domains of cognitive function in an overweight/obese middle aged (30-60 years) sample.

The investigation of the relationship between PA (using objective measures) and cognitive function is a relatively new research area, especially in obese, middle-aged samples. Much research has been conducted in older/elderly adults across a spectrum of cognitive ageing and neurodegeneration. The only available research using objective measures of PA conducted in obese and younger/middle-aged adults

was conducted in bariatric (morbid) patients (Galioto et al., 2014; Langenberg et al., 2015). Once somatic comorbidity and depressive symptoms were controlled for, PA was not significantly associated with cognitive function. Additionally, the sedentary nature of the samples may have explained the lack of findings as they were not doing a high enough volume of MVPA to elicit benefit. These findings cannot be generalised to an overweight/obese, non-patient population or to those that are accumulating more minutes of MVPA.

3.11.1 Interpretation of findings

The most consistent finding was that age and IQ were the greatest predictors of the cognitive function outcomes examined in this chapter. This was as expected, and confirmed the inclusion of these two causally prior variables in the first stage of each regression model. It is known that cognitive function declines with age (Chapter 1), although the trajectory of change is complicated and non-linear (Fjell et al., 2013). It is thought that around the age of 60 years, the trajectory of change increases but this varies greatly between individuals. IQ, measured using the seven-subtest version of the Wechsler Adult Intelligence Scale-Revised (WAIS-R), has been shown to be predictive of performance on 28 neuropsychological test outcomes (derived from 16 tests including verbal memory, spatial memory, attention, executive function) in 221 adults aged between 20-91 years (Diaz-Asper et al., 2004). Due to time constraints, the four-subtest version was used for this thesis, however, the relationship described by Diaz-Aser and colleagues was apparent in the data examined for this chapter. One interesting finding from Diaz-Asper et al's study was that the strength of the relationship between IQ and test performance was weaker in those who were categorised as above average. Those with above average IQ outperformed those with average IQ on every test variable however the effect size was small. Comparing above-average to average IQ yielded a smaller effect size (*d*= .41), whereas comparing the average IQ to a below-average group gave a larger effect size (*d*= .73). This has been attributed to ceiling effects achieved on the cognitive tests for those with above average IQ. This may have implications for the participants examined in this chapter as many were above average for IQ score. It is a possibility that it is less likely participants with high IQ will show cognitive change in relation to other variables as their performance is already high. If participants are close to reaching ceiling effects there is less scope to identify a strong relationship with other variables over and above the effect of IQ.

3.11.1.1 Principal component 1 (moderate activity)

Another key finding was that the principal component describing moderate-intensity activity (PC1) did not predict any verbal memory, spatial memory, working memory, or attention. This reflects the null findings observed by (Galioto et al., 2014; Langenberg et al., 2015) between MVPA and cognition in morbidly obese adults. When moderate-intensity activity has been examined as a predictor of cognitive function, null findings were observed for Corsi performance and AVLT scores (Langenberg et al., 2015) and the findings for this chapter replicated this. Additionally, the null findings between moderate-intensity activity and the VSLT outcomes (spatial memory) also reflect the extant literature. A direct association was not observed between spatial memory and MVPA in older adults, but one that was mediated through hippocampal volume (Makizako et al., 2014). This highlights the issue that the relationship between PA and cognitive outcomes may not be direct, but mediated through unmeasured variables known to impact cognitive function.

It was beyond the scope of this PhD research to conduct any form of brain imaging. However, it is known that hippocampal volume, and also memory (both verbal and spatial) are associated with glucose regulation and insulin sensitivity. Fasting glucose had been measured in a subsample only, but this variable could not be included in the analysis for the full sample. It is possible that the inclusion of fasting glucose may increase the variance explained by the multiple regression models. Additionally, the low volume (minutes of) of moderate-intensity accumulated by the sample may explain the lack of findings for the cognitive outcomes. The current sample was homogenous in terms of moderate-intensity activity, and only included people at the lower end of the spectrum. Only 3 participants were meeting the guidelines for moderate-intensity exercise (30-minutes accumulated in bouts >10 minutes). The majority of the current sample were accumulating just one 10-minute bout of moderate-intensity exercise per day. The sample does not represent overweight/obese adults that are doing higher amounts of moderate-intensity activity. Therefore, without an adequate range of time spent in moderate-intensity activity, there was not enough variation to allow firm conclusions to be drawn regarding the relationship between moderate-intensity activity and cognitive outcomes. It is not known if increasing time spent in moderate-intensity activity can lead to an improvement in cognitive outcomes in obese/low active adults.

3.11.1.2 Principal component 2 (adiposity)

The association between a principal component loaded on percentage body fat, BMI and waist circumference (PC2) and attention is consistent with extant literature. Previous research has demonstrated poorer performance on the D2 attention endurance test in obese women when compared to healthy weight counterparts (Cserjesi et al., 2009). The null findings with verbal memory and spatial memory were unexpected as markers of obesity have been associated with multiple cognitive outcomes (Prickett et al., 2015). However, these differences are normally observed when obese individuals are compared to healthy weight individuals. The current sample only included those that were classed as overweight and obese (according to body fat percentage and BMI). Healthy weight participants were not included and morbidly obese individuals were under-represented. Therefore, the sample showed a lack of variation in terms of body composition values.

3.11.1.3 Principal component 3 (sedentary behaviour)

An association between PC3 and slower (i.e. increased) reaction times for the Bakan Test (attention) was observed, however, there is no available data on objectively measured sedentary time and cognitive outcomes in overweight adults to allow for comparisons with other research. There were some unexpected findings observed for increased sedentary behaviour and superior performance on spatial and spatial working memory. This would indicate that prolonged sedentary time is associated with better spatial and working memory, and this is after controlling for age and IQ. This highlights the pitfalls of cross-sectional data, as causality cannot be established and unmeasured variables may be driving unexplained relationships. It must be noted that PC3 score included both sedentary behaviour and light-intensity activity, although loadings were in opposing directions (positive and negative respectively). It would be preferable to keep the two differing PA summaries distinct, as opposed to amalgamated into one composite factor. This is because the minimal literature available indicates that sedentary behaviour would have a negative impact on cognitive function, and that light-intensity activity would have a (subtle) beneficial impact. The presence of two opposing PA summaries in one composite score ‘dilutes the effect of each summary, and prevents exploration of the impact each has on cognitive function.

3.11.1.4 Principal component 4 (WHR and vigorous-intensity activity)

Increased PC4, “WHR + VPA” score showed a trend towards a significant negative relationship with reaction time for correct responses (i.e increased PC4 associated with reduced reaction time) on the spatial working memory task. It is an unexpected finding that faster reaction times for Bakan correct responses were associated with higher scores on PC4 “WHR + VPA”. Reaction times on a vigilance task were previously shown to improve with increased cardiorespiratory fitness (Monleón et al., 2015) and exercise is typically associated with faster reaction times. It must be highlighted that waist-hip ratio made the greatest contribution to PC4, not vigorous-intensity activity. It is unclear why waist-hip ratio would be the greatest contributor to a distinct PC (PC4), whilst the other 3 measures of body composition loaded on PC2 “adiposity”. The interpretation of this PC may be further complicated by the inclusion of both men and women in the same sample. Men and women typically show differing fat distribution, and a WHR value that would be considered healthy for a man, might be unhealthy for a woman. Additionally, the range of vigorous-intensity activity was extremely low prior to PCA. In terms of vigorous-intensity activity, the majority (75%) were not doing any at all, only 2 participants were accumulating >5 minutes per day. It is possible that the lack of association between vigorous-intensity PA and cognitive function outcomes is due to the possibility that the current sample were not doing enough exercise to drive cognitive benefit. The pairing of WHR and vigorous-intensity activity creates a PC that is difficult to reconcile, and, the findings relating to PC4 must be interpreted with great caution.

3.11.1.5 Interim summary

In this overweight/obese and low-active sample, age and IQ were greater predictors of cognitive function outcomes than any of the PA and body composition PCs. It could be interpreted that IQ exerts a protective effect on the impact that obesity and sedentary behaviour has on cognitive outcomes. However, due to the homogenous nature of the sample, there was insufficient variation within the PA variables to draw firm conclusions. The aim was to explore whether variation in PA and body composition PCs predicted variation in cognitive function. However, the PA variables were restricted by the low activity of this sample, which was concentrated one end of the spectrum of PA behaviour. Without a full range of PA behaviours, firm conclusions about MVPA and cognitive function in a sample accumulating minimal levels of MVPA cannot be drawn. If age- and IQ-matched participants accumulating higher daily minutes of moderate- and vigorous-intensity activity were added to the sample, this

would allow comparison of the contributions of IQ and exercise (MPA and VPA) across a range of activity patterns. The unexpected findings serve to highlight the limitations of cross-sectional research. Causality cannot be established, it is only possible to observe the relationships that occur within the confines of the sample. These relationships will be impacted upon by the characteristics of that particular sample, and are not more widely generalisable.

3.11.2 Limitations

This study found some null (but expected) findings, alongside some significant but unexpected relationships. Therefore, limitations to the approach used must be considered upon completion of data collection, since decisions regarding data processing and data analysis present the greatest "opportunity" for error. The following section discusses the statistical approach employed followed by a discussion of the accelerometer data processing and the limitations of this.

3.11.2.1 Critique of the statistical approach adopted.

3.11.2.1.1 Application of PCA to the data set

Principal component analysis was a statistically sound strategy to apply as it reduced the dimensionality of a data set that comprised of a large number of interrelated variables, whilst retaining ~77% of the variation present in the data set. This permitted consideration of a range of measured variables despite a limited cases to variable ratio (Tabachnick & Fidell, 2007) However, multidimensional data sets, such as for this chapter, are difficult to interpret as with increasing numbers of variables, the structure of the data set cannot be visualized (Gharibnezhad et al., 2015). Additionally, redundant variables create empty space and PCA is the best tool to tackle all of these issues.

Using PCA, it is possible to quantify the importance of each dimension, as the first PC produced explains the greatest variance, and relative importance decreases with each successive PC (Shlens, 2014). For this data set, PC1 "MPA + steps" was the most important dimension and explained 28% of variance in the data set. The second most important contribution to variation in the data set was PC2 Adiposity, contributing a further 21% to explained variance. A further 17% of variance was explained by PC3 sedentary behaviour. The dimension that explained the lowest portion (11%) of variance was PC4 vigorous-intensity. In simplified terms, PC1 "MPA + steps" explained the greatest variation in the data set. It also shows, that despite

the sample being categorised as overweight/obese (and typically treated as being the same in research) the dimension including adiposity measures (PC2 “Adiposity”) showed the second largest amount of variation.

One issue of classical PCA is that it fails to process missing data, and the deletion of cases with missing data loses important information. The data set in this study was no exception and was reduced from 73 to 63 cases following dimension reduction due to missing data on some variables. An alternative to this would be to use expectation maximisation (EM), an iterative process which computes the model’s parameters and fills in the missing information directly. This can be used in conjunction with a robust version of PCA (Stanimirova et al., 2007).

3.11.2.1.2 Quality of the PCA model

The quality of the PCA model was evaluated using a bootstrapping cross-validation technique, parallel analysis (Horn, 1965). This is an accurate and well-regarded empirical method for determining the number of components to retain (Cota et al., 1993; Dinno, 2014; Hayton, Allen, & Scarpello, 2004). This parallel analysis (PA) revealed the fourth principal component “WHR + VPA” fell just below the 95th percentile criterion for PA, and therefore should not be retained. The decision about how many components to retain is important. Both types of misspecifications (specifying too few and too many) lead to substantial error, but specifying too few is deemed more serious a mistake (Ford, MacCallum, & Tait, 1986). Under-extraction of PCs compresses variables into a smaller factor space, losing information and neglecting potentially important factors and increasing erroneous loadings (O’Connor, 2000). This means measured variables that would have loaded on the excluded component, are either not included in the model; forced (and falsely loaded) on one of the included components such that loadings of variables on included components are distorted (Hayton et al., 2004). If the fourth component had been ignored, and the PCA forced to 3 components, one of the variables theoretically important to this thesis (vigorous-intensity activity) would have been lost. When looking at the raw data, the sample were accumulating such low amounts of vigorous activity that the majority of the sample were doing no minutes daily. When boxplots were inspected for outliers, all those who accumulated more than zero minutes were considered unusual. There were only 2 participants who accumulated >5 minutes daily, and these were considered outliers in a statistical sense. This highlights that no-one in the sample was meeting the current guidelines for VPA. It is possible that these “outliers” drove the creation of the fourth principal component. Therefore, PC4 only describes the

behaviour of those who were doing some (although minimal) amounts of vigorous-intensity activity and does not represent the majority (75%). The decision was made to retain four principal components and interpret their effects with caution.

3.11.2.1.3 Limitations of principal components extracted

The principal components did not incorporate variables from both physical activity and body composition categories. The components represented one or the other. This may in part be explained by the fact that the data set was fairly homogenous in terms of activity level and body composition (highly sedentary and all overweight/obese). It would be beneficial to create components using a larger sample, including individuals accumulating more MPA and VPA, and those in the healthy range for indices of body composition. Although dimension reduction is essential when analysing data sets with lots of inter-correlating variables, the ability to explore the contribution of specific variables (i.e. VPA, steps per day) is lost. It is therefore not possible to isolate specific types of PA that would be eligible for intervention. Additionally, the fractionation of a PA summary i.e. MPA in bouts versus non-bouts) has shown to have distinct implications for health (Chapter 1). As these variables would be so highly correlated, due to being a function of each other, it is likely that when entered into PCA they would load on the same component and no distinction would be made between them. Evidence of this was observed in the data set following application of PCA. Principal Component 1 loaded on 3 measures of MPA; total accumulated moderate-intensity minutes (non-bouts), MVPA bouts (>10 minutes); MVPA total counts (>10 minute bouts). All measures are valid (raw data versus processed data, sustained versus accumulated) and cited in the literature as a research focus. Additionally, PC3 “Sedentary behaviour” loaded positively on total accumulated minutes sedentary (non-bouts) and sedentary bouts (>60 minutes). Sustained sedentary time is a new area of research as it likely has a different impact on health, when compared to shorter non-bouts. If fractionation of PA volume is the research focus then PCA may not be appropriate to use.

3.11.2.2 Accelerometer data processing

The raw accelerometer data (signals detected by the accelerometer) have to be converted to meaningful PA outcomes, but there are many different prediction equations or raw count cut-points within the literature and these are placement-site specific (hip, wrist) (Strath et al., 2013). It is known that the intensity, frequency and duration of PA estimates vary according to the methods used to process the data (Ham et al., 2007). There is substantial variability in the cut-points and prediction equations developed, with the minimum threshold for MPA ranging from 200 to 2000 counts/min (Strath et al., 2013). The variation in raw counts between participants at a particular speed/work rate is the greatest source of error in PA estimates (Aadland & Steene-Johannessen, 2012). Activity classification can differ substantially according to the analytic method used to determine PA level (cut points, wear time validation).

3.11.2.2.1 Cut-points alter with cardiovascular fitness

The Freedson adult cut-points (Freedson et al., 1998) were selected and rationale for this is provided in Chapter 2 (section 2.9.1). However it is difficult to determine whether the Freedson adult cut-points selected were the optimum analytical approach in this sample, as it is not possible to confidently identify another set of cut-points that would have been superior (Loprinzi et al., 2012). Further complicating the issue of classifying PA level using absolute cut-points is the diversity in (and influence of) cardiovascular fitness, age and body composition of any sample or population. The application of one set of cut-points to a data set (as is current practice) assumes that all individuals performing a velocity of motion (defined by a set number of counts) will experience the same physiological response indicative of an intensity domain (i.e. heart rate, breathlessness, RPE/exertion). Unless these additional measures are collected, the domains identified by accelerometer count cannot be cross-referenced against biological markers of exertion, and therefore cannot be confirmed.

The cut points may over or underestimate the levels of PA as they do not take into account the fitness level of an individual. Interindividual variability in Actigraph accelerometer counts has been demonstrated at moderate- (40% HRR) and vigorous intensity (60% HRR) during a submaximal exercise test (Ozemek, Cochran, Strath, Byun, & Kaminsky, 2013). Participants across a range of cardiorespiratory fitness (VO_{2max}: 27.9 to 58.5 ml·kg^{-1}) showed variability at 40% HRR of 1455-7520 activity counts·min^{-1} and variability at 60% HRR of 3459-10066 counts·min^{-1}. This was

significantly impacted by fitness group (<10 MET, 10-13 MET, >13 MET). It is suggested that cut points appropriate for fitness level should be derived. However, this would mean a maximal or sub-maximal exercise test would have to be performed by all individuals.

3.11.2.2.2 Impact of age

The sample studied for this thesis range in age from 30 to 60 years. The metabolic cost of walking increases with age (Peterson & Martin, 2010) and body weight (Browning, Baker, Herron, & Kram, 2006; Lafortuna et al., 2008; Morris et al., 2014). Age is associated with declines in metabolic and force-producing capacity (Peterson & Martin, 2010). Body weight is an important determinant of the energy expenditure required to propel the body forward. A study by Lafortuna et al. (2008) found that metabolic energy utilised during a treadmill walk at the same velocity and incline was 2.3-fold higher in an obese group compared to a normal weight group. This is thought to be influenced by the work required to redirect and accelerate the centre of mass and the work required to generate force in order to support body weight (Grabowski, Farley, & Kram, 2005). The influence of age and body weight are not captured by accelerometers, and cut-points validated against one criterion (ie. age) cannot account for variations in another (i.e. body weight). Furthermore, the relationship between age and body weight is not linear. The normalisation of energy expenditure to body weight may be essential to determine clear/correct PA intensity thresholds. Alternative (lower) cut-points for MPA (612 counts·min^{-1}) and VPA (4780 counts·min^{-1}) have been suggested by Aadland and Anderssen (2012). However, this was validated using the Actigraph GT1M model which only measures acceleration in 1 plane (vertical) and so are not comparable to the newer models of Actigraph, such as the GT3X used for this thesis.

The cut-point selection impacts on the ability to compare the findings presented in this chapter to research that has utilised different cut-points and processing criteria. The Freedson ault (1998) cut points were selected as they have been widely used in research conducted in obese samples which allowed for the comparison of the data presented in this thesis with the literature. Appropriate cut-points to define PA intensity are known to vary according to age and weight status. The sample for this thesis ranged in age from 30-59 years, and in BMI from 25- to 44.5 kg/m^2.Therefore, no cut-point available can account for variation in both of these factors.

3.11.2.2.3 Misclassification of PA

The most widely applied algorithm to classify non-wear time is 60 consecutive minutes of zero counts on the vertical axis of the accelerometer, allowing for 1-2 minutes of counts ranging from 1 to 100 (Troiano et al., 2008; Tudor-Locke et al., 2010). Variation in the time window has been shown to impact on the estimates of PA and SB in normal weight and obese samples (Healy et al., 2008a; Masse et al., 2005; Miller et al., 2013), and the use of an invalid algorithm can misclassify non-wear time which impacts on the number of valid hours/days (Berendsen et al., 2014). Misclassification of sedentary time and non-wear time occurs as they both show similar outputs (Berendsen et al., 2014). Additionally, misclassification of non-wear time has been shown to be significantly higher in obese participants compared to healthy weight counterparts (Winkler et al., 2012). A potential explanation for this is that increased adiposity impacts on the tilt of the device leading to the under-detection of movement (Corder, Brage, & Ekelund, 2007). This study only had the option to categorise SB as time spent sedentary, it could not distinguish between sitting, lying, stepping behaviours. If a more accurate breakdown of SB into sitting and standing behaviours was required, an alternative accelerometer such as the ActivPal or ActiCal would be essential.

3.11.3 Considerations for future research

The findings from the present study highlight aspects of the methodology that could be enhanced for future research investigating the relationship between objectively measured PA and cognitive function in overweight/obese adults. The following modifications are suggested for future studies:

I. Study a larger sample.

Although PCA reduced the number of predictor variables to a small number of components, due to the ratio of cases to variables the study was underpowered. With 63 cases and 7 predictor variables/PCs, the current study pushed the limits of the number of variables that could be entered into a regression model, i.e. 10 cases per variable (Tabachnick & Fidell, 2007).

II. Recruit a more heterogeneous sample in terms of body composition and accumulated PA

The study failed to show a relationship between MPA or VPA and any cognitive outcomes. The sample recruited was homogenous in terms of activity levels (highly sedentary and low accumulated minutes of moderate- and vigorous-intensity activity). This was because the recruitment process targeted sedentary individuals. This may potentially explain the lack of effect of observed between MVPA and cognitive outcomes. It would be pertinent to recruit overweight/obese samples who are accumulating a greater number of minutes of moderate-and vigorous-intensity activity. Exploration of the impact of MVPA on cognitive function requires samples that show a wide range of variation in MVPA (from low to high daily minutes) and indeed cognitive function.

III. Examine whether an exercise intervention aimed at increasing PA can improve cognitive function.

The use of cross-sectional data limits the interpretation of the results, relationships that coexist are reported but causality cannot be established. Additionally, this can be impacted upon by the characteristics of the sample examined or the influence of unmeasured variables. In order to examine whether PA influences cognitive function, a more direct approach is to manipulate the PA outcome of interest and assess whether cognitive function changes as a result of this. In the current sample, it was not possible to explore the relationship between vigorous-intensity activity and cognitive outcomes as the sample was limited to individuals that were doing minimal (<5 minutes) vigorous-activity.

IV. Examine PA as distinct summaries as opposed to composites

PCA reduced the separate PA summaries into a smaller number of composites. In general, this was not problematic except in the case of PC3 which amalgamated 2 markers of sedentary behaviour with light-intensity activity into one score. From a physiological perspective it is preferable to keep these variables distinct, as it is likely that they would impact on cognitive function in different ways and through different physiological pathways. A further point for consideration is the inclusion of variables that are a function of one another, but all of clinical relevance in the same PC. This is evident in PC1 “MPA + steps” which comprised time in moderate activity (mins/day), time in MVPA bouts (>10 mins), MVPA total counts and step count. It was also evident in PC3 which included time sedentary (mins/day) and number of prolonged sedentary bouts (>60 minutes). Because the variables share variance, they are included in the

same PC but this prevents exploration of the fractionation of a PA summary (i.e. bouts versus non-bouts of MVPA).

3.12 Conclusion

In conclusion, the findings show a limited number of associations between PA and adiposity composites and cognitive outcomes in overweight/obese adults. The study suggests that objectively measured PA has a limited but significant association with spatial memory, spatial working memory and attention, after controlling for age and IQ. In the current sample, age and IQ contributed more to variance in cognitive function, when compared to the physical activity and body composition composites. However, the cross-sectional design only confirms these findings in a sample that were accumulating minimal amounts of moderate- and vigorous-intensity activity. It is not possible to draw inferences about the relationship between MVPA and cognition in overweight/obese adults without a full range of MVPA behaviours. Despite this, the results offer promising evidence to suggest PA has a relationship with cognitive function in low-active, overweight/obese adults. Further exploration is warranted in larger-scale cross-sectional studies, and also in intervention studies focussed on increasing PA to examine the effect on cognitive function.

Chapter 4:
Study 2

Chapter 4 Study 2: Impact of continuous versus interval exercise training upon cardiovascular and cognitive function in overweight obese women.

4.1 Introduction

Aerobic exercise improves cognitive function in healthy weight adults (Chapter 1, section 1.2.3), but this has not been investigated in obese samples. It is suggested that the exercise-related improvements in cognitive function may be driven by a reduction in cardiovascular risk factors (Chapter1, section 1.2.5.2). Exercise is known to impact brain structure directly (section 1.2.5.1) and also indirectly through systemic changes. Based on the hypothesis that greater physiological adaptation may translate to a greater chance of improving cognitive function, it is pertinent to explore a mode/type of exercise that elicits greatest physiological adaptation.

The role that each of the parameters that underpin exercise (intensity, frequency, mode, duration) have upon neuroprotective benefit is poorly understood. The workload and duration of the interval bout drive metabolic demand, and the duration of the recovery bout can be manipulated to provide either full or partial recovery. Manipulation of these duty cycles impacts the acute metabolic or cardiopulmonary response during exercise, which subsequently impacts long-term training adaptations if repeated over time. Much of the research in section 1.2.7 indicates superior improvement following HIIT, relative to continuous exercise in many of the systemic factors associated with cognitive function (insulin sensitivity, inflammation, cardiovascular indices). However, the use of HIIT has largely been unexplored with regard to cognitive function.

4.1.1 Interval exercise and cognitive function

To date, only two studies have investigated the effects of increasing exercise or PA on cognitive function in middle-aged obese adults (Drigny et al., 2014; Monleón et al., 2015). The protocols of both studies are described in detail in Chapter 1 section 1.2.3. However, the “interval training” protocol described by Drigny and colleagues was mixed given that in addition to two interval sessions per week participants also performed aerobic training and resistance work. The programme comprised of 2 HIIT sessions per week on an ergocycle, plus an additional 60-minute session of moderate intensity continuous exercise (60% peak power output) and two 20-minute resistance

training sessions. This therefore was not a ‘pure’ assessment of interval exercise. The study yielded significant improvements in short-term memory (Forward Digit Span), attention and processing speed (Digit Symbol Substitution Test) and verbal memory (RAVLT). This coincided with significantly improved post-training cerebral oxygen extraction during both exercise and recovery. However, the statistics used were a simple pre-post t-test, with no control group for comparison. This is further compounded by a low sample size of just 6 men. The study by Monleón et al. (2015) indicated performance on a psychomotor vigilance task had improved as indicated by faster responses and fewer lapses (missed responses) relative to baseline. However, the type of exercise cannot be categorised clearly in terms of work-rate profile (i.e. interval or continuous) as it was based on dance/rhythmic activities. The training consisted of two 60-minute sessions of supervised dance/rhythmic activities per week, with an intensity target of 12-13 on the Borg rating of perceived exertion scale (moderate intensity activity).

4.1.2 Continuous work-rate exercise and cognitive function

A limited number of studies examining the impact of exercise on cognitive function in young adult samples are available in the extant literature (Chapter 1, section 1.2.2), however none of these have been conducted in obese individuals. Collectively these studies have provided heterogeneous findings, as improvements in visual-spatial memory were reported following a six-week running intervention, but no significant changes in verbal memory or attention (Stroth et al., 2009). Pereira et al. (2007) reported improvement in short term verbal memory following twelve weeks aerobic exercise training, which occurred alongside increased cerebral blood flow in the dentate gyrus of the hippocampus. Improved performance in immediate and delayed verbal recall was observed following 24 weeks of cycling, when compared to a no-exercise control and a stretching group. However, the stretching group demonstrated significant improvement in attention relative to the cycling and no-exercise control conditions. From a limited number of studies investigating the impact of continuous exercise sessions on cognitive function, many methodological differences have been identified. The protocols were different in terms of intervention duration (6 weeks – 8 months), frequency of weekly exercise sessions (2-4), duration of sessions (30-60 minutes), intensity of sessions and method used to control for intensity of sessions.

It is already known that traditional CON exercise is positively associated with cognitive performance. However, without a comparison of the two training regimes it is not known if any further benefit is derived from either INT or CON. It is not known if repeated excursions into a higher intensity have the capacity to elicit a superior physiological adaptation if both training stimuli (INT and CON) are performed within the same intensity domain and matched for work done.

4.2 Study objectives and hypotheses

Chapter 1 highlights the relationship between cognitive function and cardiovascular risk factors, and section 1.2.7 discusses the potential superior benefits of heavy-intensity aerobic interval training upon such risk factors. However, heavy-intensity interval exercise training has not been compared to work-matched, heavy-intensity continuous exercise training for either cardiovascular risk or cognitive function outcomes. The aim of this chapter was to compare the impact of two work-matched, heavy-intensity exercise regimes (INT and CON) and a no-exercise control group upon cognitive function and cardiovascular risk in sedentary, overweight/obese women. The interrelationships between changes in these variables were explored as a secondary aim. It was hypothesised that the INT and CON regimes would drive physiological changes, and that these changes would be associated with improved cognitive function relative to controls. It was also hypothesised that the INT regime would drive superior benefit in cardiovascular adaptations relative to the CON regime. It was not known whether either experimental regime (INT or CON) would have a greater impact on cognitive function outcomes.

4.3 Methods

4.3.1 Participants

Twenty-eight participants were recruited from the Leeds area from a pre-existing database listing individuals that have expressed a wish in being contacted for research purposes/future studies and/or local advertisement. All participants were healthy, pre-menopausal females with a BMI ≥27 kg/m^2 and therefore classed as overweight/obese.

4.3.1.1 Inclusion/Exclusion Criteria

In addition to the inclusion/exclusion criteria listed in section (Chapter 2, section 2.2.3). **Error! Reference source not found.** displays the additional criteria used for the work reported in this chapter.

Table 4.1 Study specific inclusion/exclusion criteria

Inclusion Criteria	Exclusion Criteria
Female (pre-menopausal)	Male
BMI ≥27 kg/m^2	BMI < 27 kg/m^2
Age 30-55 years	Age <30 or > 55
	Resting/exercise ECG indicating significant ischemia, recent myocardial infarction or other acute cardiac event or other exercise related ECG abnormalities.
	Clinical diagnosis of unstable angina

4.3.1.2 Recruitment and attrition

Figure 4.1 indicates the flow of participants through the study, from recruitment to completion. The consort diagram shows that the study received initial interest from 148 volunteers, however 83 were excluded based upon BMI <27 kg/m^2 (n=31) medication (n=27), depression (n=19), surgery (n=2), injury or chronic joint problem (n=4). A further 29 individuals did not respond to any further contact. Thirty-six eligible participants passed screening and were enrolled on the study. Six dropped out of the study during baseline tests, 1 declined and 4 did not respond. In total 25 participants completed all baseline assessments and were allocated to training groups. The INT training group (n=13) lost 3 participants from baseline to post-testing. The CON group (n=12) lost 2 participants from baseline to post-testing.

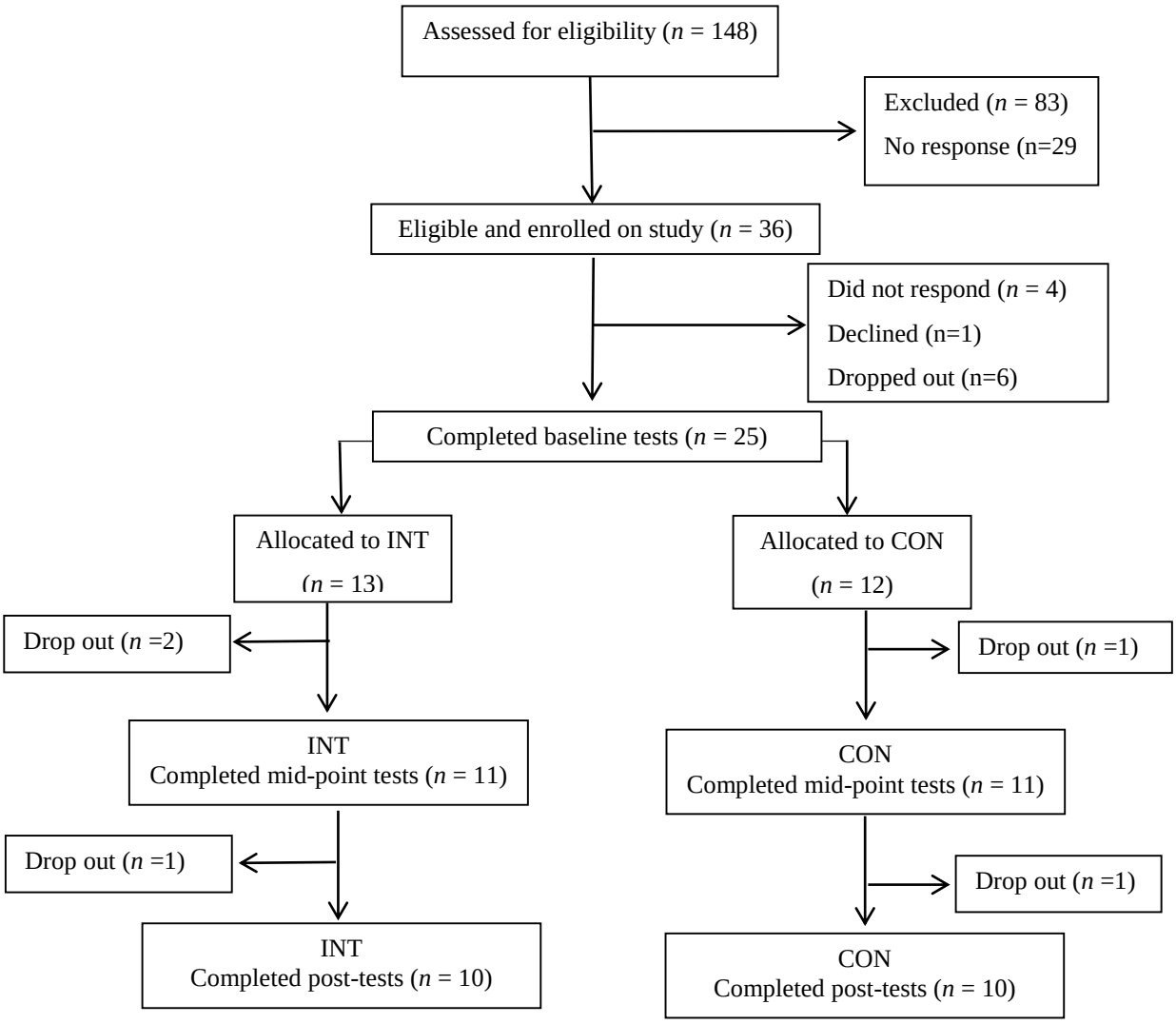

Figure 4.1 Consort diagram

4.4 Experimental Design

The study conformed to a 3x3 independent parallel groups design examining cognitive performance and cardiovascular health over a 12-week supervised exercise intervention. Twenty sedentary, overweight/obese females were randomly assigned to one of two experimental groups (INT and CON, n=10 per group). A non-exercise (NO-EX) control group (n=8) was recruited separately/retrospectively. All participants attended the laboratory at three time points (weeks 0, 6 and 13) for baseline, mid and post assessment of cognitive function, body composition and cardiopulmonary fitness.

4.5 Testing Procedure

Testing took place in the Institute of Psychological Sciences and the Faculty of Biological Sciences, University of Leeds. Each visit was completed within 90 minutes. Individuals meeting the study inclusion criteria were invited to the laboratory for a study familiarisation visit and administration of the practice cognitive test battery (Visit 1; see section 4.6.1). Seven days after completion of Visit 1, during which an accelerometer was worn to monitor PA, participants attended the lab for a baseline testing visit (Visit 2, see section 4.6.1) for assessment of cognitive function and body composition. Participants attended a separate laboratory visit for an assessment of cardiopulmonary function (Visit 3, see section 4.6.2). Visit 3 signified week 0 of the study, and the immediate initiation of the 12-week intervention phase. All measures from Visits 2 and 3 were repeated at mid-point (Visits 4 & 5, week 6) and upon completion of the 12-week intervention (Visits 6 & 7, week 13). Figure 4.2 provides a flow diagram of study visits from study familiarisation to completion.

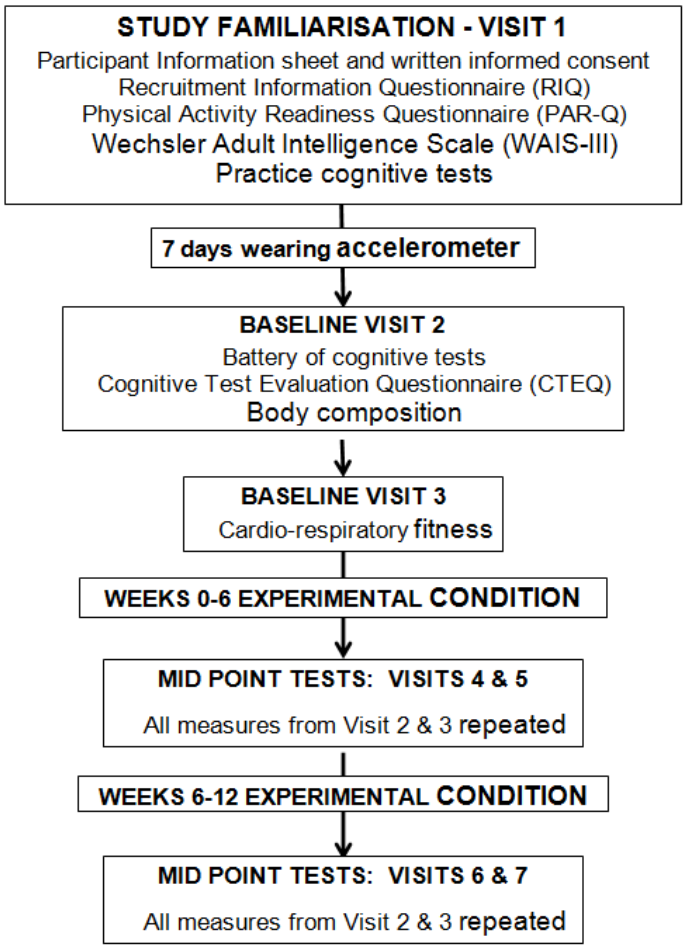

Figure 4.2 Study protocol flow diagram

4.6 Laboratory Visits

4.6.1 Baseline Visits 1 and 2 (Week 0)

Participants attended study familiarisation visit 1 and baseline visit 2, all procedures are described in Chapter 2, section2.4.

4.6.2 Baseline Visit 3 (Week 0)

In addition to the test visits described in Chapter 2, section 2.4, participants completed a cardio-respiratory fitness test on an electronically braked stationary cycle (Section 4.7.2) in week 0. Laboratory Visit 3 took 70 minutes to complete.

4.6.3 Mid-point and post-testing assessments

Baseline visit 2 (section 2.4.2) and visit 3 (4.6.2) were repeated at week 6 (mid-point) and week 13 (post-intervention)

4.7 Study Procedures

4.7.1 Assessment of cognitive function

All participants attended the cognitive test sessions in a 12 hour fasted state. Parallel versions of each cognitive test were used and administered in a counterbalanced order at mid-point and post-testing. The acute impact of exercise on cognitive function is well documented (Roig et al., 2013) and can last up to 48 hours post-exercise. Therefore, post-test cognitive function tests were administered >48 hours after the final exercise session or maximal exercise test. The cognitive test battery took approximately 44 minutes to complete, see Table 4.2 for details.

Table 4.2 Order of cognitive test presentation within the cognitive test battery

Cognitive test	Test duration (minutes)	Cognitive domain
1. Visual Spatial Learning Test▲	6	Spatial memory
2. Visual Verbal Learning Test*	12	Verbal memory
3. Corsi Block Tapping Test* (Computerised version)	4	Spatial working memory
4. Tower of Hanoi*	5	Problem solving (executive function)
5. Delayed Visual Spatial Learning Test▲	2	Delayed spatial memory
6. Grooved Pegboard▲	3	Psychomotor skill
7.Bakan Test	6	Attention
8. Delayed Visual Verbal Learning Test*	3	Delayed verbal memory
9. Word Recognition Test*	3	Delayed verbal memory

* Test administered on computer (experimenter not present)
▲Test administered by hand by the experimenter

4.7.1.1 Visual Spatial Learning Test

The Visual Spatial Learning Test (VSLT) was administered as previously described in Chapter 2, section 2.5.1.3. For this research study versions 1, 2 and 3 were administered (Appendix 6.12)

4.7.1.2 Visual Verbal Learning Test

The Visual Verbal Learning Test (VVLT) was administered as previously described in Chapter 2, section 2.5.1.1. For this research study versions 1, 2 and 3 were administered (Appendix 6.11)

4.7.1.3 Corsi Block Tapping Test

The Corsi Block Tapping Test was administered as previously described in Chapter 2, section 2.5.1.4.

4.7.1.4 Tower of Hanoi

The Tower of Hanoi (Simon, 1975) is a test of planning ability (executive function). The ToH is known to assesses several different cognitive components such as

planning, inhibition, procedural learning, explicit reasoning, working memory, and visuospatial memory (Welsh, Revilla, Strongin, & KEPLER, 2000; Welsh, Satterlee-Cartmell, & Stine, 1999). The ToH task measures planning ability as it requires the formulation and execution of strategy whilst adhering to a set of rules (Shallice, 1982; Simon, 1975). The computerised TOH consisted of a visual representation of three rods upon which 4 discs of different size and colour were placed (the physical version contains 5 discs). The screen shows a target formation of the discs, and a starting formation (Figure 4.3). The task is to copy the target formation in a limited number of moves. There are two rules: (i) a larger disc must not be placed on the top of a smaller one; and (ii) only one disc is allowed to move at a time. The difficulty level of trials depends on number of moves required to solve the task. There were ten trials per test administration, consisting of two trials for each of the five levels of 4,5,6,7 or 8 moves. There were two outcome variables: (i) the number of errors made, and (ii) the time to complete each trial (i.e. time taken to solve the problem). Impaired performance of the TOH or a similar task has been shown by frontally damaged adults(Shallice, 1982).

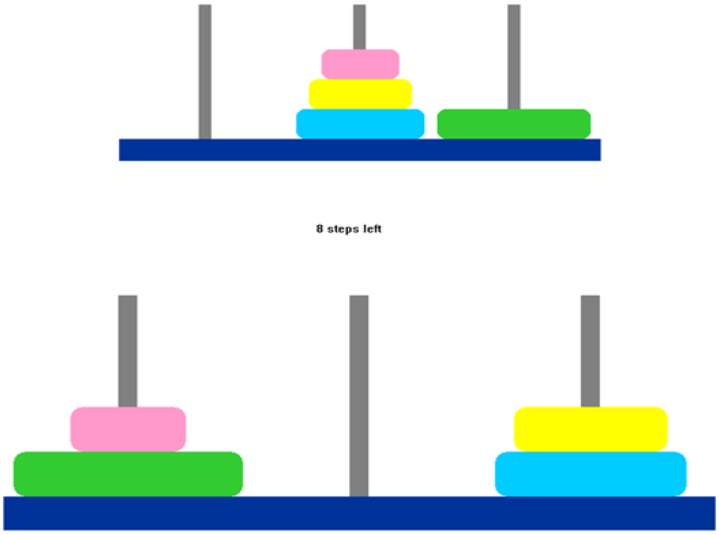

Figure 4.3 Visual configuration of a trial from the computerised Tower of Hanoi test

There was only one correct sequence of moves for each trial. This was the fewest number of moves required to match the target formation. If the participant deviated from the correct sequence the screen presented a message saying “this was not the correct sequence please try again”. Subsequently the screen refreshed to the

original starting formation. Forcing the participant to apply the fewest number of moves encourages problem solving rather than guessing. The screen informed the participant of the number of moves required to complete a trial, which was updated after each move, hence the participant was not required to retain in working memory the number of moves they had made. There was no time limit and therefore each trial had to be completed before the test concluded.

4.7.1.5 Grooved Pegboard

The Grooved Peg Board (Klove, 1963) assessed assesses manual dexterity and is a test of psychomotor skill. It consists of a metal board with a matrix of 25 holes (5 rows of 5 holes). Pegs have a ridge along one side and must be rotated to match the hole before they can be inserted. The holes are rotated to different angles such that the participant has to rotate each peg before it will fit in the holes. The task is to insert the pegs as quickly as possible into the slots in sequence, first with the dominant hand and then with the non-dominant one. The holes had to be filled in a specified order, e.g. one row at a time from left to right. Participants completed the task first. The test ends when all the pegs have been placed and the DV is the time taken to complete the task.

4.7.1.6 Bakan Test (Rapid Visual Information Processing)

The Bakan test was administered as previously described in general methods section 2.5.2.1. In this study the 6-minute Bakan test was used.

4.7.1.7 VVLT recognition Test

The VVLT recognition task was administered was as previously described in general methods section 2.5.1.2. For this research study versions 1, 2 and 3 were used, to correspond with the VVLT lists (Appendix 6.11).

4.7.2 Assessment of cardiorespiratory fitness (maximal exercise test)

A seated ramp-incremental ($12W \cdot min^{-1}$) step exercise test (RISE-105) protocol was followed for the assessment of maximal aerobic capacity ($\dot{V}O_{2\,max}$). Additional variables derived were lactate threshold (LT), work rate peak (WR_{peak}) and ramp incremental (RI) test duration. These variables were required to calculate the work-rates for the individual training sessions throughout the study duration.

An electronically braked cycle ergometer (Excalibur Sport V2.0; Lode BV, Groningen, The Netherlands) was used for all cardio-respiratory fitness tests. Participants were fitted with a mouthpiece and nose clip to allow for breath by breath analysis during the test. The sensors for carbon dioxide, oxygen and air flow were calibrated before each test to ensure accurate measurement of pulmonary gas exchange using Breeze Suite software (V.5.0 and V.7.2; Medgraphics, Medical Graphics Corporation, St Paul, MN, USA). Participants were also fitted with a 12-lead ECG to monitor heart rate at 2-minute intervals during the test. Additional measures taken every 2 minutes were blood pressure using a sphygmomanometer and Borg's scale of rating of perceived exertion (RPE).

The exercise testing protocol commenced with a 3-minute rest period, followed by 4 minutes of cycling at 20 W. During this time gas exchange was confirmed to be at steady state, quantified by a respiratory exchange ratio (RER) between 0.75-0.9. The RI test was 12 W/min and participants were encouraged to maintain a cycling cadence above 70 rpm until volitional fatigue. Volitional fatigue was determined when the cadence fell below 50 rpm. Upon completion of the RI test, a 5-minute period of unloaded cycling (20 W) was performed to allow for recovery and calculation of the work-rate for the step-exercise (SE) test. WR_{peak} was calculated as follows:

$$WR_{peak} = \text{RI test duration x ramp rate} + 20\ (W)$$

The SE test was set at a work-rate of 105% WR_{peak} and initiated at the end of the 5-minute recovery period. Participants were encouraged to maintain a cycling cadence of ~80 rpm until volitional fatigue. Upon completion of the SE participants completed 5 minutes of active recovery at 20 W and were monitored to ensure heart rate and $\dot{V}O_2$ returned to baseline values.

The breath-by-breath data were edited using OriginPro 8 software (OriginLab, Northampton, MA), and data exceeding 99.9% confidence interval were removed. $\dot{V}O_{2peak}$ was calculated from a 12-breath rolling average, for both RI and SE components of the test. $\dot{V}O_{2max}$ was reported as the average of the $\dot{V}O_{2peak}$ for RI and SE. Lactate threshold was estimated using the V-slope method (Beaver, Wasserman, & Whipp, 1986), which identifies a breakpoint in the "v-slope" where CO2 output ($\dot{V}CO_{2p}$) is plotted as a function of pulmonary oxygen uptake ($\dot{V}O_{2p}$) (Rossiter, 2011). This is confirmed by a plateau in end-tidal CO_2.

4.7.3 Assessment of anthropometric indices

The measures of anthropometric indices were assessed as previously described in section (Chapter 2, section 2.8). The variables obtained for this research chapter were body fat percentage, BMI, waist circumference (cm) and waist-hip ratio.

4.8 Exercise training protocol

Participants were matched for age and BMI and assigned to heavy-intensity interval training (INT) or heavy-intensity continuous training (CON). Participants attended the lab twice per week for 12 weeks, for supervised training on electronically braked cycle ergometers. In week 6 of the training regime (mid-point), all participants completed a maximal exercise test for appropriate adjustment of work rates.

4.8.1 Confirmation of training regime intensity domain

The first training session for both INT and CON groups was monitored to confirm individuals were exercising in the heavy-intensity domain. Breath by breath data were collected to allow for analysis of cardiopulmonary gas exchange, which was monitored continuously for the full duration of the monitored session. Fingertip capillary blood samples were assessed for blood lactate levels (Lactate Pro, Arkray, Japan). Two blood lactate measures were taken during a 5 minute seated rest period prior to commencement of exercise. During exercise, for INT blood lactate was measured every 5 minutes during the first 20-minute training session. As the CON group were matched for work, the first training sessions were shorter in duration and so blood lactate was collected every 4 minutes. The monitored training session was completed on the first training session following the baseline and mid-point maximal exercise test. If cardiopulmonary gas exchange or blood lactate values indicated that

a participant was not exercising in the heavy–intensity domain, work rates were adjusted and participants were asked to complete a second monitored training session.

4.8.2 Training stimulus

4.8.2.1 Interval training

The INT training group performed 30 – 40 minute sessions involving repeated excursions into a work rate corresponding with 70%Δ between LT and $\dot{V}O_2$ peak interspersed with recovery periods. The work:recovery ratio for the INT group was 40s:80s, with the work component performed at 70% delta between LT and $\dot{V}O_{2\ max}$, and recovery component was 20 Watts. The duty cycles selected were based on the 1:2 (work:recovery) cycles described by Turner et al. (2006). The 40s:80 s protocol utilised for this study was adapted from the previous work by Turner and colleagues (2006) to tailor the regime for a sedentary, overweight/obese and middle-aged sample. The 70% delta (Δ) work-rate was calculated by the following equation:

$$70\%\Delta = 0.7(WR_{peak} - WR_{LT}) + WR_{LT}$$

4.8.2.2 Continuous training

The CON group exercised at a steady work rate of 120% lactate threshold. The work (J) performed in each session by CON was matched to the work performed by INT participants by manipulating the CON session durations. For CON participants, the work was calculated that would have been performed had they been in the INT group. From this, the duration for the CON sessions was calculated with the following equation:

$$Time = \frac{Work}{Power}$$

Work (J) was the total amount completed during an INT session comprising of the 40s intervals at 70%Δ work-rate and 80s at 20 W. Power (J/s) was the CON session work rate at 120% lactate threshold.

4.8.2.3 Non-exercising control group

Participants were asked maintain their current diet and physical activity levels, and abstain from taking up any new physical activity or exercises throughout the 12-week duration of the study.

4.8.3 Training session duration (INT and CON)

The training session durations are shown for both INT and CON in Table 4.3.

Table 4.3 Training session durations for INT and CON groups

Intervention week	Session duration (minutes)	
	INT[1] (Total)	CON[2] (Mean ± SD)
1	20	13.3 ± 1.3
2	25	16.6 ± 1.7
3-6	30	19.9 ± 2.0
7-9	35	22.5 ± 2.1
10-12	40	25.8 ± 2.4

[1]Session duration for INT group was same for all INT participants. [2]Session duration for CON group was different among CON participants, but matched for work (kJ) performed in INT sessions.

4.9 Ethical Approval

Attainment of ethical approval is described in Chapter 2, section 2.3.

4.10 Data Analysis

The SAS-mixed models procedure (PROC MIXED) was employed to examine the potential within-subjects change in cognitive function or cardiovascular health outcome variables over the 12-week intervention period, compared with the no intervention control group examined over the same period. The analysis included two fixed factors; condition with 3 levels (INT, CON and NO-EX); and time with 2 levels (mid and post). Baseline performance (on each cognitive or cardiovascular health outcome) was retained as a covariate. IQ was included as a covariate for all cognitive

outcomes, and age was included as a covariate for all cognitive and cardiovascular outcomes. Where age or IQ were non-significant they were removed from the model. Where covariates were significant, they were plotted to determine direction of relationship with the dependent variable. When significant main effects or interactions were found, Tukey corrected post hoc tests (LSMEANS) were performed to explore these. In cases, where an interaction with baseline or other covariate was significant, the LSMEANS procedure, examines the effect at the average value of the baseline (or other covariate) and is reported where significant. For such cases average baseline score is indicated on the relevant figure by a vertical line (e.g. see **Error! Reference source not found.**).

4.11 Results

4.11.1 Participant characteristics

The sample comprised of 28 females from the Leeds area (mean age: 41.4 ± 6.8 years). Table 4.4 shows that no significant differences were present between the three groups (INT, CON, and NO-EX) for participant characteristics at baseline (largest $F(2,27)=2.31$, $p=.120$). Mean IQ score was 115.4 ± 12.3 and the sample were categorised as 'high average' (Wechsler, 2008). All participants were obese (mean body fat percentage: 42.5 ± 4.7 %; mean BMI: 32.2 ± 4.2 kg/m^2), and met the criteria for abdominal obesity (mean waist circumference: 105.5 ± 10.4 cm; mean waist-hip ratio 0.91 ± 0.07).

Table 4.4 Participant characteristics (mean ± SD) at baseline for INT, CON and NO-EX

	INT (n=10)	CON (n=10)	NO-EX (n=8)	p
Age (yrs)	41.2 ± 4.0	42.9 ± 7.2	39.8 ± 9.2	.632
IQ (score)	115.1 ± 14.5	116.2 ± 12.4	114.8 ± 10.4	.968
BMI (kg/m^2)	33.0 ± 3.7	30.9 ± 3.3	32.8 ± 5.6	.503
Body fat (%)	44.6 ± 2.3	40.3 ± 4.0	42.6 ± 6.7	.120
Fat mass (kg)	40.5 ± 8.5	34.1 ± 6.9	38.4 ± 11.3	.279
Lean tissue (%)	55.4 ± 2.3	59.7 ± 4.0	57.4 ± 6.7	.120
FFM (kg)	49.8 ± 7.6	49.9 ± 4.6	49.8 ± 3.7	.999
WC (cm)	108 ± 9.9	100.6 ± 8.1	106.9 ± 11.5	.216
WHR	0.92 ± 0.1	0.88 ± 0.1	0.92 ± 3.7	.494

IQ=intelligence quotient, BMI=body mass index, WC = waist circumference, FFM=fat free mass, WHR=waist-hip ratio

Table 4.5 shows that no significant differences were present between the three groups (INT, CON, and NO-EX) for any of the variables at baseline (largest $F(2,27)=1.68$, $p=.207$) with the exception of percentage of LT at V02max, $F(2,27)=6.11$, $p<.001$. Post hocs showed that NO-EX condition (61.4 ± 6.9 %) had significantly higher LT% at $\dot{V}O_{2max}$ than INT (50.9 ± 6.1 %, $p<.05$). Mean resting heart rate (RHR) was 66.7 ± 7.6 bpm. Average mean arterial pressure (94.3 ± 9.8 mmHg) was is in the normal range. Mean absolute $\dot{V}O_{2max}$ was 2079.8 ± 323.9 ml/min, and relative $\dot{V}O_{2max}$ was 23.9 ± 3.2 ml/kg/min, and classed as very poor according to the ACSM percentile values for maximal aerobic power (Pescatello, 2014).

Table 4.5 Indices of cardiovascular fitness (mean ± SD) at baseline for INT, CON and NO-EX

	INT (n=10)	CON (n=10)	NO-EX (n=8)	p
Resting heart rate (bpm)	66.4 ± 7.7	67.5 ± 8.8	66.3 ± 6.7	.934
SBP (mmHg)	125.9 ± 10.9	123.2 ± 15.5	115 ± 11.5	.207
DBP (mmHg)	81.9 ± 8.7	81.2 ± 10.1)	77.9 ± 8.8	.633
MAP (mmHg)	96.6 ± 9.1	95.2 ± 11.0	90.3 ± 9.3	.388
Absolute $\dot{V}O_{2max}$ (ml/min)	2138.4 ± 405.9	2067.2 ± 257.0	1969.5 ± 299.6	.757
Relative $\dot{V}O_{2max}$ (ml/kg/min)	23.8 ± 2.8	24.6 ± 2.9	21.8 ± 2.9	.658
LT ($ml \cdot min^{-1}$)	1077.1 ± 173.0	1149.1 ± 242.7	1255.1 ± 200.1	.215
Percentage LT $\dot{V}O_{2max}$	50.92 ± 6.1	55.1 ± 6.1	61.4 ± 7.0	.007

SBP=systolic blood pressure, DBP=diastolic blood pressure, MAP=mean arterial pressure, LT=lactate threshold

4.11.2 Impact of exercise intervention on cognitive function

4.11.2.1 Verbal memory (VVLT)

4.11.2.1.1 Total acquisition

In the final model, 2 outlying observations were excluded to normalise the residuals. Baseline total acquisition score was a significant covariate, $F(1,21)=28.1$, $p<.0001$, and as expected showed a positive correlation with total words recalled at subsequent test visits. There was a trend towards a main effect of condition, $F(2,21)=2.75$, $p= .09$, but no significant interactions (see Appendix 6.22). Figure 4.4 indicates that total acquisition performance was better for CON than for INT and NO-EX at average baseline score.

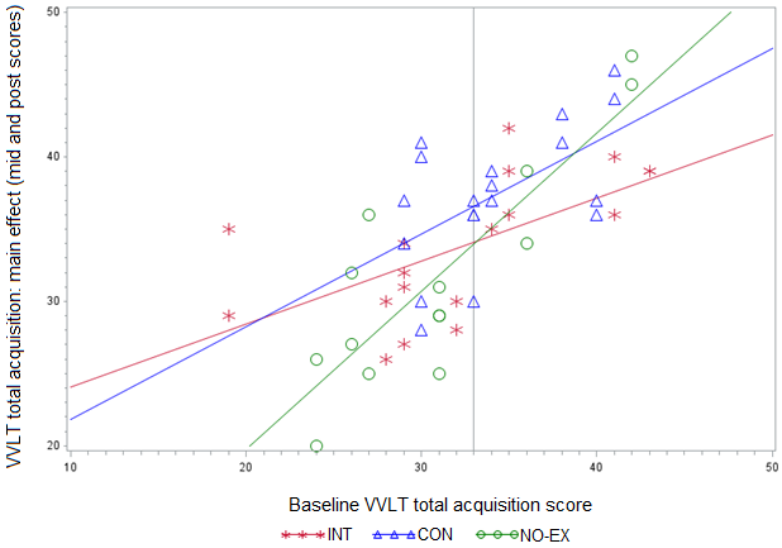

Figure 4.4 VVLT total acquisition over mid and post (vertical axis) plotted against baseline score. Vertical line indicates average baseline total acquisition

4.11.2.1.2 Delayed recall

In the final model, 1 outlying observation was excluded to normalise the residuals. Baseline score was a significant covariate, $F(1,21)=20.7$, $p<.001$, and as expected showed a positive correlation with words recalled (after 30-minute delay) at subsequent test visits. The analysis revealed no further significant main effects or interactions (see Appendix 6.22).

4.11.2.1.3 Recognition

In the final model, 2 outlying observations were excluded to normalise the residuals. Baseline score was a significant covariate, $F(1,21)=4.39$, $p< .05$, and as expected showed a positive correlation with word recognition at subsequent test visits. The analysis revealed no further significant main effects or interactions (Appendix 6.22)

4.11.2.1.4 Proactive interference

In the final model, 3 outlying observations were excluded to normalise the residuals. The analysis revealed no significant main effects or interactions (Appendix 6.22).

4.11.2.1.5 Retroactive interference

In the final model, 1 outlying observation was excluded to normalise the residuals. There was a trend towards baseline score as a significant covariate, F(1,22)=3.09, p= .09, and as expected showed a positive correlation with performance at subsequent test visits. The analysis revealed no significant main effects or interactions (Appendix 6.22).

4.11.2.2 Spatial memory (VSLT)

4.11.2.2.1 Total designs

In the final model, baseline score was a significant covariate, F(1,22)=15.1, p<.001, and as expected showed a positive correlation with designs recalled at subsequent test visits. There was a trend towards a significant visit*condition interaction, F(2,22)=3.01, p= .07. Figure 4.5 indicates that VSLT design score increased from mid to post for INT and CON, but decreased for NO-EX. The analysis revealed no significant main effects or interactions (see Appendix 6.23).

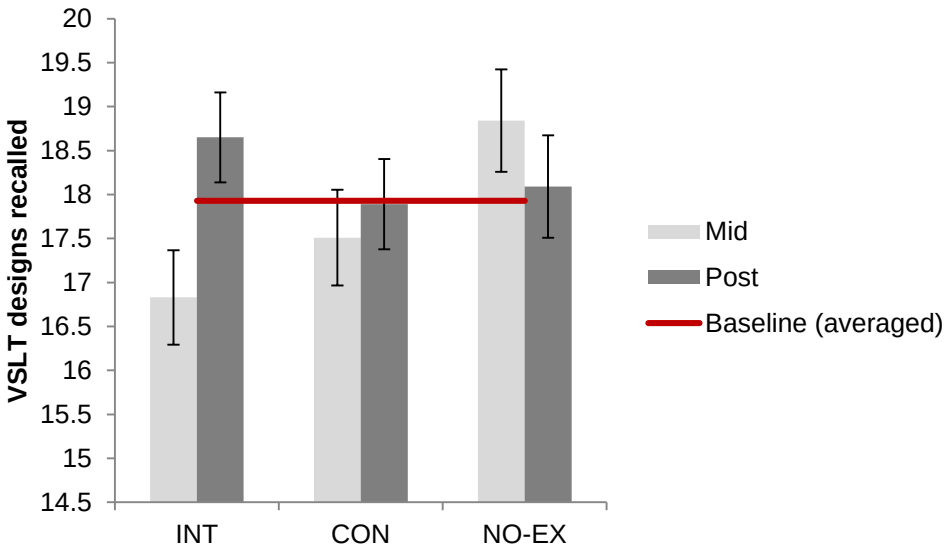

Figure 4.5 VSLT designs recalled at mid-point and post-intervention (relative to average baseline score) for INT, CON and NO-EX

4.11.2.2.2 Locations

In the final model, 1 outlying observation was excluded to normalise the residuals. Baseline score was a significant covariate, F(1,22)=5.20, p<.05, and as expected showed a positive correlation with locations recalled at subsequent test visits. There was a significant main effect of visit, F(1,21)=7.94, p<.01 which is qualified by a

significant baseline*visit interaction, F(1,21)=6.80, p< .05. Figure 4.6 shows that irrespective of condition, in those with low baseline scores, performance at post-testing was worse than at mid-point. However, no differences in mid- and post-test performance were observed in those with high baseline scores. Post hoc tests for main effect of visit were not significant and the analysis revealed no significant main effects or interactions (see Appendix 6.23).

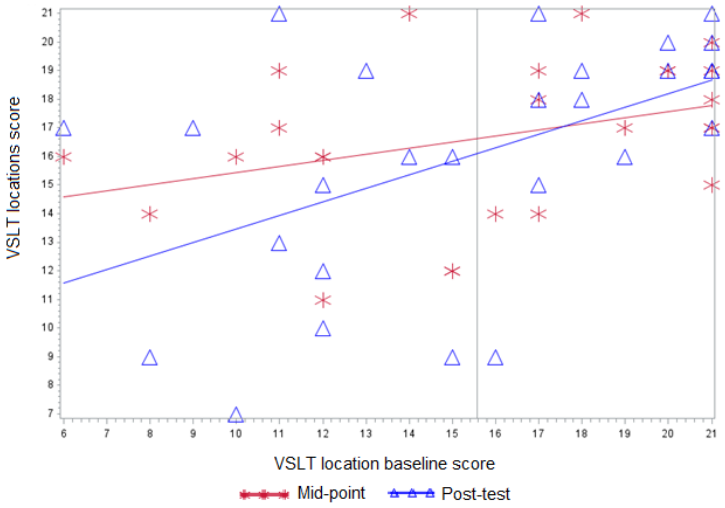

Figure 4.6 VSLT locations performance (whole sample) plotted against baseline score (horizontal axis) for mid-point and post-test. Vertical line indicates average baseline location score.

4.11.2.2.3 Designs and locations

In the final model, 1 outlying observation was excluded to normalise the residuals. Baseline score was a significant covariate, F(1,22)=4.20, p=.05, and as expected showed a positive correlation with designs/locations recalled at subsequent test visits. There was a significant main effect of visit, F(1,22)=4.18, p= .05, which is qualified by a baseline*visit interaction, F(1,22)=4.65, p< .05. Figure 4.7 indicated that in those with high baseline scores, performance was better at post-testing relative to mid-point. The analysis revealed no significant main effects or interactions (see Appendix 6.23).

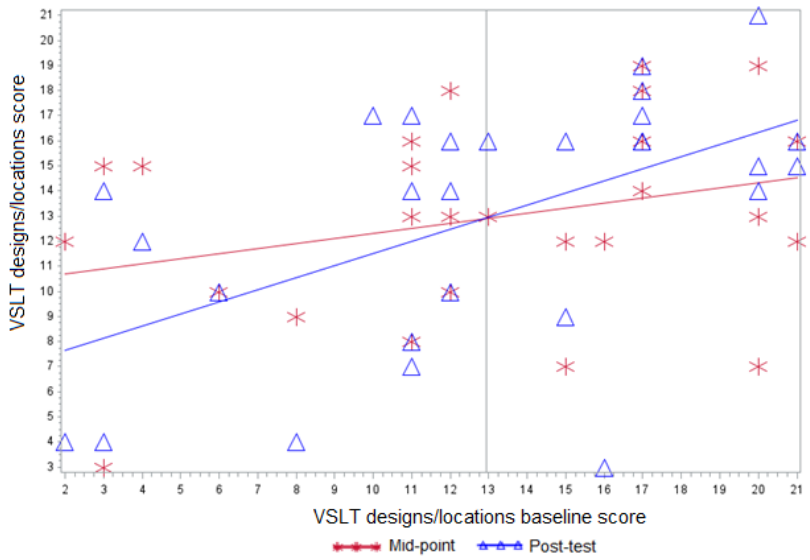

Figure 4.7 VSLT designs/locations performance (whole sample) plotted against baseline score (horizontal axis) for mid-point and post-test. Vertical line indicates average designs/locations score.

4.11.2.2.4 Delayed recall of designs and locations

In the final model, 1 outlying observation was excluded to normalise the residuals. Baseline score was a significant covariate, $F(1,22)=14.71$, $p<.0001$, and as expected showed a positive correlation with delayed designs/locations recalled at subsequent test visits. There was a trend towards a baseline*condition interaction, $F(2,22)=2.89$, $p= .08$. Figure 4.8 indicates that in those with low baseline scores, performance at subsequent testing (pooled over mid and post) was superior in INT relative to CON and NO-EX. However, in those with high baseline scores performance at subsequent testing was poorer in INT relative to CON and NO-EX. The analysis revealed no significant main effects or interactions (see Appendix 6.23).

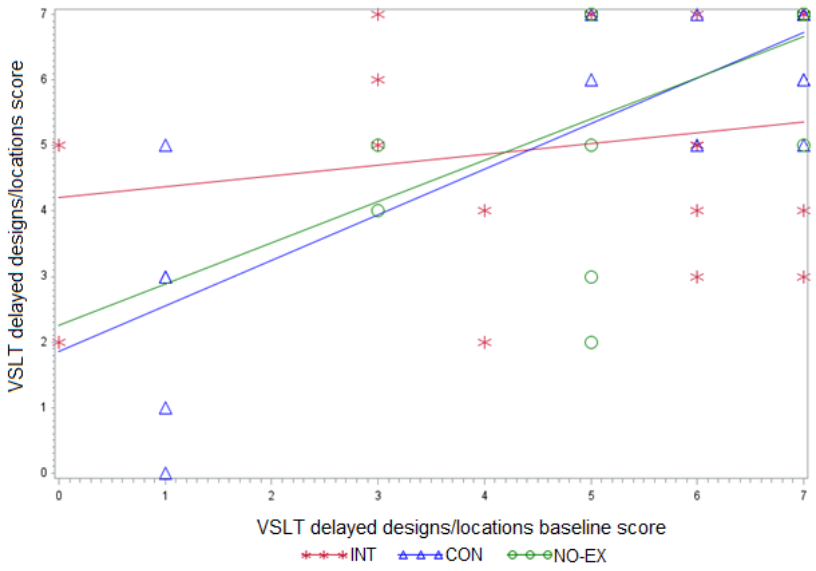

Figure 4.8 VSLT delayed designs/locations over mid- and post (vertical axis) plotted against baseline score

4.11.2.3 Attention

4.11.2.3.1 Correct hits

In the final model 1 outlying observation was excluded to normalise the residuals. Baseline score was a significant covariate, $F(1,21)=120.32$, $p<.001$, and as expected showed a positive correlation with total correct hits at subsequent test visits. The analysis revealed no further significant main effects or interactions (see Appendix 6.24).

4.11.2.3.2 Reaction time of correct responses

In the final model 1 outlying observation was excluded to normalise the residuals. Baseline score was a significant covariate, $F(1,21)=15.56$, $p<.001$, and as expected showed a positive correlation with reaction time of correct responses at subsequent test visits. The analysis revealed no further significant main effects or interactions (see Appendix 6.24).

4.11.2.3.3 Missed responses

In the final model, 1 outlying observation was excluded to normalise the residuals. Baseline score was a significant covariate, $F(1,22)=81.61$, $p<.001$, and as expected showed a positive correlation with total missed responses at subsequent test visits. There was a trend towards a main effect of visit, $F(1,21)=3.78$, $p= .07$. Post hoc tests show that, irrespective of condition, the number of errors at post-intervention (29.9 ±

1.2) were significantly lower than at mid-point (34.0 ± 1.24; t(21)=3.32, p<.01). The analysis revealed no further significant main effects or interactions (see Appendix 6.24).

4.11.2.3.4 False positive responses

In the final model, 2 outlying observations were excluded to normalise the residuals. Baseline score and age were significant covariates, F(1,21)=5.07, p<.05, and F(1,21)=10.1, p<.01, respectively. As expected baseline score was positively correlated with performance at subsequent testing, however false-positive responses were higher in younger participants. There was a significant main effect of condition, F(2,21)=9.76, p< .001, and a trend towards a baseline*condition interaction, F(2,21)=2.66, p= .09, as indicated in Figure 4.9. Post-hoc comparisons showed overall false-positive responses for NO-EX (10.2 ± 1.1) were significantly higher than INT (5.5 ± 0.9;t(21)=-3.26, p< .01) and CON (5.4 ± 1.0; t(21)=-3.23, p< .01). The analysis revealed no further significant main effects or interactions (see Appendix 6.24).

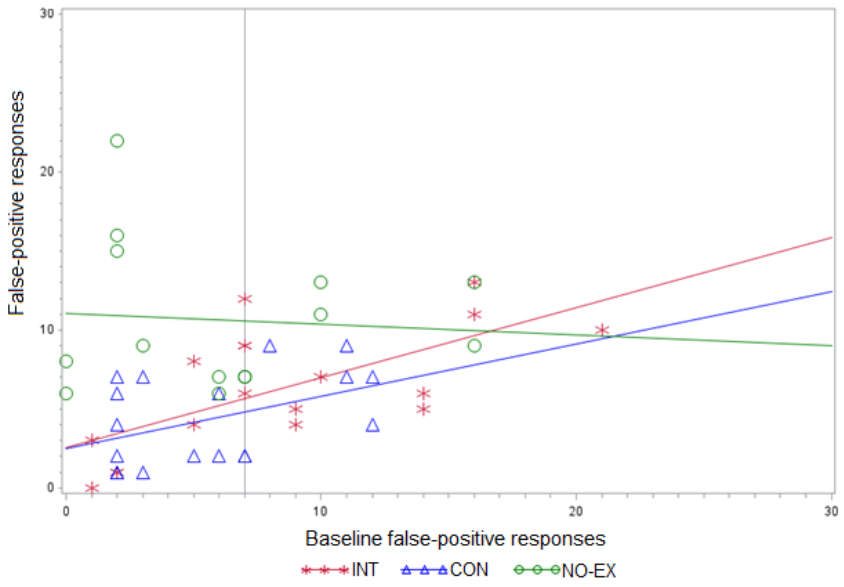

Figure 4.9 False-positive responses over mid-and post (vertical axis) plotted against baseline for INT, CON and NO-EX. Vertical line indicates average baseline false positive responses.

4.11.2.4 Spatial working memory (Corsi)

4.11.2.4.1 Correct responses

In the final model, 1 outlying observation was excluded to normalise the residuals. Baseline score and IQ were significant covariates, $F(1,21)=92.76$, $p<.0001$, and $F(1,21)=9.71$, $p<.01$, respectively. As expected both baseline score and IQ showed a positive correlation with performance at subsequent testing. There was a significant main effect of condition, $F(2,21)=5.44$, $p< .01$, which is qualified by a significant baseline*condition interaction, $F(2,21)=5.97$, $p<.01$. There was also a trend towards a baseline*visit interaction, $F(1,21)=3.85$, $p= .06$. The baseline by condition interaction is evident in Figure 4.10, as those with low baseline scores (average score = 61.2) show superior performance in INT and CON relative to NO-EX. However, in those with above-average baseline score performance is worse for INT relative to CON and NO-EX. The analysis revealed no further significant main effects or interactions (see Appendix 6.25).

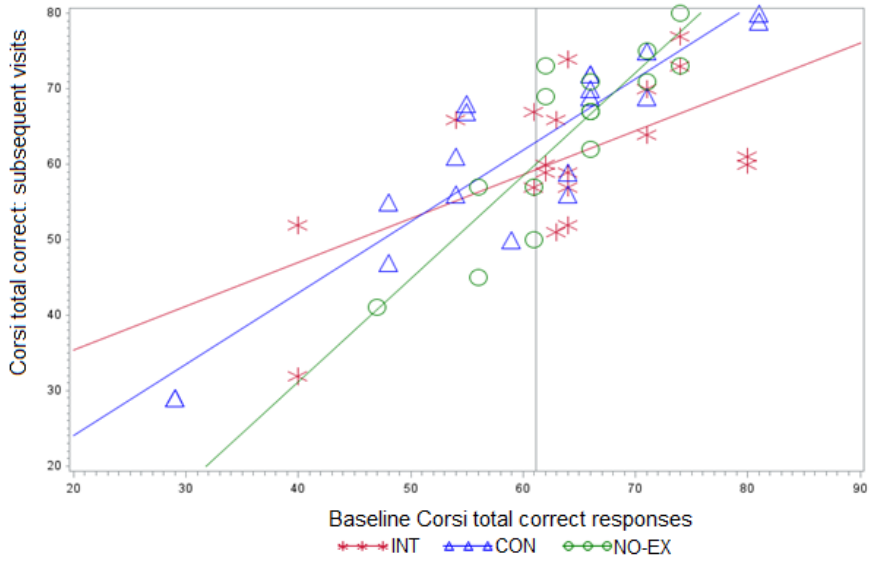

Figure 4.10 Corsi (total correct) over mid-and post (vertical axis) plotted against baseline scores for INT, CON, and NO-EX. Vertical line indicates average baseline total correct responses.

4.11.2.4.2 Reaction time for correct responses

In the final model, 2 outlying observations were excluded to normalise the residuals. Baseline score and IQ were significant covariates $F(1,20)=27.3$, $p<.001$ and $F(1,20)=5.58$, $p< .05$, respectively. Baseline score showed a positive correlation with

performance at subsequent test visits, and reaction time decreased as IQ increased. The analysis revealed no further significant main effects or interactions (see Appendix 6.25).

4.11.2.4.3 Correct responses: crossing trials

In the final model, baseline score and IQ were significant covariates, $F(1,20)=16.51$, $p<.001$, and $F(1,20)=4.73$, $p< .05$, respectively. As expected both baseline score and IQ showed a positive correlation with performance at subsequent testing. Age showed a trend towards being a covariate, $F(1,20)=3.42$, $p= .07$, and showed a negative correlation with performance. The analysis revealed no further significant main effects or interactions (see Appendix 6.25).

4.11.2.4.4 Correct responses: non-crossing trials

In the final model, baseline score was a significant covariate, $F(1,22)=12.58$, $p<.01$, and as expected showed a positive correlation with performance at subsequent visits. The analysis revealed no further significant main effects or interactions (see Appendix 6.25).

4.11.2.5 Executive Function (ToH)

4.11.2.5.1 Errors

In the final model, 3 outlying observations were excluded to normalise the residuals. Baseline score was a significant covariate, $F(1,21)=10.19$, $p<.01$, and as expected showed a positive correlation with performance at subsequent visits. The analysis revealed no further significant main effects or interactions (see Appendix 6.26).

4.11.2.5.2 Completion time

In the final model, 3 outlying observations were excluded to normalise the residuals. Baseline score was a significant covariate, $F(1,21)=69.19$, $p<.0001$, and as expected showed a positive correlation with completion time at subsequent visits. There was a main effect of visit $F(1,20)=6.38$, $p< .05$, and a trend towards an effect of condition, $F(2,21)=3.25$, $p= .06$. There was a significant baseline*condition interaction, $F(2,21)=6.25$, $p< .01$, as indicated in Figure 4.11. In those with slower baseline completion time, performance at subsequent visits was faster for INT relative to CON and NO-EX. No differences between the conditions were evident in those with fast completion times at baseline. There was a significant baseline*visit interaction,

F(1,20)=10.57, p< .01, and a trend towards a visit*condition interaction, F(2,20)=2.88, p= .08. Post hoc analysis showed that, irrespective of condition, completion time at post-testing (216.4± 7.8) was significantly faster than mid-point (230.3 ± 8.1; t(20)=1.95, p= .06) but just failed to reach significance. Post hoc tests for the visit by condition interaction also just failed to reach significance, but indicated at mid-point testing completion time for INT (199.3 ± 12.0) was significantly faster than CON (250.3 ± 12.1; t(20)= -3.00, p= .07).

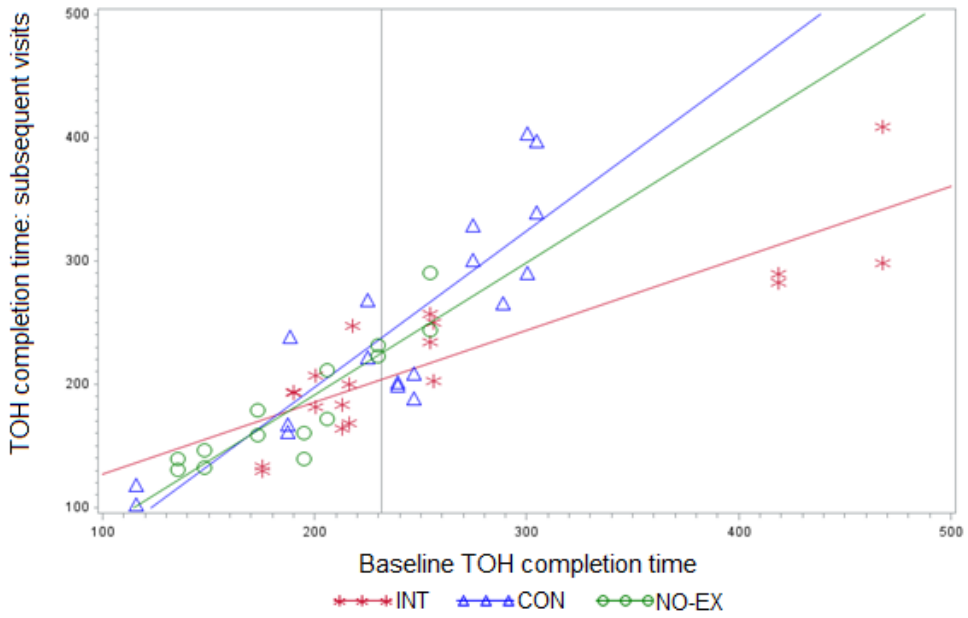

Figure 4.11 ToH completion time over mid-and post (vertical axis) plotted against baseline scores for INT, CON, and NO-EX. Vertical line indicates average baseline ToH completion time.

4.11.2.6 Psychomotor skill (Grooved Peg Board)

4.11.2.6.1 Completion time (dominant hand)

In the final model, baseline completion was a significant covariate, F(1,21)=146.83, p<.0001, and as expected showed a positive correlation with completion time at subsequent testing. There was a significant main effect of condition, F(2,21)=7.60, p< .01, as qualified by a significant baseline*condition interaction, F(2,21)=7.74, p< .01. The analysis revealed no further significant main effects or interactions (see

Appendix 6.27). The baseline by condition interaction is evident in Figure 4.12 as in those with slower baseline completion times, performance at subsequent testing is superior in INT relative to NO-EX and CON. In those with faster completion times at baseline, performance is superior in CON relative to NO-EX and INT.

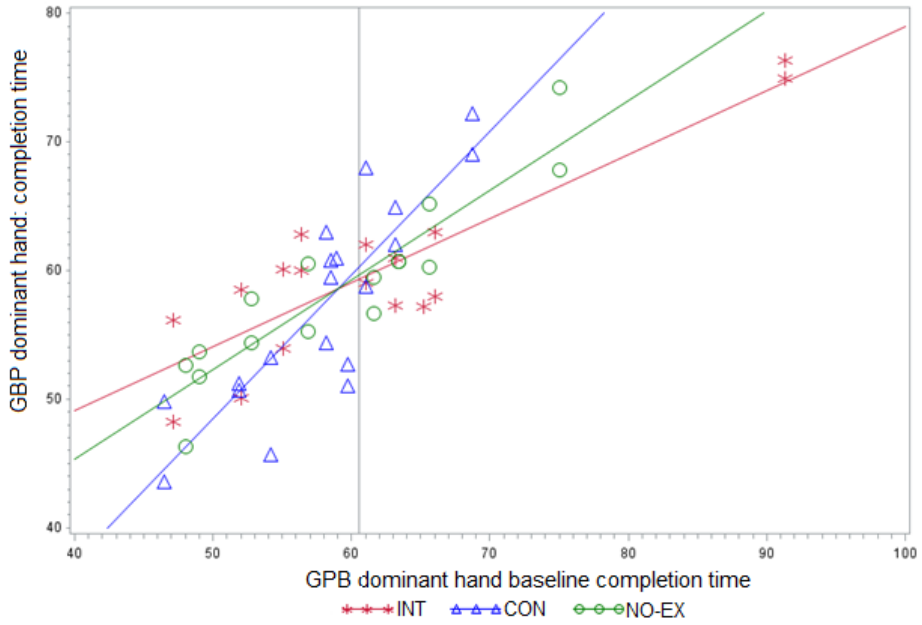

Figure 4.12 GPB (dominant hand) completion time over mid-and post (vertical axis) plotted against baseline scores for INT, CON, and NO-EX. Vertical line indicates average baseline completion time.

4.11.2.6.2 Completion time (non-dominant hand)

In the final model, 1 outlying observation was excluded to normalise the residuals. In the final model, baseline completion time was a significant covariate, $F(1,21)=80.96$, $p<.001$, and as expected showed a positive correlation with completion time at subsequent testing. There was a main effect of condition, $F(2,21)=4.82$, $p<.05$ as qualified by a significant baseline*condition interaction, $F(2,21)=4.59$, $p<.05$. Figure 4.13 indicate that in those with faster completion times at baseline, performance at subsequent testing is better in CON relative to INT and NO-EX. In those with slower completion times at baseline, performance at subsequent testing is superior in NO-EX relative to INT and CON. The analysis revealed no further significant main effects or interactions (see Appendix 6.27).

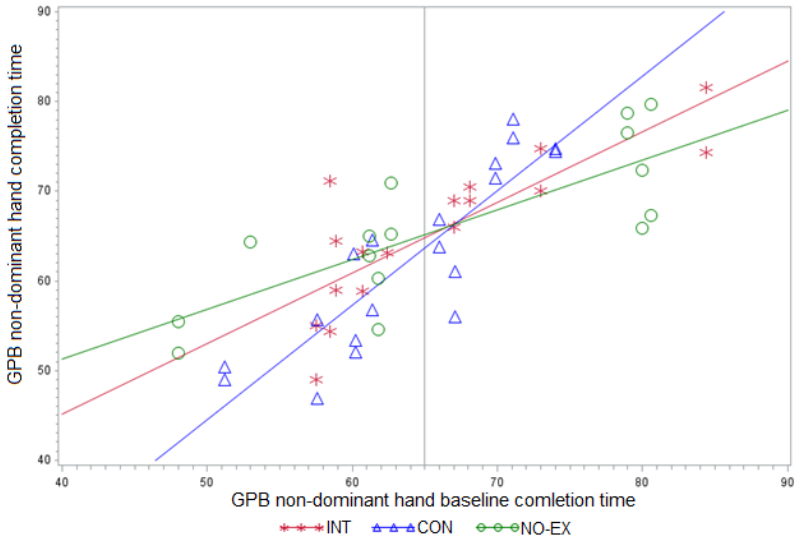

Figure 4.13 GPB (non-dominant hand) completion time over mid-and post (vertical axis) plotted against baseline scores for INT, CON, and NO-EX. Vertical line indicates average baseline completion time.

4.11.3 Impact of intervention on health

4.11.3.1 Cardiovascular fitness

Absolute $\dot{V}O_{2max}$, relative $\dot{V}O_{2max}$, lactate threshold (LT) and percentage LT of VO_{2max} had not significantly altered post-intervention after controlling for baseline values (**Error! Reference source not found.**, p >.05). Mean arterial pressure (MAP) was lower in NO-EX relative to INT and CON, as confirmed by a main effect of condition (p<.05).

Table 4.6 Cardiovascular fitness (mean ± SD) at baseline and post-intervention for INT, CON and NO-EX

	INT		CON		NO-EX	
	Baseline	**Post**	**Baseline**	**Post**	**Baseline**	**Post**
Absolute $\dot{V}O_{2max}$ (ml/min)	2138.4 ± 405.9	2221.6 ± 406.1	2067.2 ± 257.0	2103.4 ± 226.9	1969.5 ± 299.6	2052.7 ± 316.9
Relative $\dot{V}O_{2max}$ (ml/kg/min)	23.8 ± 2.8	25.2 ± 3.1	24.6 ± 2.9	25.2 ± 2.6	21.8 ± 2.9	22.2 ± 5.1
Lactate Threshold ($ml \cdot min^{-1}$)	1077.1 ± 173.0	1195.8 ± 235.6	1149.1 ± 242.7	1124.8 ± 158.8	1255.1 ± 200.1	1191.5 ± 174.4
Percentage LT of $\dot{V}O_{2max}$ x (%)	50.9 ± 6.0	54.6 ± 7.8	55.1 ± 6.1	53.5 ± 4.9	61.4 ± 6.9	56.8 ± 9
Mean Arterial Pressure (mmHg)*	96.6 ± 9.1	93.1 ± 8.6	95.2 ± 10.9	95.0 ±10.8	90.3 ± 9.3	88.1 ± 6.8

*Indicates significant group differences at post-intervention after controlling for baseline score ($p<.05$).

4.11.3.2 Absolute $\dot{V}O_{2max}$

In the final model, baseline absolute $\dot{V}O_{2max}$ was a significant covariate, F(1,16)=180.79, p<.0001, and as expected showed a positive correlation with absolute $\dot{V}O_{2max\ x}$ at subsequent testing. The analysis revealed no further significant main effects or interactions (see Appendix 6.28).

4.11.3.2.1 Relative $\dot{V}O_{2max}$

In the final model 2 outlying observations were excluded to normalise the residuals. In the final model, baseline relative $\dot{V}O_{2max}$ was a significant covariate, F(1,18)=130.82, p< .0001, and as expected showed a positive correlation with relative VO_{2max} at subsequent testing. The analysis revealed no further significant main effects or interactions (see Appendix 6.28).

4.11.3.2.2 Lactate threshold

In the final model, baseline lactate threshold was a significant covariate, F(1,19)=14.04, p<.001, and as expected showed a positive correlation with lactate threshold at subsequent testing. The analysis revealed no further significant main effects or interactions (see Appendix 6.28).

4.11.3.2.3 Percentage LT of $\dot{V}O_{2max}$

In the final model, baseline percentage LT of $\dot{V}O_{2max}$ was a significant covariate, F(1,18)=4.23, p<.05, and as expected showed a positive correlation with LT percentage of VO_{2max} at subsequent testing . The analysis revealed no further significant main effects or interactions (see Appendix 6.28).

4.11.3.2.4 Mean arterial pressure

In the final model, baseline mean arterial pressure (MAP) was a significant covariate, F(1,18)=39.84, p<.001, and as expected showed a positive correlation with MAP at subsequent testing. There was a significant main effect of condition, F(2,18)=8.15, p<.01 and a significant baseline*condition interaction, F(2,18)=4.77, p<.05. There was a trend towards significance for age as a covariate, F(1,18)=3.31, p=.08, such that MAP increased with age. Figure 4.14 indicates that in those with highest MAP at baseline, values at subsequent testing were lower in INT and NO-EX relative to CON.

In those with lower baseline MAP, values at subsequent testing were lowest in CON and NO-EX relative to INT. The analysis revealed no further significant main effects or interactions (see Appendix 6.28).

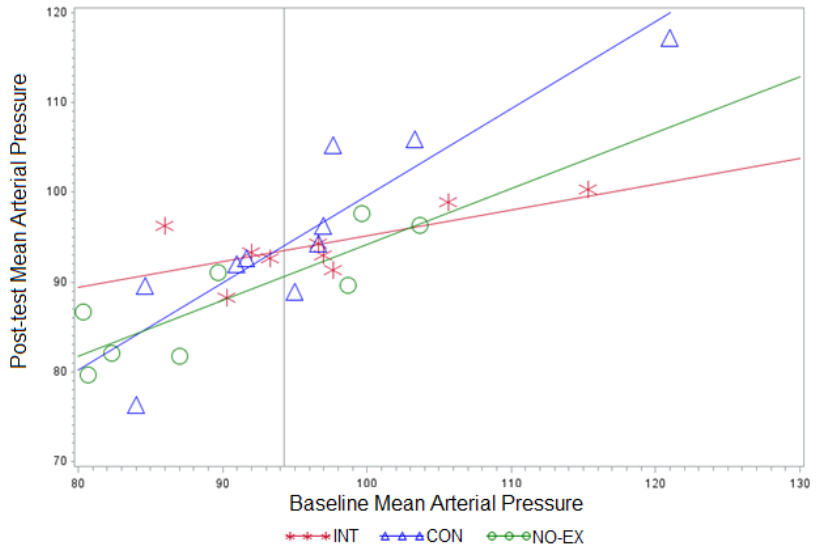

Figure 4.14 Mean arterial pressure (MAP) at baseline plotted against MAP at post-test for INT, CON and NO-EX. Vertical line indicates average baseline MAP.

4.11.3.3 Indices of obesity

4.11.3.3.1 Body mass Index (BMI)

In the final model, 4 outlying observations were excluded to normalise the residuals. Baseline BMI was a significant covariate, $F(1,20)=958.5$, $p<.0001$, and as expected showed a positive correlation with BMI at subsequent testing. There was a significant visit*condition interaction, $F(2,19)=3.67$, $p< .05$. Figure 4.15 indicates that from mid- to post-intervention BMI increased in NO-EX, decreased in CON and did not change for INT. The analysis revealed no further significant main effects or interactions (see Appendix 6.29Appendix 6.28).

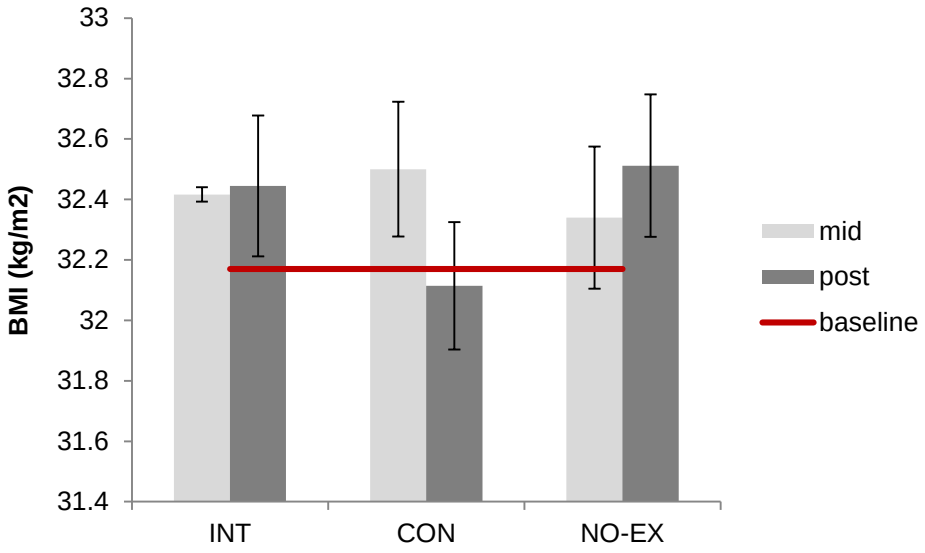

Figure 4.15 BMI at mid- and post-intervention (controlling for baseline BMI) for INT, CON and NO-EX

4.11.3.3.2 Body fat percentage

In the final model, 1 outlying observation was excluded to normalise the residuals. Baseline body fat percentage was a significant covariate, $F(1,22)=77.79$, $p<.001$, and as expected showed a positive correlation with body fat percentage at subsequent testing. There was a trend towards a main effect of visit, $F(1,20)=3.10$. $p= .09$. The analysis revealed no further significant main effects or interactions (see Appendix 6.29). Raw values suggested that body fat percentage increased over the 12 weeks of intervention irrespective of condition.

4.11.3.3.3 Waist circumference

In the final model, baseline waist circumference was a significant covariate, $F(1,21)=399.40$, $p< .001$, and as expected showed a positive correlation with WC at subsequent testing. The analysis revealed no significant main effects or interactions (see Appendix 6.29).

4.11.3.3.4 Waist-hip ratio

In the final model, baseline WHR was a significant covariate, $F(1,22)=105.43$, $p<.001$, and as expected showed a positive correlation with WHR at subsequent testing. There was a visit*condition interaction, $F(2,21)=3.82$, $p< .05$, as indicated in Figure 4.16. This indicates that from mid- to post-intervention WHR decreased for NO-EX

and did not change for INT and CON. There was a trend towards a significant main effect of visit, F(1,21)=3.15, p= .09 and a trend towards a baseline*visit interaction, F(1,21)=3.66, p= .07. The analysis revealed no further significant main effects or interactions (Appendix 6.29).

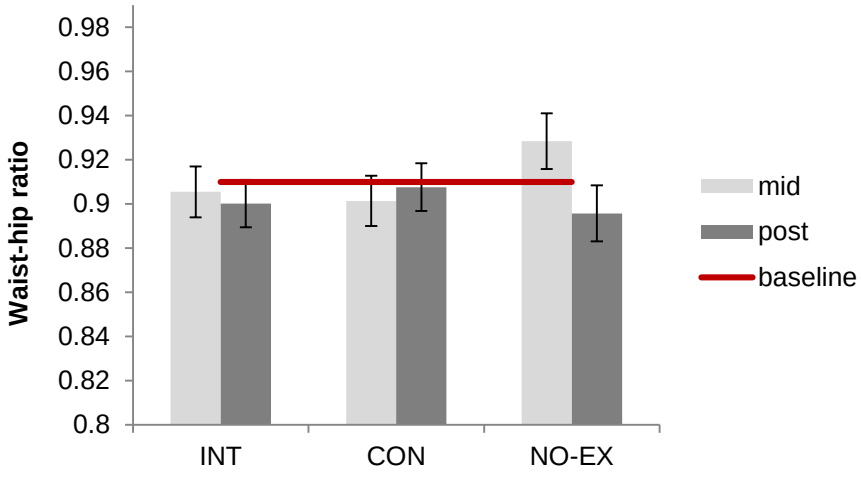

Figure 4.16 WHR at mid- and post-intervention (controlling for baseline WHR) for INT, CON and NO-EX

4.11.4 Summary of findings

4.11.4.1 Impact of 12-week intervention on cognitive function

A tabulated summary of the effect of the intervention on cognitive function is shown in Table 4.7.

- As expected, baseline cognitive performance was the greatest predictor of performance at subsequent tests visits for all verbal memory (excluding proactive interference), spatial memory, spatial working memory, attention, executive function and psychomotor skill outcomes.
- Performance on the executive function task (ToH) was altered following the intervention, showing faster completion times for INT relative to CON and NO-EX. This effect was more pronounced at mid-point testing (visit*condition).

- Performance on a spatial memory outcome (designs) improved for INT and CON from mid to post, but decreased for NO-EX (a trend for visit*condition interaction).
- Baseline scores showed significant (or a trend for) interactions with condition for Corsi correct responses, ToH completion time, GPB completion time (dominant and non-dominant hand) and VSLT delayed designs/locations. For VSLT, corsi and ToH in participants with poorest baseline performance, INT showed superior performance at subsequent testing relative to CON and NO-EX.
- Baseline score showed significant (or a trend for) interactions with visit for VSLT (locations and designs/locations), ToH completion time and Corsi (total correct). For VSLT and corsi outcomes, those with lowest baseline scores were showing a decline in performance from mid-point to post. Those with high baseline scores were not affected. For ToH, performance improves from mid to post in those with the slowest baseline completion times
- Overall, age and IQ did not impact change in cognitive score over time for the majority of cognitive function outcomes. Irrespective of condition, IQ was associated with better performance in spatial working memory task (accuracy, RT correct, accuracy: crossing trials). Age was a significant covariate for attention (false-positive responses) indicating that performance was worse in younger participants. Age showed a trend for an association with working memory (accuracy of crossing trials) indicating performance decreased with age.

Table 4.7 Tabulated summary of cognitive function outcomes

	Main effects		Covariates			Interaction terms				
Cognitive outcome	**Visit**	**Cond**	**Baseline**	**Age**	**IQ**	**B*Visit**	**B*Cond**	**Visit*Cond**	**Age*Cond**	**IQ*Cond**
VERBAL MEMORY										
Total Acquisition	N	Trend p= .09	Sig. p< .001	-	-	N	N	N	-	-
Delayed recall	N	N	Sig. p< .001	-	-	N	N	N	-	-
Recognition	N	N	Sig. p< .05	-	-	N	N	N	-	-
Retroactive Interference	N	N	Trend P= .09	-	-	N	N	N	-	-
Proactive Interference	N	N	N	-	-	N	N	N	-	-
SPATIAL MEMORY										
Designs	N	N	Sig. p< .001	-	-	N	N	Trend p=.07	-	-
Locations	Sig. p< .01	N	Sig. p< .05	-	-	Sig. p< .05	N	N	-	-
Designs/locations	Sig. p< .05	N	Sig. p< .05	-	-	Sig. p< .05	N	N	-	-
Delayed designs/locations	N	N	Sig. p< .001	-	-	N	Trend p= .08	N	-	-
ATTENTION										
Hits	N	N	Sig. p< .001	-	-	N	N	N	-	-
Reaction time hits	N	N	Sig. p< .001	-	-	N	N	N	-	-
Missed responses	Trend p= .07	N	Sig. p< .001	-	-	N	N	N	-	-
False-positives	N	Sig. p< .001	Sig. p< .05	Sig. p< .01	-	N	Trend p= .09	N	-	-

NB cond = condition, B*Visit = baseline*visit, B*Cond = baseline*condition; - indicates term removed from final model for best fit (lowest AICc score)

	Main effects		Covariates			Interaction terms				
Cognitive outcome	**Visit**	**Cond**	**Baseline**	**Age**	**IQ**	**B*Visit**	**B*Cond**	**Visit*Cond**	**Age*Cond**	**IQ*Cond**
SPATIAL WORKING MEMORY										
Correct responses	trend p<.07	Sig. p< .01	Sig. p< .001	-	Sig. p< .01	Trend p= .06	Sig. p< .01	N	-	-
Reaction time of correct responses	N	N	Sig. p< .001	-	Sig. p< .05	N	N	N	-	-
Correct responses: crossing trials	N	N	Sig. p< .001	Trend p= .07	Sig. p< .05	N	N	N	-	-
Correct responses: non-crossing trials	N	N	Sig. p< .001	-	-	N	N	N	-	-
EXECUTIVE FUNCTION										
Errors	N	N	Sig. p< .01	-	-	N	N	N	-	-
Completion time	Sig. p< .05	Trend p= .06	Sig. p< .001	-	-	Sig. p< .01	Sig. p< .01	Trend p= .08	N	N
PSYCHOMOTOR PERFORMANCE										
Completion time: Dominant hand	N	Sig. p< .01	Sig. p< .001	-	-	N	Sig. p< .01	N	-	-
Completion time: Non-dominant hand	N	Sig. p< .05	Sig. p< .001	-	-	N	Sig. p< .05	N	-	-

NB cond = condition, B*Visit = baseline*visit, B*Cond = baseline*condition; - indicates term removed from final model for best fit (lowest AICc score)

4.11.4.2 Effects of 12-week intervention on health parameters

A tabulated summary of the effect of the intervention on indices of cardiovascular fitness and obesity is shown in Table 4.8.

- As expected, the baseline cardiovascular fitness and anthropometric parameters were the strongest predictors of the corresponding post-intervention parameters.
- MAP was significantly reduced post-intervention for NO-EX but not the exercising conditions, this was also from a lower baseline MAP.
- Baseline MAP showed a significant interaction with condition indicating those with highest baseline values showed greatest improvement following INT.
- Evidence suggests NO-EX showed a subtle increase in BMI but a decrease in WHR post-intervention relative to mid-point.
- Raw data (see Table 4.8) indicated small improvements in absolute and relative $\dot{V}O_{2max}$ but these failed to reach significance after controlling for baseline value. The NO-EX control group also showed signs of increasing absolute $\dot{V}O_{2max.}$

Table 4.8 Tabulated summary of outcomes: Indices of cardiovascular fitness and obesity

	Main effects		Covariates		Interaction terms			
	Visit	**Condition**	**Baseline**	**Age**	**B*Visit**	**B*Cond**	**Visit*Cond**	**Age*Cond**
Indices of cardiovascular fitness								
Absolute $\dot{V}O_{2max}$	-	N	Sig. p< .0001	-	-	N	-	N
Relative $\dot{V}O_{2max}$	-	N	Sig. p< .0001	-	-	N	-	-
Lactate Threshold	-	N	Sig. p< .001	N	-	N	-	N
LT Percentage of $\dot{V}O_{2max}$	-	N	Sig. p< .05	N	-	N	-	N
Mean Arterial Pressure	-	Sig. p< .01	Sig. p< .001	Trend p= .08	-	Sig. p< .05	-	N
Indices of obesity								
Body fat (%)	Trend p= .09	N	Sig. p< .001	-	N	N	N	-
BMI	N	N	Sig. p< .0001	-	N	N	Sig. p< .05	-
WC	N	N	Sig. p< .001	-	N	N	N	-
WHR	Trend p= .09	N	Sig. p< .001	-	Trend p= .07	N	Sig. p< .05	-

NB cond = condition, B*Visit = baseline*visit, B*Cond = baseline*condition, BMI=body mass index, WC=waist circumference, WHR= waist-hip ratio

4.12 Discussion

Contrary to expectations, there was minimal evidence to support a different pattern of change in cognitive function over time between the interval, continuous or no-exercise control groups in this sample of obese, middle-aged women. The domains of executive function and spatial memory showed improvement following the intervention. Furthermore, participants with the lowest baseline scores for spatial memory, spatial working memory and executive function showed the greatest improvement following INT training. However, given the large number of cognitive outcomes tested, this study only found limited support for INT and CON regimes relative to a no-exercise control condition. The training regimes resulted in equivalent improvements in cardiovascular fitness, and minimal changes in body composition. It is possible that this may explain why only a limited number of cognitive outcomes were altered following the exercise regimes.

4.12.1 Cognitive function

The greatest support for an improvement following the exercise intervention was the executive function measure Tower of Hanoi (ToH), with superior improvement observed following the INT regime. The total time to complete the task was reduced, which is thought to indicate improved quality of executive planning once solution templates are implemented (Chang et al., 2011). This effect was most pronounced in those with the poorest baseline performance (slowest completion time). Performance on ToH is known to impacted by cerebral blood flow (Fincham, Carter, van Veen, Stenger, & Anderson, 2002). Cerebral haemodynamics during the Tower of Hanoi Task (ToH) have been assessed using Transcranial Doppler sonography (TCD) in the left and right middle cerebral artery (MCA) and anterior cerebral artery (ACA). Schuepbach et al. (2002) reported that CBF prominently increased in both MCAs and ACAs during the TOH task within 40s of onset of the task. The medial and orbital parts of the frontal lobe are supplied by the ACAs, and lateral areas by the MCAs (Tatu, Moulin, Bogousslavsky, & Duvernoy, 1998). Additionally, the ACAs supply the medial parts of the temporal lobe, and the MCAs supply the parietal lobe. This increase in CBF indicate activation of the medial and lateral parts of the frontal cortex. Furthermore, activation in the prefrontal and parietal regions has shown to respond in proportion to how much planning preceded a move in TOH (Fincham et al., 2002). Although unmeasured for

this thesis, it is possible that improved cerebral blood flow may have support the favourable impact of INT on executive function task.

Improved performance (mid- to post-intervention) following training was evident in one measure of spatial memory (immediate designs) in both the INT and CON groups, whereas a decrease was observed in the no-exercise control. However, on the basis that this effect was observed for this measure of spatial memory but not the others from the same test (locations, designs/locations and delayed designs/locations) this finding should be interpreted with caution.

A decline in performance from mid-point to post-intervention was observed for a number of measures, but only in those with the lowest baseline scores. This was irrespective of group, and indicated that those with the lowest baseline scores for spatial memory (immediate locations and designs/locations) and spatial working memory (Corsi) outcomes were showing a decline in performance from mid- to post-intervention. The potential causes of this effect would be based on speculation, but could possibly reflect changes in motivation for the cognitive tests, concentration, or fatigue for example. However, it is of interest that this effect only occurs in those with low performance at baseline. Those with high baseline scores were able to maintain this at both mid- and post-intervention testing. This effect was limited to spatial memory and spatial working memory only.

For all cognitive domains, baseline score had the biggest impact on subsequent cognitive performance, and once this was controlled for this seemed to override any effects of exercise. It is likely that over a relatively small time-frame of 3 months, the cognitive changes that could possibly occur would be small. Although this robust approach removes the potential problem of baseline variance driving effects, this may be too strict to detect significant improvements as it is highly likely that those with the lowest baseline performance were most likely to show improvements.

In this study, age and IQ had little impact on the cognitive outcomes at subsequent testing. Both covariates were associated with spatial working memory measures (Corsi), in the expected direction, in that performance increased with higher IQ and decreased with age. It has been suggested that age-related decline in cognitive performance can occur in healthy educated adults from as early as 20-30 years old (Salthouse, 2009). This is due to a number of studies showing continuous declines in indices of brain structure and function from the age of 20 years, including brain volume (Pieperhoff et al., 2008), metabolites (Kadota, Horinouchi, & Kuroda, 2001) and myelin integrity (Hsu et al., 2008). In the current study, increasing age showed a negative association with performance on spatial working memory

but only in crossing-trials which are more challenging than non-crossing trials. The interaction of age with crossing-trials only perhaps indicates that more challenging cognitive tests are required to detect subtle differences in this middle-aged obese/overweight sample. It is possible that this sample were not demonstrating any detectable age-associated decline, as all participants (except for one age 51 years old) were between the ages of 30 to 50 years. In the current sample there is also evidence of age showing a relationship with an attention measure (false-positive responses) in an unexpected direction. Younger participants were making more false-positive responses at both baseline and subsequent testing. This may indicate the younger participants in this sample were more impulsive than older participants.

4.12.2 Cardiovascular fitness and body composition

Although the raw data indicated that absolute and relative $\dot{V}O_{2max}$ increased in both INT and CON, these findings were not significant and also did not show significant difference to the no-exercise control group. Analysis of the cardiorespiratory fitness data was impacted by missing data at mid-point for the no-exercise control group only. This group were added retrospectively when availability of the exercise-testing laboratory was limited. Despite mid-point maximal exercise test data being available for INT and CON, it was omitted from the analysis leaving only one time-point (post-test) entered in the analysis. Through the process of normalising the residuals, the two participants that showed the greatest increase in $\dot{V}O_{2max}$ were removed from the analysis and they were both from the INT condition. Both participants showed plausible increments in absolute $VO_{2\,max}$ of ~100-200ml/min at mid- and again at post-testing. However, with baseline retained as a covariate and only post-test data entered into the analysis, these responses to training were identified as outliers. The removal of these 2 participants from one group (INT), with already low numbers (n=10), may have diminished the capacity of the analysis to detect group differences and watered down the effects of the intervention. This highlights the limitations of the small sample studied.

4.12.2.1.1 “No-exercise” control group

The raw data indicate the 2 individuals within the NO-EX control group increased absolute $\dot{V}O_{2max}$.This is not possible without adaptation to exercise which raises an issue of compliance to the no-exercise control condition. The analysis did not identify them as outliers, and without evidence they had failed to comply it would have been wrong to remove them as this would have constituted “cherry picking” the data to manipulate the findings. Additionally, analysis of the body composition data indicated that the only significant changes were an increase in BMI and a reduction in WHR for NO-EX only. Irrespective of

what may be causing these changes, these findings highlight that the control group have not behaved as expected. This may explain why the INT and CON groups were not found to be statistically different to NO-EX

It was expected that both exercise regimes would induce a change in cognitive performance relative to a no-exercise control. It is difficult to draw inferences from the extant literature as no other studies have compared the impact of interval and continuous exercise on cognitive function. Typically, one type of exercise regime (INT or CON) has been compared to a no-exercise control group, or it is been examined pre-to post with no control group or experimental condition. The work carried out for this chapter builds on previous work by directly comparing the impact of both interval and continuous exercise on cognitive function relative to a no-exercise control group. Furthermore, the INT and CON regimes were matched in terms of work-done and intensity domain, in order to establish the impact of the greater excursions into the heavy intensity domain induced by INT training.

4.12.3 Impact of interval exercise on cognitive function

The findings of this study are inconsistent with the literature detailed in section 4.1 showing improvements following training regimes (either interval or continuous) for multiple cognitive test outcomes. Therefore, it is helpful to compare the methodology of the current study to the relevant extant literature. Only one study examined the impact of high-intensity-interval-training (HIIT) on cognitive function in obese adults (section 4.1.1). The current study utilised a different exercise protocol to that of Drigny et al. (2014), who observed improvements in short-term memory, verbal memory, attention and processing speed following 4 months of interval training. Relative to the current study, the interventions differed in terms of study duration, exercise frequency, mode of exercise and interval training protocol. The sample examined for this thesis exercised twice per week, as opposed to four, and did not perform any resistance work or moderate intensity continuous exercise. Therefore, it is possible that exercising twice per week, irrespective of mode, was not sufficient to drive sufficient changes in health or cognitive function. Secondly, Drigny et al. (2014) examined outcomes from pre-to post in 6 men, and made no comparisons to either a no-exercise control group or alternative exercise condition. This crude type of analysis increases the chance of type I error, and it is not possible to rule out confounding effects due to the lack of control group. Due to the large number of methodological differences, it is not possible to make comparisons between studies. The differences highlighted between these two studies alone identify a large number of factors that can be manipulated when designing a HIIT protocol. Manipulation of such factors may possibly mediate the effects of exercise on cognitive function.

4.12.4 Impact of continuous exercise on cognitive function

The current findings were also inconsistent with literature showing improvement in cognitive function in young adults following a continuous exercise intervention (Chapter 1, section 1.2.2). Collectively these studies provided evidence that continuous exercise improved spatial memory and verbal memory, which were both measured as part of this chapter. Given the different duration of intervention, frequency of sessions, modes of exercise and uncontrolled exercise intensity it is not possible to make comparisons between the studies. A review of the literature examining the impact of exercise interventions on memory in adults aged 18-65 years concluded that effects were subtle but negligible (Roig et al., 2013). However, the studies were conducted in non-obese samples, and did not examine mechanisms such as cardiovascular risk factors. The research showing a positive change in cognitive function (Drigny et al., 2014; Monleón et al., 2015) used statistical methods that did not control for baseline performance (a factor found to be driving all relationships for the current study). There is very limited literature regarding the impact of exercise (either continuous or INT) on cognitive function in a younger adult and obese sample. However, there are multiple studies investigating the impact of various INT/CON regimes on physiological parameters that help to show how manipulation of such regimes can have a differential impact on health.

4.12.5 Possible explanations of the null findings

While the sample size limits the ability to detect differences, it must also be considered that the exercise regimes were not sufficient to stimulate physiological adaptation or indeed drive improvements in cognitive function.

4.12.5.1 Exercise protocols

Both training groups exercised twice per week for three months, it is possible that the frequency of exercise and duration of study were not sufficient to drive physiological adaptation nor cognitive change. A meta-analysis on the impact of long-term exercise interventions on memory found that interventions of 6-months or more showed the greatest effect sizes (Roig et al., 2013). For studies showing significant improvements in cognitive outcomes after 3-4 months (Drigny et al., 2014; Pereira et al., 2007), participants were exercising 4 times per week. The shortest intervention showed improved cognitive function after 6-weeks (Stroth et al., 2009) but the protocol involved running on 5 days per week. The only other study that had participants exercising twice per week was by (Hötting, Schauenburg, & Röder, 2012b) and this lasted 6 months.

With regard to health parameters, research demonstrating larger improvements in $\dot{V}O_{2max}$ (increase ~19.4%) have utilised interval training protocols with intervals of 4-minutes high-intensity interspersed with 3 minutes of active recovery (Rognmo et al., 2004; Schjerve et al., 2008; Tjønna et al., 2008; Wisløff et al., 2007). Therefore, to adapt the current protocol to stimulate greater cardiorespiratory adaptation would be to increase the duration of the high-intensity bouts (without changing work-rate). One mechanism to explain how AIT translates to superior improvements in fitness is the upregulation of mitochondrial biogenesis. PGC-1α regulates cellular energy metabolism, promoting mitochondrial biogenesis and the remodeling of muscle tissue and regulates carbohydrate and lipid metabolism (Liang & Ward, 2006). PGC-1α has been correlated with improved $\dot{V}O_{2peak}$ following aerobic interval training indicating a mechanistic link (Tjønna et al., 2008; Wisløff et al., 2007). It has been suggested (Daussin et al., 2008) that fluctuation in ATP turnover seen in interval training activates signalling pathways leading to increased peroxisome proliferator-activated receptor-gamma coactivator (PGC-1α). Additionally, both Tjønna et al. (2008) and Wisløff et al. (2007) reported increased rate of Ca^{2+} reuptake into the sarcoplasmic reticulum by 50-60%, which is associated with reduced muscle fatigue and improved function, thereby improving CRF.

The interval bouts may also be manipulated in terms of work-rate corresponding to a higher intensity. Despite the sample assessed for this chapter exercising within the heavy domain, it is possible that the physiological strain induced from the bouts at 70%Δ was not sufficient stimulus for adaptation. The sprint interval protocols have demonstrated that they can improve insulin sensitivity in a very short time frame of 2 weeks (Babraj et al., 2009; Richards et al., 2010; Whyte, Gill, & Cathcart, 2010). All protocols employed repeated 30s “all-out” Wingate sprints, completing only 6 sessions per intervention. Insulin function was not assessed for this chapter but is a theoretically important variable associated with verbal and spatial memory.

For this thesis study, the work:recovery ratio was 1:2 at 40s:80s. Manipulation of the duty cycles (without altering work-rate) is known to impact on average exercise intensity (Turner et al., 2006). It is known that shortening the recovery bouts reduces the time available for the body to clear the lactic acid build up in the blood stream. Therefore, by shortening the recovery bouts in duration, this can elevate the intensity of the whole exercise session. Additionally, shortening the recovery bouts will reduce the duration of the entire session which may be preferable for some individuals. The work-rate for the work bouts for this chapter was set at 70% Δ LT $\dot{V}O_{2max}$ which was high intensity, but also sub-maximal. At a higher work-rate the increased exertion elevates blood pressure/flow which in turn increases

the shear stress exerted on the vascular walls. With higher intensity exercise, muscle glycogen depletion is increased (Colberg et al., 2010).

This study tightly controlled the intensity domain that the INT and CON groups exercised within. The methodological issues relating to the prescription of exercise intensity according to a single parameter such as % $\dot{V}O_{2max}$ or % Lactate threshold have previously been described. For continuous exercise, percentage of maximal oxygen uptake (% VO_{2max}) is frequently used to determine exercise intensity (Lansley, Dimenna, Bailey, & Jones, 2011; Rossiter, 2011; Scharhag-Rosenberger, Meyer, Gäßler, Faude, & Kindermann, 2010; Whipp et al., 2005). The validity of this has been disputed as great inter-individual variability is observed in parameters such as lactate threshold (LT), critical power (CP), and ˙Vo2max (Rossiter, 2011; Whipp et al., 2005). The assumption is that physiological demand on individuals exercising at the same % VO_{2max} is similar, however, large variation in physiological and metabolic responses have been observed at the same relative intensity. In the current study the % Δ concept was utilised (Lansley et al., 2011), which is considered a more robust method to control for exercise intensity. The accurate characterisation of exercise intensity is central to understanding the impact of exercise interventions on both health parameters and cognitive function. It is possible that, once intensity domain and work were matched between INT and CON groups, any additional benefit from brief excursions at a higher work-rate for INT were negligible. This may explain why differences were not observed between the INT and CON exercise groups.

4.12.5.2 Possible reasons for lack of detected effects between control and exercise groups

Central to determining the impact of an exercise intervention on cognitive function, relative to a no-exercise control group, is the assumption that the control group does not change. The statistical analysis for this chapter examined differences between the three groups (INT, CON and NO-EX) over time, when baseline performance on cognitive outcome was controlled for. It was not expected, that the control group would improve on cognitive function or cardiovascular health outcomes. Inspection of the raw data indicated that individuals within the no-exercise control group increased absolute and relative $\dot{V}O_{2max,}$ something that is not possible without improving fitness (and/or losing body weight for relative VO_2 max only). Additionally, over the 12 week intervention, the no-exercise control group demonstrated improvements in a small number of outcomes for spatial memory, spatial working memory, and attention. It must be noted that the standard error for the control group was often higher than the two exercise conditions. This highlights the issues of using a

control group in a medium term (12-weeks) free living intervention study. It is not known whether a degree of change in cognitive function is to be expected over 12 weeks. Normative trajectories of cognitive change have not been established, particularly in an obese-middle aged sample. The purpose of a control group is to act as a reference point to the experimental conditions. Therefore, if the control group show change in an unexpected direction then this undermines interpretation of the data set as a whole. Finally, it highlighted the possibility that those effects were driven by some unmeasured variable. This will have been compounded by the small size of the control group as this firstly undermines the chance of detecting a true effect and secondly reduces the chance that significant findings reflect a true effect (Button et al., 2013). Increasing the sample size reduces the variability of the sample mean, which increases the power of a statistical test.

4.12.5.3 Statistical approach

The analysis for the current study utilised SAS PROC MIXED and retained baseline score as a covariate. This approach has been evaluated as the optimal statistical method in terms of bias, precision and power (Egbewale, Lewis, & Sim, 2014; Vickers, 2001; Zhang et al., 2014). ANCOVA accounts for imbalance by including baseline values in a regression model, which yields unbiased estimates of treatment effect (Egbewale et al., 2014). Variance in baseline score is considered unexplained noise, so including it as a covariate acts as noise reduction, allowing for greater confidence in the treatment effects. Covariates explain some of the variation between individuals, leading to smaller standard errors (SE) for the effect of condition/treatment which can increase statistical power (Kahan, Jairath, Doré, & Morris, 2014). Larger increases in power are observed when the covariate is highly correlated with the outcome (Pocock, Assmann, Enos, & Kasten, 2002). This approach has been found to be equally beneficial in small and large randomised controlled trials (Thompson, Lingsma, Whiteley, Murray, & Steyerberg, 2014). Therefore, in terms of evaluating the statistical approach used across studies, the one for the current study is considered more robust than the approach utilised by (Drigny et al., 2014; Hötting et al., 2012b; Monleón et al., 2015; Pereira et al., 2007; Roig et al., 2013; Stroth et al., 2009). Significant improvement in cognition following interval training was reported by Drigny et al. (2014), however a t-test was used to examine pre-post data, and with no comparison group which is a crude comparison of treatment effect.

The findings from the current study indicate that baseline cognitive performance was a significant covariate for all cognitive domains, and ideally should be controlled of in analysis. The analysis controlled for the variation in baseline score, and once all cases were treated

as if baseline score was the same (and balanced between conditions), no further group differences were observed at subsequent testing.

4.12.6 Mechanisms underpinning cognitive change

4.12.6.1 Cardiovascular fitness and cerebral oxygenation

It is thought that long-term exercise participation serves to reduce cognitive decline by enhancing neuronal plasticity and also reducing the comorbidities/risk factors associated with cognitive decline (Hotting et al. (2012). It is not known if a change in cardiovascular fitness (the primary goal of exercise interventions) is essential in order for cognitive change to occur. The sample studied for this chapter showed minimal increase in $\dot{V}O_{2max}$. If increase in cardiovascular fitness is essential for improvement in cognitive function, then this may explain why significant improvements in cognitive outcomes were not observed in the sample. However, the literature gives mixed findings on whether this physiological adaptation is the key mechanism driving cognitive change.

The positive changes in a number of cognitive outcomes observed by Drigny occurred alongside significant improvements in cerebral oxygenation, but the changes in $\dot{V}O_{2max}$ were not significant. This presents us with the possibility that $\dot{V}O_{2max}$ was not essential for cognitive change, however it must be noted that the small sample size (6 adults) meant the analysis may have been underpowered to detect significant pre-post differences.

Two studies observing improvements in cognitive function following continuous exercise regimes found that improvements in verbal memory correlated with improvements in $\dot{V}O_{2peak}$ (Hötting et al., 2012b; Pereira et al., 2007). Both studies showed selective improvement in different aspects of verbal memory. Cardiovascular fitness predicted improvement in recognition of words after a 30-minute delay, but not immediate memory (total acquisition over 3 trials) or attention in the 6-month trial by (Hötting et al., 2012b). At a 1-year follow up, those that had maintained their cardiovascular fitness had preserved their enhanced recognition performance, whilst those below the group median for cardiovascular fitness had lost their gains in recognition performance. After the initial 6-month intervention 74% sample continued to exercise for an average of 2.5 hours per week. This suggests that enhancing and maintaining cardiovascular fitness can prevent declines in memory performance over longer time frames. Pereira et al. (2007) observed improved $\dot{V}O_{2max}$ was predictive of performance in trial 1 of immediate learning only, but not other verbal memory

outcomes (total acquisition over 3 trials and delayed recall) that had also significantly improved over the 3-month trial. This study also measured cerebral blood volume (CBV) in the hippocampus, and found significant improvements in the dentate gyrus. Individual changes in dentate gyrus CBV were correlated to individual changes in $\dot{V}O_{2max.}$ However, the relationship between performance trial 1 and increases in dentate gyrus CBV just failed to reach significance (p=.052).

Changes in cognitive function have occurred alongside improvements in $\dot{V}O_{2max}$, however it is not known if change in $\dot{V}O_{2max}$ is a prerequisite for change in cognitive function. It is difficult to isolate the impact of cardiovascular fitness upon cognitive function due to the number of other effects driven by cardiovascular fitness. This includes a cascade of changes within the brain impacting neuroplasticity, meaning markers such as BDNF, IGF-1, could become primary targets for intervention. Additionally, participation in exercise and consequent changes in cardiovascular fitness reduce a number of chronic systemic risk factors associated with cognitive decline. All these factors must be incorporated into investigations to fully elucidate the impact of exercise (and specific parameters within that) upon cognitive function.

4.12.7 Exercise for optimal brain health

If preservation of cognitive function is the goal, we need to establish what central and systemic mechanisms are most important for neurocognitive health. If these are identified then exercise prescription can target specific mechanisms accordingly. On a systemic level, a wealth of research advocates glucose hormeostasis and insulin sensitivity, inflammation, endothelial function and alterations in adipokines as the likely systemic factors mediating the relationship between exercise and neurocognitive health (Obisesan et al., 2012). An exercise stimulus can differentiate in terms of intensity, duration, frequency, mode, and work-rate profile. The exercise stimulus induces physiological strain in terms of mechanical tension (shear stress), neuronal activation, oxidative stress, and energy substrate flux. Therefore, manipulation of the exercise stimulus leads to differential induced physiological strain. This will have implications for the humoral, metabolic and molecular signalling/sensoring and transcription. Functional adaptations include vasoreactivity, cognition, neurovascular coupling, and substrate content. It is essential that approaches to optimize exercise for brain-related health or disease outcomes are explored.

4.12.7.1 Central pathway

Structural adaptations associated with exercise are cerebral blood flow/volume, angiogenesis, vessel compliance, grey matter volume, white matter integrity, structural networks, neuroplasticity, dendritic density (Lucas et al., 2015). These measures are beyond the scope of this thesis, but are essential to understanding the mechanistic link between exercise and brain health. It is plausible that INT duty cycles may be manipulated with an aim of generating shear stress surges that result in optimal cerebrovascular adaptation. The impact on HIIT on adaptation of the cerbrovasculature (and subsequent impact on cognitive function) has not been assessed (Lucas et al., 2015). One concern relating to HIIT is that it is yet to be confirmed that HIIT does not lead to cerebrovascular damage, particularly in clinical populations that present higher risk of stroke or vascular dementia. High intensity exercise has been shown to increase blood-brain barrier permeability due to impaired cerebral autoregulation (Bailey et al., 2011). HIIT by nature can result in sudden increases in systemic blood pressure, and if this goes beyond the autoregulatory range of the brain, there is elevated risk of a cerebrovascular event (Lucas et al., 2015). Nevertheless, the role of different exercise parameters, such as blood flow rate/profile, on cerebrovascular endothelium has not been studied. It is possible that interval exercise can be explored as a method of accelerating cerebrovascular adaptation.

4.12.8 Conclusion

The general consensus is that HIIT is superior to MICT, for reduction in systemic cardiovascular risk factors associated with cognitive decline. However, the use of HIIT in relation to cognitive function research is new. As described in 1.2.7, the infinite number of HIIT protocols provide limitless potential for the physiological strain induced by the exercise stimulus. If a reduction in systemic health factors is a key goal, then interval training provides greater opportunity for optimal physiological adaptation than continuous exercise. This is due to there being a larger number of factors that can be manipulated in order to change the exercise stimulus when compared to continuous work-rate exercise. Continuous exercise can be altered in terms of the work-load set (which remains constant) and the duration of the individual sessions. Exercise above the lactate threshold, and at higher intensities will see a continual accumulation of blood lactate, meaning the session duration will be limited by individuals reaching fatigue. Interval exercise has a greater number of variables that can be manipulated such as peak workload and peak-workload duration, mean workload, intensity and duration of recovery, number of intervals (Tschakert & Hofmann, 2013). This

presents us with the opportunity to manipulate just one variable or multiple variables to directly affect the acute physiological responses during exercise. Knowledge of the duty cycles can help prescribe an exercise stimulus that allows for exercise at a high intensity to drive adaptation, but with recovery bouts ensuring a session is manageable/enjoyable. It is not known which systemic/central factors are the most important targets for intervention in order to drive cognitive change. It is likely this may be different for individuals with differing baseline metabolic profile.

The aim of this study was to compare the impact of two work-matched, heavy-intensity exercise regimes (INT and CON) and a no-exercise control group upon cognitive function and cardiovascular risk in sedentary, overweight/obese middle-aged women. It was hypothesised that INT and CON regimes would drive physiological changes, and that these changes would be associated with improved cognitive function relative to controls. It was also hypothesised that the INT regime would drive superior benefit in cardiovascular adaptations relative to the CON regime. Training effects were observed for executive function task (ToH) following INT, relative to CON. This occurred alongside equivocal improvements in cardiovascular fitness between groups. It remains to be seen if HIIT presents the optimal strategy to improve cognitive function. There is no evidence to support that, when matched for work done or intensity, that INT has any superior benefit relative to CON. However, there are two potential advantages of INT over CON. First, it allows individuals to exercise at a high intensity for a longer period of time than would be possible in one continuous bout. Secondly, even when matched for intensity, the work-rate profile of INT generates an oscillating blood flow which may have implications for long-term cerebrovascular adaptations. This has yet to be assessed in humans. The current study failed to show any superior effect of either supervised INT or CON regimes relative to a no-exercise control group on cognitive outcomes. This may be due to an insufficient training stimulus and/or limitations of sample studied. Informal comments from the participants indicate that INT was perceived as being more enjoyable, which may have implications for exercise adherence.

Chapter 5:
Study 3

Chapter 5 Study 3: Impact of differing walking dose on cognitive function and indices of health in sedentary, overweight/obese middle-aged adults.

5.1 Introduction

Chapter 1 indicated that participation in physical activity is associated with cognitive benefit. This cognitive benefit may have been driven by cardiovascular or metabolic mechanisms associated with an increase in PA or conversely by a decrease in time spent inactive and the cellular damage associated with sedentariness. Accredited public health recommendations are available for MVPA, but it is not currently known how much light activity is required for health benefits when moving from sedentariness to light-active. There is much scope for evidence based research to inform public health recommendations with regard to light activities, using a metric that allows for the objective tracking of activity in real-world application. It is not yet known whether increasing time spent in light activities may confer improvements in cognitive function.

5.2 Objective measurement of physical activity

Instruments such as pedometers and accelerometers are used to objectively measure physical activity, both at a cross sectional level and to detect change longitudinally. Individuals are typically classified in terms of physical activity levels by daily step count (section 1.2.1). Step counting is now widely accepted as a method of translating physical activity research to real-world application as it assesses and tracks physical activity doses/volumes in a metric that can be understood and achieved by the general population (Tudor-Locke, Craig, Thyfault, & Spence, 2012).

5.3 Step count and cognition

Despite the association between physical activity and cognitive function, there is a paucity of research linking objectively measured step counts or walking targets with cognitive function outcomes. Additionally, most published research has been conducted in older adults and is therefore not applicable to younger or middle aged adults. In a sample of 18,700 older females, a weekly accumulation of 1.5h hours of walking was associated with improved category fluency and working memory when compared to those accumulating less than 40 minutes (Weuve et al., 2004). Increasing daily steps from approximately 5600 to 7000, to accumulate a total weekly increase of 90 minutes walking over 3 months lead to

improvements in word fluency scores relative to controls (Maki et al., 2012). Finally, a prospective study conducted by Abbott et al. (2004) showed elderly men (aged 71-93 years) walking less than 0.25 miles daily had a 1.8 fold increased risk of dementia compared to those with a daily accumulation of >2 miles.

In terms of health outcomes, the research conducted to date indicates that those at the lowest end of the physical activity spectrum elicit the greatest benefit from increases in ambulatory or light activity. However, these studies report great heterogeneity in terms of average step count at baseline, target increase in steps (relative to baseline) and also in the health outcome variables assessed. It is therefore not known if a dose response or threshold effect occurs for specific health outcomes. It has yet to be determined whether increases in ambulatory activity have an impact on cognitive function in a middle-aged, obese sample. The impact of moving individuals from the lower end of the physical activity spectrum upwards by means of accumulated step counts upon cognitive function has also not been explored. Hence, the aim of the work in this chapter was to examine the impact of increasing ambulatory activity upon measures of cognitive function and cardiovascular health in sedentary and low-active, overweight/obese middle-aged adults, and to explore any relationships between changes in these variables.

5.4 Objectives and Hypotheses

The primary objective of the study presented in this chapter was to compare the impact of two different step count goals, (taking into account baseline daily step count) compared to a no-exercise control group (who maintained usual sedentary levels of PA) upon indices of cognitive performance cardiometabolic health and obesity over a 12-week period. Attainment of the step count goals was guided by the use of pedometers, a method that the public can utilise and incorporate into real-world application. It was hypothesised that after 12 weeks, achieving both step-count goals would lead to benefits in cardiometabolic health and anthropometric variables, with a greater benefit associated with the larger step count goal. It was hypothesised that the larger step count goal would be required to drive change in any cognitive function outcomes. A secondary hypothesis was that any observed changes in cognitive parameters would be associated with changes in cardiometabolic parameters.

5.5 Methods

5.5.1 Participants

Thirty-three non-diabetic participants were recruited from the Leeds area (10 Males and 25 females) with a BMI of ≥25 kg/m^2). Eligibility was assessed by the researcher during a screening telephone call to ensure participants met the criteria listed below All participants included were classed as sedentary or low-active (<10,000 steps/day) according to the step defined sedentary lifestyle index (Tudor-Locke et al., 2013) following 7 days objective measurement with an Actigraph accelerometer (section 2.9.1). The screening procedure followed has previously been described in section (Chapter 2, section 2.2).

5.5.2 Inclusion/exclusion criteria

In addition to the inclusion/exclusion criteria listed in (Chapter 2, Table 2.4), the following inclusion/exclusion criteria applied:

Inclusion

- *Age 30-60 years old*
- *Daily step-count below 10,000 steps/day*

Exclusion

- *Age <30 years or >60 years*
- *Step count >10,000 steps/day*
- *A mobility issue that impacted upon walking capacity, or condition worsened by walking.*

5.5.3 Recruitment and attrition

Figure 5.1 indicates the flow of participants through the study, from recruitment to completion. The consort diagram shows that the study received initial interest from 67 volunteers, however 22 were excluded based upon BMI <27 kg/m^2 (n=5) medication (n=11), and depression (n=6). Fifty eligible participants passed screening and were enrolled on the study. A further 5 individuals did not respond to any further contact. In total 45 participants completed all baseline assessments and were allocated to training groups. Seventeen participants were allocated to the +6000 steps/day group, however, 5 dropped out and a further 7 asked to change to the +3000 group. Twenty-eight were allocated to the +3000 steps/day, however this gained 7 members from the +6000 group and lost 15 drop-outs by mid-point testing. Twenty people completed mid-point assessments in the +3000 group and only 5 in the +6000 group. Both conditions lost 1 participant each from mid-point to post testing. Leaving a total of n=19 for the +3000 group and n=4 for the +6000 group.

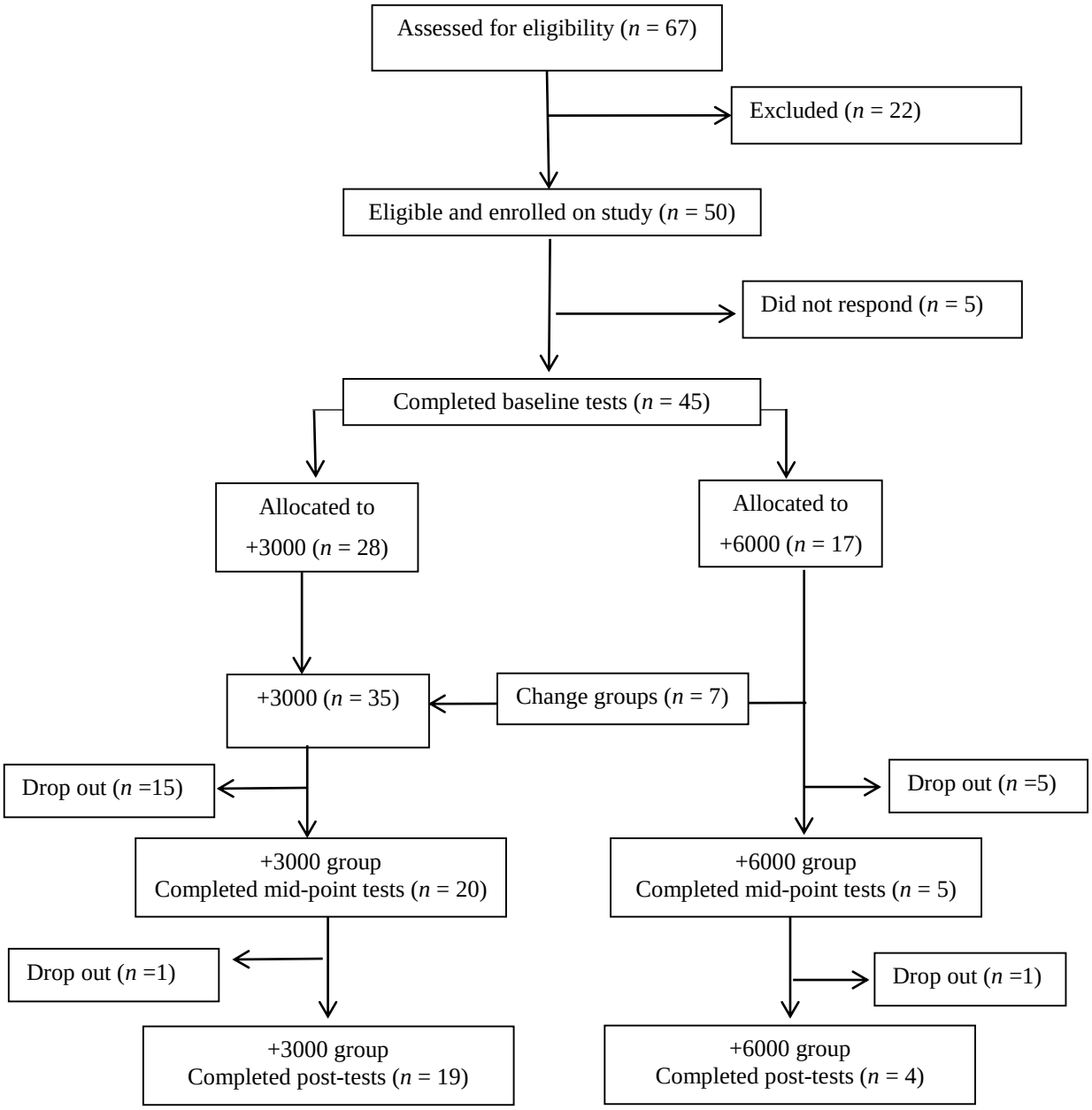

Figure 5.1 Consort diagram

5.6 Experimental Design

The study was initially planned to conform to a 3x3 independent parallel groups design examining cognitive performance and indices of cardiovascular health over a 12-week physical activity intervention. Sedentary, overweight/obese adults were assigned to one of two experimental groups (between-subject factor); low walking dose, high walking dose. A no-exercise control group were added retrospectively. All participants attended the

laboratory at three time points (weeks 0, 6 and 13, within-subject factor) for baseline, mid and post assessment of cognitive function, mood and cardiovascular health.

5.6.1 Experimental protocol

All testing took place in the School of Psychology, and each testing visit was completed within 90 minutes. Individuals meeting the study inclusion criteria were invited to the laboratory for a study familiarisation visit and administration of the practice cognitive test battery (Visit 1; see section 5.7.1). Between Visit 1 and Visit 2 all participants wore an accelerometer for a 7-day assessment of baseline physical activity level. Upon completion of the 7-day PA assessment, participants attended the lab for baseline testing visit (Visit 2, see section 5.7.2) for assessment of cognitive function, body composition, blood pressure and glycaemic control. Visit 2 signified week 0 of the study, and the immediate initiation of the 12-week intervention phase. All measures from Visit 2 were repeated at mid-point (Visit 3, week 6) and upon completion of the 12-week intervention (Visit 4, week 13). Figure 5.2 shows the study flow from study familiarisation to completion.

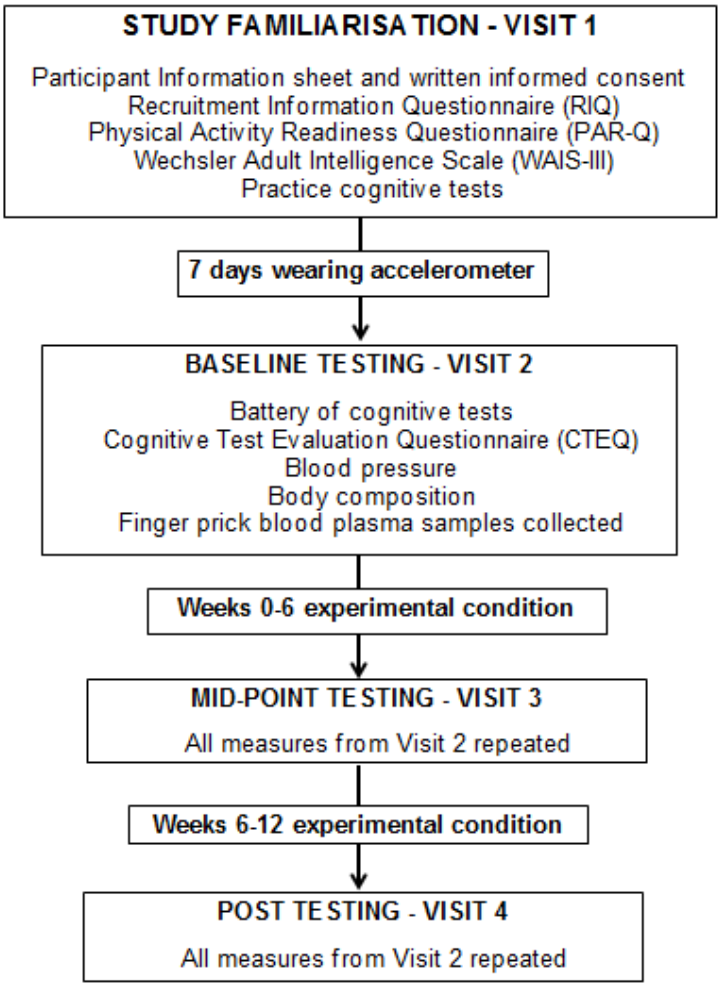

Figure 5.2 Intervention study flow diagram

5.7 Laboratory Visits

5.7.1 Study Familiarisation - Visit 1

The procedures for the familiarisation visit have been previously described in Chapter 2, section 2.4.1.

5.7.2 Baseline Testing - Visit 2

Participants attended the lab in a 12 hour fasted state to complete the 38-minute battery of cognitive tests, listed in further detail in section 5.8.5. Systolic and diastolic blood pressure measures were taken (Chapter 2, section 2.7) along with simple measures of body weight,

height and waist circumference. A fingertip-capillary blood sample was collected to assess fasting insulin and glucose, see section 5.8.4. Participants returned the accelerometer at this visit so that their step count data could be downloaded. Laboratory Visit 2 took 75 minutes to complete.

5.7.3 Mid-point Testing – Visit 3

All procedures listed in section 5.7.2 were repeated at week 6 of the intervention.

5.7.4 Post Testing – Visit 4

All procedures listed in section 5.7.2 were repeated upon completion of the 12-week intervention at week 13.

5.8 Study Procedures

5.8.1 Assessment of ambulatory activity

Ambulatory activity was assessed using a GT3X Actigraph accelerometer as previously described in Chapter 2, section 2.9.1. The variable obtained for this study was daily step count.

5.8.2 Assessment of anthropometric indices

The measures of anthropometric indices were assessed as previously described in Chapter 2, section 2.8. The variables collected for this study were body fat percentage, BMI, waist circumference (cm) and waist-hip ratio.

5.8.3 Assessment of blood pressure

Systolic and diastolic blood pressure were taken at the left arm using an automated Omron M7 BP cuff after participants had been seated for forty minutes with an appropriately sized cuff. Three measures were taken with a minimum of one minute between measurement trials, and the average recorded. The IPSEC approved SOP details the procedure (Appendix 6.14).

5.8.4 Assessment of fasting blood insulin and glucose

Fingertip sampling was performed using Unistik extra, single use safety lancets and blood samples (~750 µL) were collected in Microvette CB 300 tubes (Sarstedt) for the analysis of

fasting insulin and glucose. Fingertip-capillary blood sample collection is less invasive than venous samples. High correspondence between capillary blood and venous blood has been demonstrated in fasted conditions (Kuwa, Nakayama, Hoshino, and Tominaga (2001) The YSI 2300 Instrument (YSI) used here has been compared against the previous gold standard instrument (Glucose Analyzer II (BMG) Beckman's Instruments), and showed no deviations in glucose measurements up to approximately 13 mmol/L (Nowotny, Nowotny, Strassburger, & Roden, 2012).

5.8.4.1 Fasted plasma insulin

Immediately after blood sampling, 600 µL of capillary blood was pipetted into Eppendorf tubes and centrifuged (2000G/5min/4°C) to obtain plasma samples. A minimum of 150 µL blood plasma was pipetted into new Eppendorf tubes and immediately stored at -80°C in preparation for transport to the Leeds University Dental Institute where the assay was performed. This volume of blood plasma allowed for duplicate measurements. Capillary insulin levels were then measured using enzyme-linked immunosorbent assays (ELISA) using the ALPCO insulin ELISA kit. There are no definitive guidelines on healthy levels of fasting insulin. The NHANES III Survey indicated the average fasted insulin level in a US population study was 8.4 μIU/ml in women and 8.8 μIU/ml in men (Harris et al., 2002b). Previous research in non-western samples reported ranges of 3-6 μIU/ml (Lindeberg, Eliasson, Lindahl, & Ahrén, 1999).

5.8.4.2 Fasted glucose

The remaining capillary blood sample (~150 µL) was used for the analysis of blood glucose levels using an YSI glucose analyser. The IPSEC approved SOP details the procedure (IPSEC ref 12-0078, see Appendix 6.30). The World Health Organisation classifications of fasting blood glucose indicate 3.9-5.5 mmol/L as normal, 5.6-7.0 mmol/L as impaired fasting glucose or pre-diabetes, and greater than 7.0mmol as diabetes (Alberti & Zimmet, 1998).

5.8.4.3 Insulin-sensitivity (HOMA-IR)

Based on (Zhou et al., 2010) who applied the homeostasis model assessment of insulin resistance (HOMA-IR) (Matthews et al., 1985) to capillary blood samples, the following formula was applied:

[HOMA-IR = (fasting insulin (μIU/ml) x fasting glucose (mmol/L))/22.5]

A value of 2.5 is traditionally accepted as being indicative of insulin resistance (Muniyappa, Lee, Chen, & Quon, 2008; Singh, Garg, Tandon, & Marwaha, 2013).

5.8.5 Assessment of cognitive function

All participants attended the cognitive test sessions (Visits 2, 3 & 4) in a 12 hour fasted state. All cognitive outcome variables were measured in both the high and moderate step exercise groups and the control group at baseline, mid-point (Week 6) and after the intervention period (Week 13).

The following battery of tests lasted approximately 38 minutes, see Table 5.1

Table 5.1 Order of cognitive test presentation within the cognitive test battery

Cognitive test	Test duration (minutes)	Cognitive domain
1. Visual Verbal Learning Test	12	Verbal memory
2. Corsi Block Tapping Test	4	Spatial working memory
3. Trail Making Task (A&B)	5	Cognitive flexibility (Executive function)
4.Bakan Test	6	Attention
5.Delayed Visual Verbal Learning Test	3	Delayed verbal memory
6. Word Recognition Test	3	Delayed verbal memory
7. Stroop Task (word/colour)	5	Executive Function

5.8.5.1 Visual Verbal Learning Task

The Visual Verbal Learning Test (VVLT) was administered as previously described in Chapter 2, section 2.5.1.1. Parallel versions 4, 5 and 6 were administered (Appendix 6.11).

5.8.5.2 Corsi Block Tapping Task

The Corsi Block Tapping Test was administered as previously described in Chapter 2, section 2.5.1.4.

5.8.5.3 Trail Making Test: Parts A & B (pen and paper version)

The Trail Making Test (TMT) was originally designed for the Army Individual Test Battery (1944) and then incorporated into the Halstead-Reitan Battery (Reitan & Wolfson, 1985), one of the most widely used batteries in cognitive testing. The TMT is one of the most widely used cognitive tests and measures processing speed and task switching (Tombaugh, 2004). Research utilising fMRI in participants whilst performing the TMT has shown distinct patterns of prefrontal cortex activity during the TMT-B, particularly in the ventro- and dorsolateral prefrontal regions (Allen, Owens, Fong, & Richards, 2011; Müller et al., 2014).

The test is made up of two parts (Parts A and B). For both parts A and B, participants were presented with 25 circles distributed across a sheet of paper. For part A, the circles were numbered 1-25, and participants traced across the sheet with a pencil connecting the numbers in ascending order. For part B, the circles included both numbers (1-13) and letters (A-L). The participants had to connect the circles in an ascending pattern, but had to alternate between numbers and letters (e.g. 1-A-2-B-3-C, etc). Figure 5.3 shows the configurations for parts A and B.

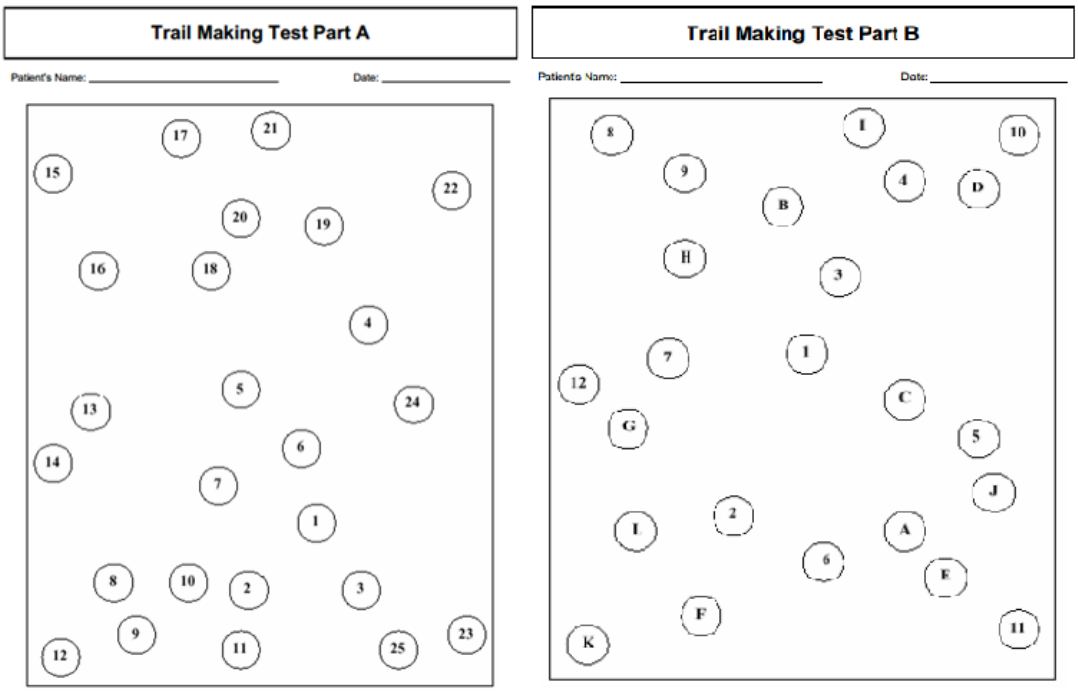

Figure 5.3 Trail Making Test: Parts A and B

Participants were instructed to connect the circles as quickly as possible, and time to complete the task was taken as the outcome variable. If participants made an error the experimenter told them immediately, and participants had to correct their move as quickly

as possible. The correction of errors was included in the total time to complete the task, but was not in itself collected as an outcome variable.

From the two test components, both direct and derived scores may be obtained. The direct scores of parts A and B are represented by the time taken to complete in seconds. From these scores, B minus A difference score, the B:A ratio score and the (B minus A)/A proportional score have all been clinically applied to detect different aspects of frontal lobe dysfunction (Perianez et al., 2007). Sanchez-Cubillo et al. (2009) investigated the construct validity of both the direct and derived TMT scores. Of the direct scores, TMT-A performance primarily assesses visuoperceptual abilities, whereas TMT-B primarily requires working memory, and then task-switching ability. Of the derived scores B minus A demonstrated reduced demand on the visuoperceptual and working memory systems, thus providing a more “pure” indicator of executive control.

Normative data stratified by both age and education have been provided for TMT scores from multiple sources (Perianez et al., 2007; Tombaugh, 2004). Normative data provided on adults (mean age 38.9 years) with approximately 13 years education suggests scores for TMT-A, TMT-B and B-A as being 31.7±13.7s, 68.1±43.2s, and 36.4±35.1s respectively (Perianez et al., 2007). The normative data, as per age and education stratification level was taken into consideration when analysing the TMT scores for specific participant/patient groups within the thesis.

5.8.5.4 Bakan Task (Rapid Visual Information Processing)

The Bakan test was administered as previously described in general methods section 2.5.2.1. 2.5.2.1In this study the 6-minute Bakan test was used.

5.8.5.5 VVLT Recognition

The VVLT recognition task was administered was as previously described in Chapter 2, section 2.5.1.2. Parallel versions 4, 5 and 6 were used, to correspond with the VVLT lists (Appendix 6.11).

5.8.5.6 Stroop colour/word interference test

The Stroop color-word interference test (Stroop, 1935) is one of the most widely used measures of prefrontal cortex function (Demakis, 2004; Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2006; Yanagisawa et al., 2010), more specifically it is a test of selective attention and inhibitory control (Spieler, Balota, & Faust, 1996). A meta-analysis evaluating

tests of frontal lobe function in frontal versus nonfrontal participants, found the Stroop task to be the most strongly and consistently sensitive test to frontal lobe dysfunction or damage (Demakis, 2004). The colour-word naming task has also demonstrated sensitivity to impaired glucose regulation within a non-diabetic sample of young adults (mean age 35 years) (Gluck et al., 2013) which is highly relevant to participant samples included in this thesis.

The task was administered on a computer (using E-prime) and participants responded to a visual stimulus by pressing one of four keys on a response box. The response box keys corresponded to the correct response. The stimuli consisted of words presented in one of four ink colours (red, green, blue or yellow) which formed three conditions: congruent, incongruent or control. Trials were equally weighted in terms of congruent, incongruent or neutral trials. The stimuli for congruent trials consisted of the names of colours written in the same ink colour as the semantic meaning of that word (e.g. the word “red”, written in red). Incongruent trials consisted of the names of colours written in a different ink colour to the meaning (e.g. the word “blue”, written in green). Neutral trials consisted of words written in an ink colour with no semantic meaning (e.g. the word “valley”, written in yellow). The task consisted of 60 trials including 20 congruent, 20 incongruent and 20 neutral word stimuli presented in a randomised order. Participants were instructed to respond only to the ink colour that each word was written in, and not the semantic meaning of the word. The response box keys ‘1’, ‘2’, ‘3’ and ‘4’ corresponded with the answers “red”, “green”, “blue” and “yellow” respectively.

During incongruent trials, the conflict between the relevant (colour of word) and irrelevant (name of word) sources of information produces a breakdown in inhibitory processing known as Stroop interference. This is typified by a prolonged response time in the incongruent trials, when compared to neutral and congruent trials. Relative to congruent or neutral trials, a faster response time in incongruent trials would be indicative of a selective attentional system that supresses the irrelevant information more efficiently (Pilli, Naidu, Pingali, Shobha, & Reddy, 2013). The magnitude of Stroop Interference is therefore used as a proxy for efficiency of the inhibitory system (Spieler et al., 1996).

Reaction time (ms) and accuracy (% errors) under each of the three conditions were the outcome variables generated. From this Stroop interference was calculated by subtracting the reaction time of the neutral trails (N-RT) from the reaction time of the incongruent trials (I-RT); Interference = (I-RT)-(N-RT). Stroop interference was also calculated as a percentage, in accordance with Langenecker, Nielson, and Rao (2004) using the following equation: $(RT_I - RT_N)/RT\text{-}_N$

5.9 Physical activity protocol

At week 0 of the intervention, participants were randomly allocated to one of two intervention arms. A non-exercise control was added retrospectively. The intervention arms comprised of a low dose walking group or a high dose walking group. Baseline daily step count was calculated for all participants following a 7-day period wearing a GT3X Actigraph accelerometer (Chapter 2, section 2.9.1). Relative to individual baseline steps, participants were either given a target increase of +3000 steps/day “low dose” or a target increase of +6000 steps/day “high dose.” Yamax SW-200 pedometers (Yamax Corp., Tokyo, Japan) were used by particpants throughout the duration of the study. To verify the accuracy of the pedometers participants were instructed to walk 20 steps, if a measurement error > 1 step was observed the positioning of the device was adjusted until an accurate reading was achieved. The pedometers displayed step count only, which participants were able to view. Participants were asked to record their total accumulated step count at the end of each day (including rest days) on log sheets (Appendix 6.31). The weekly log was returned to the researcher at the end of each intervention week, and reviewed with the participant in a weekly telephone call to aid motivation and compliance. All participants were asked not to engage in any calorie-restricting diets or any additional exercise above their prescribed step count during the study.

5.9.1 Non-exercising control group

Participants were asked maintain their current diet and physical activity levels, and abstain from taking up any new physical activity or exercises throughout the 12-week duration of the study. The control group were not given a pedometer to use during the study to report daily step count as research has shown the monitoring device itself can motivate increases in step counts.

5.10 Ethical approval

Attainment of ethical approval is described in Chapter 2, section 2.3.

5.11 Data Analysis

The SAS-mixed models procedure (PROC MIXED) was employed to examine the potential within-subjects change in cognitive function or cardiometabolic health outcome variables over the 12-week intervention period, compared with the no intervention control group examined over the same period.

The initially planned analysis was to include two fixed factors; condition with 3 levels (+3000 steps, +6000 steps, and NO-EX), and time with 2 levels (mid and post) with baseline steps included as a covariate. However, high attrition rates and failure to adhere to the +6000 steps condition resulted in insufficient sample size within each condition to permit the planned analysis. Therefore, the two exercise conditions were combined into one "pedometer" condition, and post-intervention step count was included as a covariate. Since no step count data was collected for the NO-EX condition at mid-point this time-point could not be entered into the model. Therefore, the factor "time" was omitted from the analysis and participants were examined at post-testing only.

Participant ID was entered as a random factor and condition was entered as a fixed factor. Baseline performance (on each cognitive or cardiometabolic health outcome) was retained as a covariate. Age and post-intervention step count were also initially included as covariates but removed from models if non-significant. For cognitive outcomes only, IQ was also included as a covariate. Where covariates were significant, they were plotted to determine direction of relationship with the dependent variable. When significant main effects or interactions were found, Tukey corrected post hoc tests (LSMEANS) were performed to explore these. In cases, where an interaction with baseline or other covariate was significant, the LSMEANS procedure, examines the effect at the average value of the baseline (or other covariate) and is reported. For such cases average baseline score is indicated on the relevant figure by a vertical line (e.g. see Figure 5.10).

5.12 Results

5.12.1 Participant characteristics

5.12.1.1 Three experimental conditions (+3000, +6000 and NO-EX)

Participant characteristics at baseline for the three original experimental conditions are presented in Table 5.2. Systolic blood pressure was significantly higher in participants assigned to the +6000 steps/day condition (133.7 ± 16.8 mmHg) relative to NO-EX (117.0 ± 12.3 mmHg; $F(2,32)=3.63$, $p<.05$). Diastolic blood pressure was significantly higher in participants assigned to the +6000 steps/day condition (95.9 ± 12.6 mmHg) relative to NO-EX (79.2 ± 9.2 mmHg; $F(2,32)=5.59$, $p<.01$). There were trends for differences between groups at baseline for age, $F(2,32)=2.72$, $p=.08$, and IQ, $F(2,32)=2.72$, $p=.08$ No further differences at baseline were evident between the experimental conditions.

Table 5.2 Participant characteristics (mean ± SD) at baseline (three conditions)

	Pedometer			
	+3000 (n=19)	**+6000 (n=5)**	**NO-EX (n=9)**	**p**
IQ	116.6 ± 9.8	127.0 ± 4.2	115.8 ± 10.2	.079
Age	48.8 ± 6.7	44.2 ± 9.8	41.2 ± 9.7	.082
Body fat (%)	40.6 ± 8.7	34.8 ± 8.4	42.5 ± 6.3	.242
BMI	34.1 ± 6.5	33.5 ± 5.3	32.3 ± 5.4	.770
WC	115.2 ± 12.3	117.0 ± 8.2	106.5 ± 10.8	.118
WHR	0.98 ± 0.1	0.99 ± 0.1	0.93 ± 0.1	.133
Fasting glucose	5.3 ± 0.9	5.2 ± 0.2	4.97 ± 0.6	.691
Fasting Insulin	6.7 ± 3.9	10.2 ± 4.1	8.7 ± 4.7	.541
HOMA-IR	1.7 ± 1.1	2.2 ± 0.9	2.1 ± 1.4	.667
Systolic blood pressure	123.6 ± 9.0	133.7 ± 16.8	117.0 ± 12.3	.038
Diastolic blood pressure	86.5 ± 7.9	95.9 ± 12.6	79.2 ± 9.2	.009
Daily step count	6123.7 ± 2027.8	6667.1 ± 2708.7	5840.2 ± 1531.4	.800

Figure 5.4 shows baseline and post-intervention average daily step count for the three experimental conditions. The figure indicates little change in the no exercise group as expected, and increases in step-count post-intervention in both the +3000 and +6000 groups $F(2,27)=4.71$, $p<.05$. However, step-count achieved in the +6000 group was not different to the +3000 group meaning the high dose group were not achieving the prescribed increase in step count, $F(2,27)=2.15$, ns.

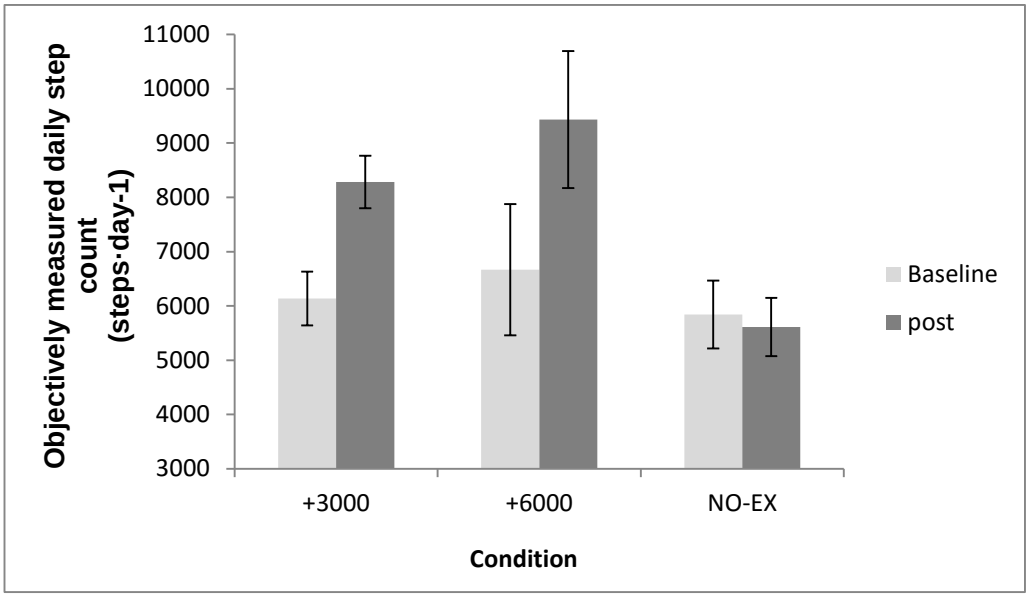

Figure 5.4 Objectively measured (Actigraph GT3X) average daily step count at baseline and post intervention by group (+3000, +6000 and NO-EX)

5.12.1.2 Two experimental conditions (pedometer and NO-EX)

Due to the low number of participants in the +6000 condition (n=5) and failure to comply with the prescribed target, the high (+6000) and low (+3000) dose pedometer conditions were collapsed into one group ('pedometer'). The participant characteristics for the pedometer and no exercise groups used in subsequent statistical analysis are presented in Table 5.3. At baseline, diastolic blood pressure was significantly higher in the pedometer group (88.5 ± 9.6 mmHg) relative to NO-EX (79.2 ± 9.2; $t(31)=2.5$, $p<.05$). Age was also significantly higher in the pedometer condition (48.3 ± 7.2 years) than in the NO-EX condition (41.2 ± 9.7; $t(31)=2.26$, $p<.05$). Systolic blood pressure was marginally higher in the pedometer condition (125.7 ± 11.2 mmHg) relative to NO-EX (117.0 ± 12.3; $t(31)=1.94$, $p=.06$). No further differences between the pedometer and NO-EX conditions were evident at baseline.

Table 5.3 Participant characteristics (mean ± SD) at baseline (two conditions)

	Pedometer (n=24)	NO-EX (n=9)	p
IQ	118.8 ± 9.8	115.8 ± 10.2	.451
Age	48.3 ± 7.2	41.2 ± 9.7	.031
Body fat (%)	39.4 ± 8.8	42.5 ± 6.9	.329
BMI	33.9 ± 6.1	32.3 ± 5.4	.487
WC	115.9 ± 11.2	106.5 ± 10.8	.992
WHR	0.99 ± 0.1	0.93 ± 0.1	.887
Fasting glucose	5.3 ± 0.9	5.0 ± 0.6	.405
Fasting Insulin	6.9 ± 3.8	8.7 ± 4.3	.452
HOMA-IR	1.7 ± 1.0	2.0 ± 1.4	.297
Systolic blood pressure	125.7 ± 11.2	117.0 ± 12.3	.062
Diastolic blood pressure	88.5 ± 9.6	79.2 ± 9.2	.018
Daily step count	6241.9 ± 2136.3	5840.2 ± 1531.4	.670

Figure 5.5 shows the significant time*condition interaction for daily step count $F(1,28)=9.13$, $p<.05$ such that from baseline to post-intervention participants in the the pedometer condition increased daily step count (average increase of 2274.8 ± 1971.4 steps) whereas participant in the NO-EX group did not.

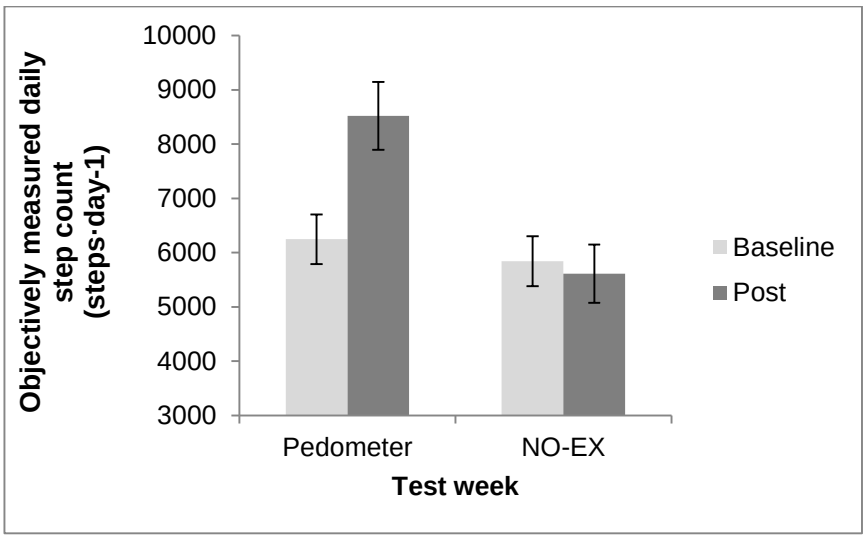

Figure 5.5 Objectively measured (Actigraph GT3X) average daily step count at baseline and post intervention by group (pedometer and NO-EX)

5.12.2 Cognitive function

5.12.2.1 Verbal memory

Total acquisition, delayed recall, recognition, retroactive interference and proactive interference were unaltered following 12-weeks pedometer or NO-EX conditions (Table 5.4; p>.05). As expected, baseline performance was a significant covariate and showed a positive correlation with post-test performance for total acquisition, delayed recall and recognition, $F(1,22)=22.30$, $p<.001$, $F(1,21)=41.83$, $p<.0001$ and $F(1,21)=18.10$, $p<.001$, respectively. All further effects are reported under the respective subsection for verbal memory outcomes.

Table 5.4 Visual verbal learning test (VVLT) outcomes at baseline and post for pedometer and NO-EX conditions

	Pedometer group		NO-EX	
	Baseline	**Post**	**Baseline**	**Post**
Total Acquisition[1]	33.4 ± 5.7	36.2 ± 6.2	31 ± 6.3	32.4 ± 7.5
Delayed recall[2]	10.8 ± 3.6	11.6 ± 2.9	9.7 ± 2.8	9.4 ± 3.1
Recognition (List A)[2]	13.2 ± 1.7	13.6 ± 2.2	12.4 ± 2.1	12.0 ± 2.6
Proactive Interference	1.4 ± 1.5	1.5 ± 3.2	1.7 ± 1.4	2.6 ± 2.1
Retroactive interference	2.5 ± 2.3	2.1 3.6	3.1 ± 2.4	2.9 ±2.3

No main effects of condition were found (p>.05). 1 Maximum score= 48; 2 Maximum score =16

5.12.2.1.1 Total acquisition

The analysis revealed no significant main effects or interactions (see Appendix 6.32).

5.12.2.1.2 Delayed recall

Step-count and IQ showed trends towards significance as covariates, $F(1,21)=3.11$, $p=.09$ and $F(1,21)=3.14$, $p=.09$ respectively. Both IQ and post-intervention step-count showed a positive correlation with delayed recall. The analysis revealed no significant main effects or interactions (see Appendix 6.32).

5.12.2.1.3 Recognition

IQ showed a trend towards significance as a covariate, $F(1,21)=3.81$, $p=.06$, and showed a positive correlation with recognition score The analysis revealed no significant main effects or interactions (see Appendix 6.32).

5.12.2.1.4 Proactive interference

In the final model the analysis revealed no significant main effects or interactions (see Appendix 6.32).

5.12.2.1.5 Retroactive interference

In this analysis 2 outlying observations were excluded to normalise the residuals. In the final model the analysis revealed no significant main effects or interactions (see (see Appendix 6.32)

5.12.2.2 Spatial memory

Recall of immediate designs, locations, designs/locations and delayed designs/locations were unaltered following the 12-week pedometer or NO-EX conditions (Table 5.5; p>.05). Baseline performance was not a significant covariate for any of the spatial memory outcomes. All other effects are reported under the respective subsection for spatial memory outcomes.

Table 5.5 Visual spatial learning test (VSLT) outcomes at baseline and post for pedometer and NO-EX conditions

	Pedometer group		NO-EX	
	Baseline	**Post**	**Baseline**	**Post**
Designs[1]	18.0 ± 1.9	17.8 ± 2.0	18.5 ± 1.6	18.25 ± 1.7
Locations[1]	15.1 ± 3.4	15.2 ± 4.5	14.8 ± 3.2	16.3 ± 4.2
Designs/Locations[1]	9.9 ± 4.1	10.4 ± 5.6	14.8 ± 3.2	13.9 ± 3.5
Delayed designs/locations[2]	3.5 ± 2.8	4.7 ± 2.5	5.8 ± 1.4	4.7 ± 2.1

No main effects of condition were found (p>.05). [1] Maximum score= 21; [2] Maximum score=7

5.12.2.2.1 Total designs

In the final model, step-count showed a trend towards significance as a covariate and a positive correlation with total designs recalled, F(1,19)=3.64, p=.07. The analysis revealed no significant main effects or interactions (see Appendix 6.33).

5.12.2.2.2 Locations

In the final model, the analysis revealed no significant main effects or interactions (see Appendix 6.33).

5.12.2.2.3 Designs and locations

In the final model, the analysis revealed no significant main effects or interactions (see Appendix 6.33).

5.12.2.2.4 Delayed designs and locations

In the final model, step-count and age showed trends towards significance as covariates, $F(1,16)=3.67$, $p=.07$ and $F(1,16)=3.66$, $p=.07$ respectively. Both IQ and post-intervention step-count showed a positive correlation with delayed recall of designs/positions. The analysis revealed no significant main effects or interactions (see Appendix 6.33).

5.12.2.3 Attention: Bakan

Total correct, reaction time of correct and missed responses were unaltered following the 12-week pedometer or NO-EX conditions (Table 5.6; $p>.05$). Post-intervention, false positive responses decreased for the pedometer group and increased in NO-EX and the main effect of condition was significant ($F(1,19)=7.92$, $p<.01$). As expected, baseline performance was a significant covariate and showed a positive correlation with post-test performance for total correct and reaction time of correct and missed responses, $F(1,19)=64.65$, $p<.0001$, $F(1,17)=5.08$, $p<.05$, and $F(1,18)=59.64$, $p<.0001$ respectively. All further effects are reported under each subsection for Bakan outcomes.

Table 5.6 Bakan rapid visual information processing (RVIP) outcomes at baseline and post for pedometer and NO-EX conditions

	Pedometer group		NO-EX	
	Baseline	**Post**	**Baseline**	**Post**
Total correct[1]	25.3 ± 10.7	25.8 ± 12.5	28 ± 10.0	25.8 ± 13.5
Reaction time of correct (ms)	452.2 ± 46.7	467.5 ± 75.7	437.4 ± 64.3	398.6 ± 19.9
Missed responses	34.7 ± 10.7	34.2 ± 12.5	32.1 ± 10.0	31.2 ± 13.5
False-positive responses*	7.7 ± 8.5	6.3 ± 4.8	6.1 ± 4.9	9.4 ± 7.0

* indicates a significant main effect of condition ($p<.05$) for false-positive responses. No main effects of condition were found for total correct reaction time of correct and missed responses ($p>.05$). [1] Maximum score= 60)

5.12.2.3.1 Total correct hits

There was a significant age*condition interaction, $F(2,19)=14.32$, $p<.001$. Age and total correct were negatively correlated in the pedometer condition, but performance at post-testing for NO-EX did not differ according to age. There was a significant IQ*condition interaction, $F(2,19)=6.14$, $p<.01$. The correlation between IQ and total correct was negative for NO-EX and positive for the pedometer group. The analysis revealed no further significant main effects or interactions (see Appendix 6.34).

5.12.2.3.2 Reaction time of correct hits

There was a significant baseline*condition interaction, $F(1,17)=4.55$, $p<.05$. The baseline*condition interaction is evident in Figure 5.6. The divergence of slopes indicates that the relationship between performance at baseline and post-intervention was different according to condition. For those with slower baseline reaction time (RT), post-intervention performance was better in NO-EX and unchanged in the pedometer condition. This effect appears to be driven by the smaller number of data points for NO-EX. The analysis revealed no further significant main effects or interactions (see Appendix 6.34).

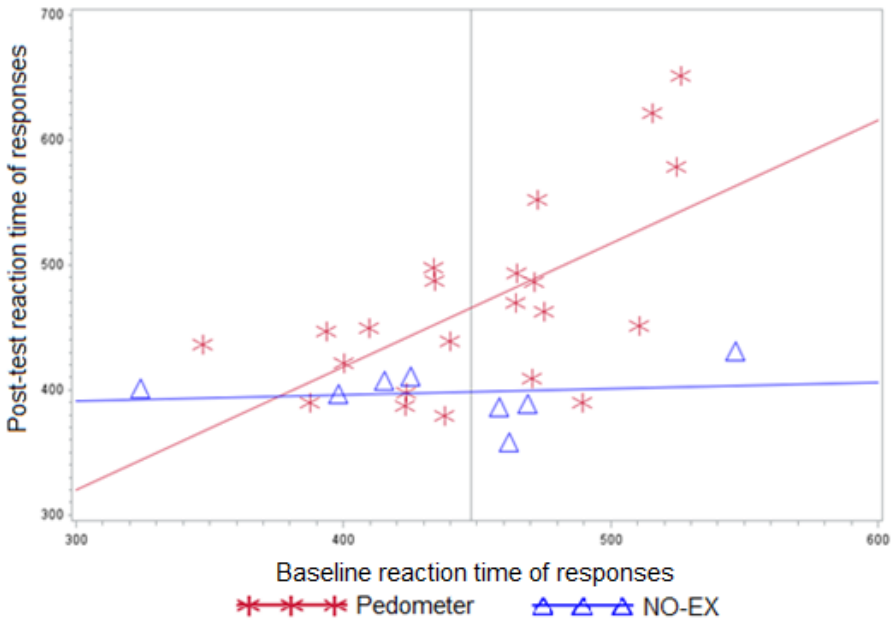

Figure 5.6 Reaction time of responses (BAKAN) at baseline (horizontal axis) and post-testing (vertical axis) for pedometer and NO-EX groups. Vertical line indicates average baseline RT.

5.12.2.3.3 Missed responses

In this analysis 1 outlying observation was excluded to normalise the residuals. There was a significant age*condition interaction, $F(1,18)=16.87$, $p<.001$. The pedometer condition showed the expected correlation between increasing age and worse performance (more missed responses), whereas for NO-EX post-intervention performance was unaffected by age. There was also an IQ*condition interaction, $F(1,18)=8.46$, $p<.01$. The pedometer condition showed the expected correlation between increasing IQ and better performance (fewer missed responses), whereas for NO-EX post-intervention performance was unaffected by IQ. The analysis revealed no further significant main effects or interactions (see Appendix 6.34).

5.12.2.3.4 False-positive responses

In the final model, there was a significant main effect of condition, $F(1,19)=7.92$, $p<.01$, indicating that the pedometer group were making less false-positive responses than NO-EX. However, post hoc tests for the main effect of condition were not significant, ($p>.05$). There was a trend towards an age*condition interaction, $F(2,19)=2.75$, $p=.09$, such that older people had worse performance (higher false-positive responses) in the pedometer group relative to NO-EX. The analysis revealed no further significant main effects or interactions (see Appendix 6.34).

5.12.2.4 Spatial working memory

Total correct responses, reaction time for correct responses, and accuracy of crossing trials were unaltered following the 12-week pedometer or NO-EX conditions (Table 5.7; $p>.05$). Post-intervention, accuracy of crossing trials increased for NO-EX and decreased for the pedometer group as indicated by a significant main effect of condition. As expected baseline performance was a significant covariate and showed a positive correlation with post-test performance for total correct responses, reaction time for correct responses and accuracy of crossing trials ($F(1,18)=20.14$, $p<.001$, $F(1,18)=10.21$, $p<.01$, and $F(1,21)=4.98$, $p<.05$ respectively. All further effects are reported under each subsection for spatial working memory outcomes.

Table 5.7 Spatial working memory (Corsi) outcomes at baseline and post for pedometer and NO-EX conditions

	Pedometer group		NO-EX	
	Baseline	Post	Baseline	Post
Accuracy (total correct)	58.3 ± 11.0	56.3 ± 11.5	62.7 ± 8.0	65.3 ± 10.9
Reaction time (correct)	1023.7 ± 143.8	1015.8 ± 202.4	980.3 ± 200.1	969.8 ± 139.7
Accuracy: crossing	18.6 ± 6.3	19.0 ± 6.5	23.6 ± 5.5	24.0 ± 7.6
Accuracy: non-crossing*	39.6 ± 6.1	37.5 ± 6.7	39.0 ± 4.1	41.3 ±4.8

No main effects of condition were found for total correct, reaction time of correct, and accuracy of crossing trials (p>.05).

5.12.2.4.1 Accuracy (total correct responses)

There was a steps*condition interaction, F(1,18)=6.58, p<.05 and a baseline*condition interaction, F(1,18)=5.82, p<.05. Within the pedometer condition, higher post-intervention step-count was positively associated with more total correct responses. For NO-EX, all participants had low post-intervention step-count (as a function of the intervention), but had better performance relative to those with low step-count in the pedometer condition. It must be noted 2 participants in the pedometer condition had lower step counts than NO-EX. The analysis revealed no further significant main effects or interactions (see Appendix 6.35). The baseline*condition interaction is evident in Figure 5.7.

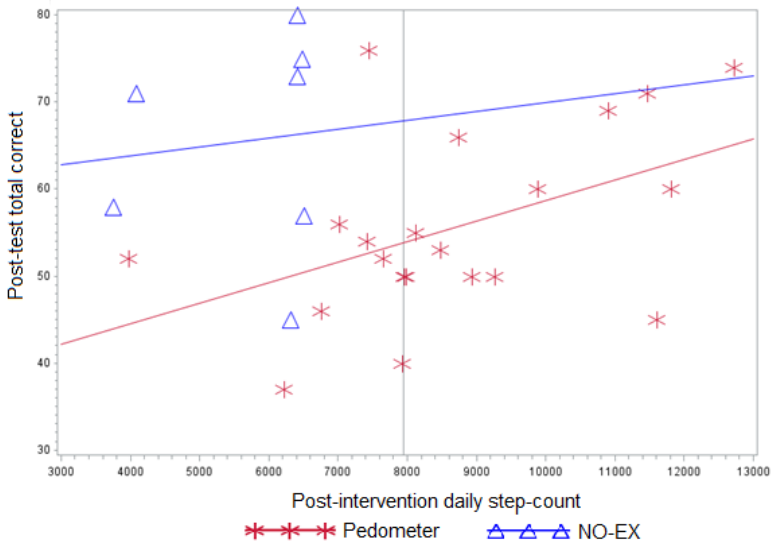

Figure 5.7 Post-intervention total correct (Corsi) plotted against step-count for pedometer and NO-EX. Vertical line indicates average post-intervention daily step count.

5.12.2.4.2 Reaction time for correct responses

The analysis revealed no further significant main effects or interactions (see Appendix 6.35).

5.12.2.4.3 Accuracy: crossing trials

The analysis revealed no significant main effects or interactions (see Appendix 6.35).

5.12.2.4.4 Accuracy: non-crossing trials

In this analysis 3 outlying observations were excluded to normalise the residuals. In the final model, there was a significant main effect of condition, $F(1,17)=5.03$, $p<.05$. Post hoc tests showed that after controlling for baseline score (average = 39.55), performance was better in NO-EX (41.4 ± 1.7) relative to the pedometer condition (36.8 ± 0.8; $f(17)=-2.24$, $p<.05$). This is evident in Figure 5.8. Age and IQ were significant covariates, $F(1,17)=5.39$, $p<.05$ and $F(1,17)=5.07$, $p<.05$, respectively. As expected, age showed a negative and IQ showed a positive correlation with accuracy. The analysis revealed no further significant main effects or interactions (see Appendix 6.35).

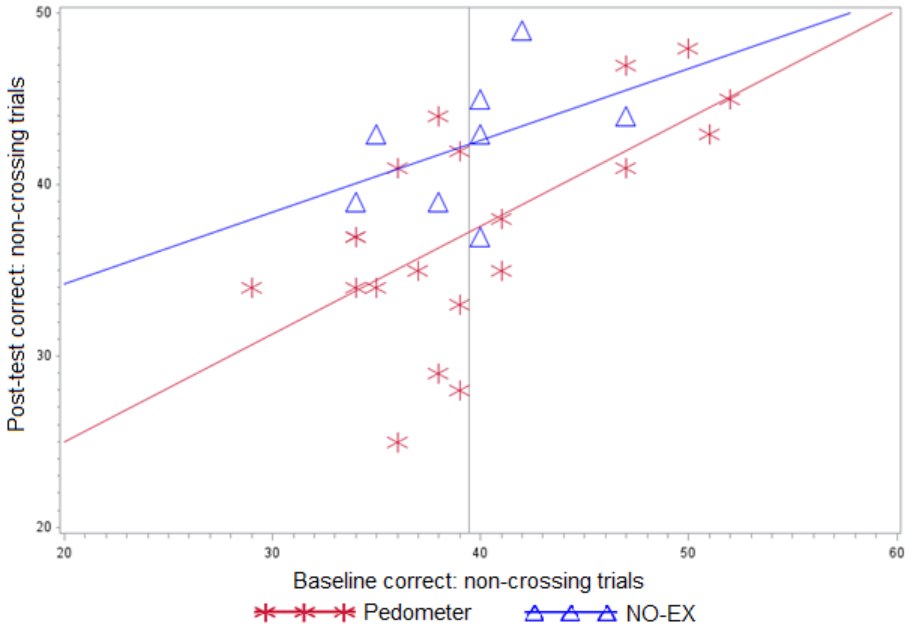

Figure 5.8 Correct responses for non-crossing trials (Corsi) at baseline (horizontal axis) and post-testing (vertical axis) for pedometer and NO-EX groups. Vertical line indicates average baseline correct: non-crossing trials.

5.12.2.5 Executive Function

All outcomes for the Trail Making Test (TMT) and Stroop colour/word test were unaltered following 12-weeks pedometer or NO-EX conditions (Table 5.8**Error! Reference source not found.**; p>.05). As expected, baseline performance was a significant covariate and showed a positive correlation with post-test performance for TMT (part B) and TMT (B minus A), F(1,16)=19.30, p<.001, and F(1,16)=47.63, p<.0001 respectively. All further effects are reported under each subsection for executive function outcomes.

Table 5.8 Executive function outcomes (Trail Making Test and Stroop colour/word Test) at baseline and post for pedometer and NO-EX conditions

	Pedometer group		NO-EX	
	Baseline	**Post**	**Baseline**	**Post**
TMT part A	21.1 ± 6.9	19.2 ± 7.1	17.6 ± 3.5	18.0 ± 10.6
TMT part B	51.7 ± 26.8	41.5 ± 1.8	38.6 ± 13.9	34.8 ± 11.9
TMT (B minus A)	30.6 ± 22.7	22.3 ± 16.3	18.5 ± 14.4	16.7 ± 9.6
Stroop Interference (ms)	158.6 ± 187.0	201.7 ± 168.9	94.1 ± 141.8	129.9 ± 137.8
Stroop: Reaction time of incongruent (ms)	1169.6 ± 310.8	1150.1 ± 313.2	1055.2 ± 250.3	948.4 ± 283.8

No main effects of condition were found (p>.05).

5.12.2.5.1 Trail Making Test: Part A (TMT A)

In the final model, step-count was a significant covariate and showed a positive correlation with performance on TMT part A, F(1,19)=6.85, p<.05. The analysis revealed no significant main effects or interactions (see Appendix 6.36).

5.12.2.5.2 Trail Making Test: Part B (TMT B)

In this analysis 2 outlying observations were excluded to normalise the residuals. There was a significant age*condition interaction, F(1,16)=6.87, p<.05, such that older participants had worse performance (slower completion time) in NO-EX, relative to the pedometer condition. There was a trend towards an IQ*condition interaction, F(1,16)=3.26, p=.09, in that as IQ increased performance increased for the pedometer condition, but not for NO-EX. The analysis revealed no significant main effects or further interactions (see Appendix 6.36).

5.12.2.5.3 Trail Making Test: B minus A

In this analysis 3 outlying observations were excluded to normalise the residuals. Steps, and IQ were significant covariates, $F(1,16)=10.39$, $p<.01$, and $F(1,16)=8.05$, $p<.01$, respectively. Irrespective of condition, increasing post-intervention step-count was correlated with faster completion times whereas IQ was negatively correlated with performance (higher B minus A score). The analysis revealed no significant main effects or further interactions (see Appendix 6.36).

5.12.2.5.4 Stroop interference

In this analysis 4 outlying observations were excluded to normalise the residuals. In the final model, there was a significant baseline*condition interaction, $F(1,17)= 5.67$, $p<.05$. The divergence of slopes in Figure 5.9 indicates that the relationship between baseline and post-intervention performance is different according to condition. For those with greater interference at baseline, post-intervention performance is better in NO-EX relative to the pedometer group. However, this appears to be driven by just 2 individuals in the NO-EX condition with high baseline interference scores. The analysis revealed no significant main effects or further interactions (see Appendix 6.36).

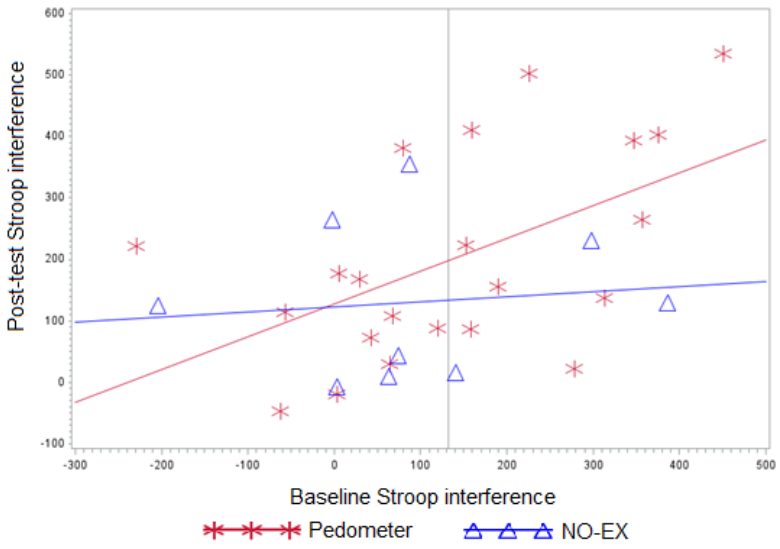

Figure 5.9 Stroop interference at baseline (horizontal axis) and post-testing (vertical axis) for pedometer and NO-EX groups. Vertical line indicates average baseline Stroop interference.

5.12.2.5.5 Stroop: reaction time for incongruent stimuli

In this analysis 1 outlying observation was excluded to normalise the residuals. In the final model, age was a significant covariate and showed a positive correlation with reaction time for incongruent responses, $F(1,21)=4.98$, $p<.05$. The analysis revealed no significant main effects or interactions (see Appendix 6.36).

5.12.3 Health parameters

The impact of the 12-week intervention on indices of cardiometabolic health and obesity are presented as follows:

5.12.3.1 Indices of cardiometabolic health

Fasting glucose, HOMA-IR, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were unaltered following 12-weeks pedometer or NO-EX conditions as evident from Table 5.9). The raw data indicate that fasting insulin levels declined in both groups, but the main effect of condition on post intervention fasting insulin levels, $F(1,17)=4.47$, $p<.05$ reflected reduced fasting insulin levels in the NO-EX group

Table 5.9 Indices of cardiometabolic health at baseline and post for pedometer and NO-EX conditions

	Pedometer group		NO-EX	
	Baseline	**Post**	**Baseline**	**Post**
Fasting glucose	5.3 ± 0.8	5.4 ± 0.7	4.9 ± 0.5	5.2 ± 0.6
Fasting Insulin*	6.9 ± 3.9	6.3 ± 4.2	8.7 ± 4.2	7.1 ± 4.3
HOMA-IR	1.7 ± 1.0	1.6 ± 1.3	2.0 ± 1.3	1.7 ± 1.1
Systolic blood pressure	125.7 ± 11.2	123.6 ± 13.5	117.0 ± 12.3	113.4 ± 9.6
Diastolic blood pressure	88.5 ± 9.6	84.1 ± 11.7	79.2 ± 9.2	77.4 ± 6.0

* indicates a significant post-intervention effect of condition ($p<.05$) for fasting insulin. No main effects of condition were found for fasting glucose, HOMA-IR, systolic blood pressure and diastolic blood pressure ($p>.05$).

As expected, baseline value was a significant covariate and showed a positive correlation with post-test value for fasting glucose, fasting insulin and HOMA-IR, $F(1,17)=4.38$, $p=.05$, $F(1,17)=79.86$, $p<.0001$ and $F(1,16)=76.38$, $p<.0001$ respectively. Baseline SBP and DBP were significant covariates and showed a positive correlation with post-intervention value, $F(1,23)=39.54$, $p<.0001$, and $F(1,21)=21.53$, $p<.0001$, respectively All further effects are reported under the respective subsection for indices of cardiometabolic health.

5.12.3.1.1 Fasting glucose (capillary plasma sample)

In this analysis 3 outlying observations were excluded to normalise the residuals. In the final model, there was a trend towards a significant step*condition interaction, $F(1,17)=4.04$, $p=.06$. However, Figure 5.10 shows that post-intervention fasting glucose was higher in NO-EX relative to the pedometer group, regardless of step count. Post-intervention step-count

was a significant covariate, and showed a weak positive correlation with fasting glucose, however this was within the healthy range (3.6 - 5.5 mmol/L), F(1,17)=5.76, p<.05. Age was a significant covariate and showed a positive correlation with post-intervention fasting glucose, F(1,17)=6.94, p<.05. There were no further significant main effects or interactions (see Appendix 6.37).

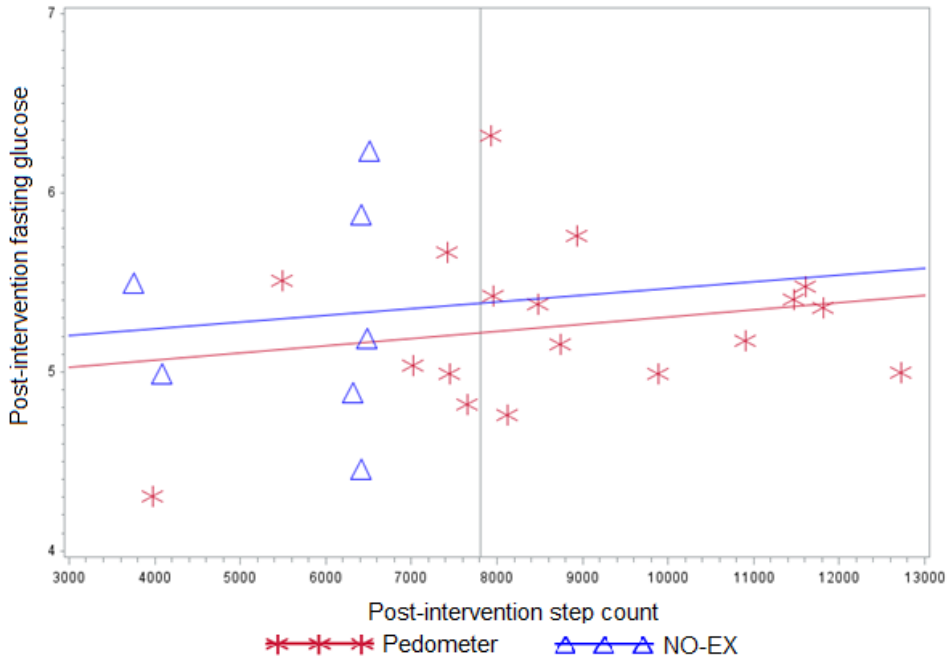

Figure 5.10 Post-intervention step-count (horizontal axis) and fasting glucose (vertical axis) for pedometer and NO-EX groups. Vertical line indicates average post intervention step count.

5.12.3.1.2 Fasting Insulin (capillary plasma sample)

In the final model, there was a significant main effect of condition, F(1,17)=4.47, p<.05. Post hoc tests showed that after controlling for baseline fasting insulin (average = 7.16 µIU/ml), post-intervention values were higher in the pedometer condition (7.11 µIU/ml) relative to NO-EX (3.22 µIU/ml; t(17)=2.98, p<.01. Figure 5.11 shows that the NO-EX had fewer participants with higher values which may have affected the results. Age was a significant covariate, and showed a negative correlation with fasting insulin (see Appendix 6.38) which was unexpected, F(1,17)=9.18, p<.01, however the data indicate that this was driven by a low number of young individuals with high fasting insulin. The analysis revealed no significant main effects or interactions (see Appendix 6.37).

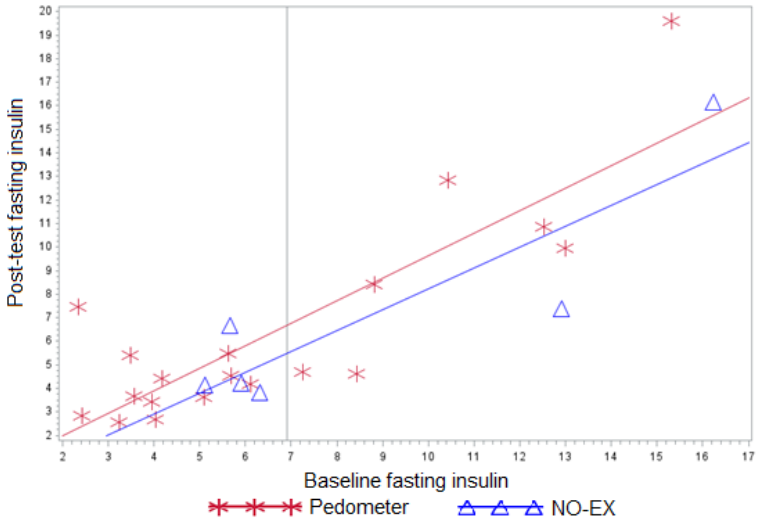

Figure 5.11 Fasting insulin at baseline (horizontal axis) and post-testing (vertical axis) for pedometer and NO-EX groups. Vertical line indicates average baseline fasting insulin.

5.12.3.1.3 HOMA-IR

In this analysis 1 outlying observation was excluded to normalise the residuals. There was a trend towards a baseline*condition interaction, $F(1,16)=3.25$, $p=.09$. The baseline*condition interaction is evident in Figure 5.12 the divergence of slopes indicates that the relationship between baseline and post-intervention HOMA-IR differs according to condition. The interaction however looks to be driven by a small number of participants in both conditions with HOMA-IR that exceeded the upper limit of the healthy range (2.5). Age showed a trend towards being a significant covariate with older age associated with higher HOMA-IR, $F(1,16)=3.16$, $p=.09$. The analysis revealed no significant main effects or interactions (see Appendix 6.37).

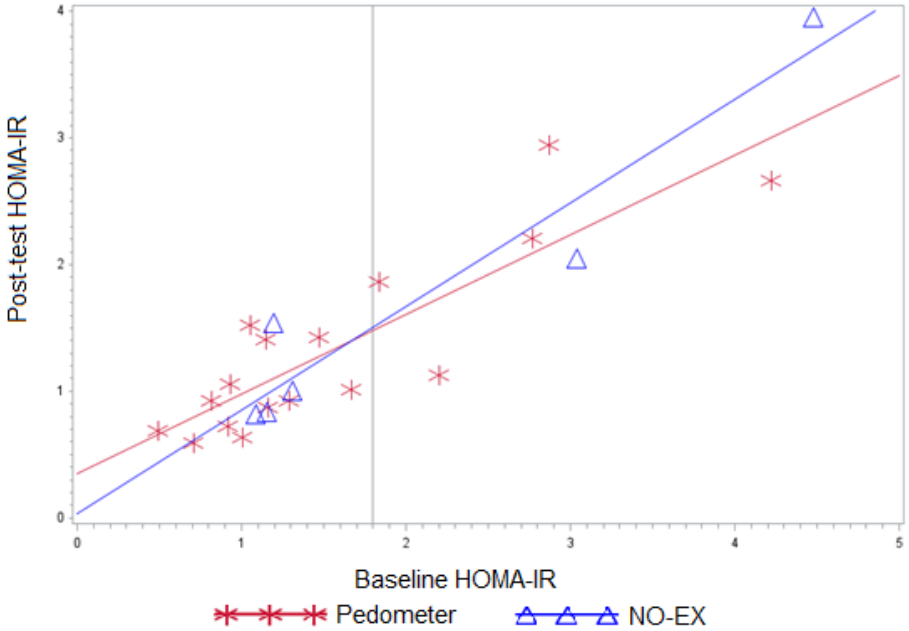

Figure 5.12 HOMA-IR at baseline (horizontal axis) and post-testing (vertical axis) for pedometer and NO-EX groups. Vertical line indicates average baseline HOMA-IR.

5.12.3.1.4 Systolic blood pressure

In this analysis 1 outlying observation was excluded to normalise the residuals. Post-intervention step-count showed a trend towards being a significant covariate, such that those with higher step-count had lower systolic blood pressure, $F(1,23)=3.41$, $p=.07$. The analysis revealed no significant main effects or interactions (see Appendix 6.37).

5.12.3.1.5 Diastolic blood pressure

There was a significant baseline*condition interaction, $F(1,21)=4.88$, $p<.05$. The baseline*condition interaction is evident in Figure 5.13, the divergence of slopes indicates that the relationship between baseline and post-intervention performance differs according to condition. This appears to be driven by NO-EX as those with low baseline DBP show higher values post-intervention than the pedometer group. This is further compounded by the fact that all participants with high baseline DBP are in the pedometer condition. The analysis revealed no significant main effects or further interactions (see Appendix 6.37).

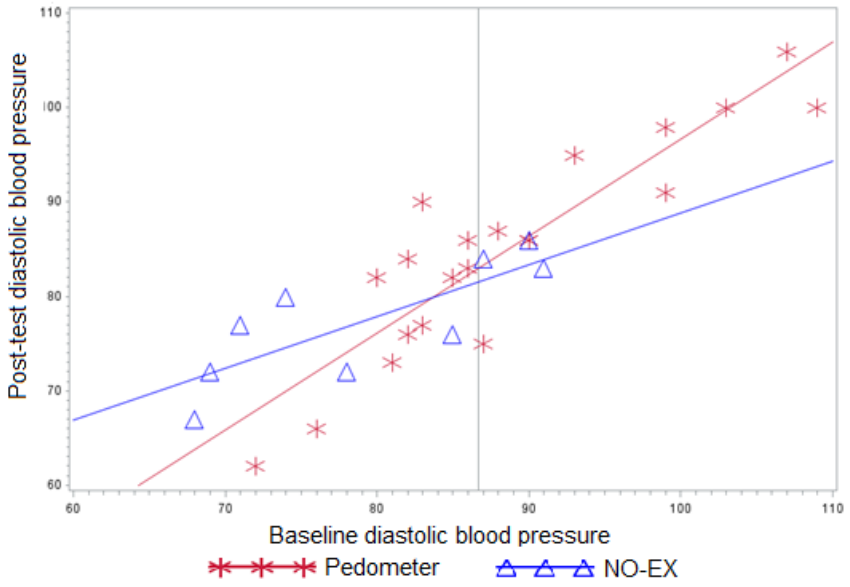

Figure 5.13 Diastolic blood pressure (DBP) at baseline (horizontal axis) and post-testing (vertical axis) for pedometer and NO-EX groups. Vertical line indicates average baseline DBP.

5.12.3.2 Indices of obesity

BMI, waist circumference (WC) and waist-hip ratio (WHR) were unaltered following 12-weeks pedometer or NO-EX conditions (Table 5.10; $p>.05$). A main effect of condition for body fat percentage is evident in Table 5.10 as the NO-EX group had higher body fat at baseline and post relative to the pedometer group. As expected, baseline value was a significant covariate and showed a positive correlation with post-test value for body fat, BMI, WC and WHR, $F(1,22)=524.72$, $p<.0001$, $F(1,23)=1325.12$, $p<.0001$, $F(1,21)=199.7$, $p<.0001$, and $F(1,21)=199.7$, $p<.0001$, respectively. All further effects are reported under the respective subsection for index of obesity.

Table 5.10 Indices of obesity at baseline and post for pedometer and NO-EX conditions

	Pedometer group		NO-EX	
	Baseline	**Post**	**Baseline**	**Post**
Body fat (%)*	39.4 ± 8.8	38.2 ± 8.2	42.5 ± 6.9	42.7 ± 5.8
BMI	33.9 ± 6.1	32.5 ± 4.9	32.3 ± 5.4	32.5 ± 5.1
WC	115.9 ± 11.2	113.9 ± 9.1	106.5 ± 10.8	105.0 ± 10.9
WHR	0.99 ± 0.1	0.98 ± 0.1	0.93 ± 0.1	0.92 ± 0.1

* indicates a significant post-intervention effect of condition (p<.05) for body fat.).

5.12.3.2.1 Body fat percentage

In this analysis 2 outlying observations were excluded to normalise the residuals. In the final model, there was a significant main effect of condition, F(1,22)=4.37, p<.05. Post hoc tests confirmed that, after controlling for baseline (average = 39.5%), post-intervention body fat was significantly higher in NO-EX (40.7 ± 0.5) relative to the pedometer group (39.3 ± 0.2; f(22)=-2.78, p<.01). There was a trend towards a significant baseline*condition interaction, F(1,22)=3.12, p=.09. The analysis revealed no significant main effects or further interactions (see Appendix 6.39).

5.12.3.2.2 BMI

In this analysis 1 outlying observation was excluded to normalise the residuals. Irrespective of group, post-intervention step-count was a significant covariate and showed a negative correlation with BMI, F(1,23)=8.33, p<.01. The analysis revealed no significant main effects or further interactions (see Appendix 6.39).

5.12.3.2.3 Waist circumference

In the final model, the analysis revealed no significant main effects or interactions (see Appendix 6.39).

5.12.3.2.4 Waist-hip ratio

In the final model, the analysis revealed no significant main effects or further interactions (see Appendix 6.39).

5.13 Summary of findings

Findings from this study are summarised as follows:

5.13.1 Effects of 12-week intervention on cognitive function

A tabulated summary of the effect of the intervention on cognitive function outcomes is shown in Table 5.11.

- As expected, baseline cognitive performance was the strongest predictor of post-intervention performance for verbal memory (total acquisition, delayed recall and delayed recognition), attention (correct hits, reaction time for correct hits, and missed responses), spatial working memory (accuracy, reaction time for correct responses and accuracy: crossing-trials), and executive function (TMT part B and TMT B minus A). However, baseline score did not predict performance at post-testing for any outcomes on the spatial memory or Stroop tests.
- Baseline values showed significant interactions with condition for attention (Bakan: reaction time for correct hits), spatial working memory (total correct) and executive function (Stroop interference).
- No post-intervention main effects of condition were observed for any verbal memory, spatial memory, attention or executive function outcomes.
- Only one outcome from the Bakan task (false-positive responses) showed an effect of intervention, indicating superior performance in the pedometer group.
- The Corsi task (accuracy:non-crossing trials) showed an effect of intervention, and indicated superior performance in NO-EX.
- Irrespective of condition, the number of steps (post-intervention) was a significant predictor of the Trail Making Test (part A, and B minus A) scores and predicted (trend) VVLT delayed recall and VSLT outcomes (designs and delayed designs/locations. In all cases, higher step-count was associated with better performance.
- Post-intervention step-count also showed an interaction with condition for one Corsi outcome (total correct) in that the least active (lower step count) had better performance in NO-EX. However, post-intervention step-count data is only available for NO-EX below 7000 steps/day so above this threshold no inferences can be made against the pedometer condition.
- Age showed an interaction with condition for Bakan outcomes (total correct, missed responses and false-positives) and TMT (part B). For NO-EX, increased age was associated with worse TMTB performance, but this relationship was not evident in the

pedometer group. For the pedometer group, increased age was associated with poorer performance in Bakan outcomes, but this was not evident in NO-EX.

- Irrespective of group, as age increased performance decreased in spatial working memory outcome (accuracy: non-crossing trials) and executive function (Stroop RT incongruent) and showed a trend for one VSLT outcome (delayed designs/locations) only.
- IQ showed an interaction with condition for Bakan outcomes (total correct and missed responses) and TMT B. In all cases, increasing IQ was associated with better performance in the pedometer condition and worse performance in NO-EX.
- Irrespective of group, as IQ increased performance increased in Corsi (accuracy:non-crossing trials), TMT (B minus A) and VVLT outcomes (trends for delayed recall and recognition)

Table 5.11 Tabulated summary of cognitive outcomes

	Main effects	Covariates				Interaction terms			
Cognitive outcome	**Condition**	**Baseline**	**Steps**	**Age**	**IQ**	**B*Cond**	**Steps*Cond**	**Age*Cond**	**IQ*cond**
VERBAL MEMORY: Visual Verbal Learning Test (VVLT)									
Total Acquisition	N	Sig. p<.001	N	N	N	N	-	N	N
Delayed recall	N	Sig. p<.0001	Trend p=.09	-	Trend p=.09	N	-	-	-
Recognition	N	Sig. p<.001	N	-	Trend p=.06	N	-	-	-
Retroactive Interference	N	N	N	N	N	N	-	-	-
Proactive Interference	N	N	N	N	-	N	-	N	-
SPATIAL MEMORY: Visual Spatial Learning Test (VSLT)									
Designs	N	N	Trend p=.07	-	-	N	-	-	-
Locations	N	N	N	N	-	N	-	-	-
Designs/locations	N	N	N	N	-	N	-	-	-
Delayed designs/locations	N	N	Trend p=.07	Trend p=.07	-	N	-	-	-
ATTENTION: Bakan									
Total correct	N	Sig. p<.0001	N	-	-	N	-	Sig. p<.001	Sig. p<.01
Reaction time hits	N	Sig. p<.05	N	N	N	Sig. P<.05	-	N	N
Missed responses	N	Sig. p<.0001	N	-	-	N	-	Sig. P<.001	Sig. p<.01
False-positives	Sig. p<.01	N	N	N	N	N	-	Trend p=.09	-

N indicates term included in final model but non-significant; - indicates term removed from final model for best fit (lowest AICc score); Cond=condition, B*cond=baseline*condition

	Main effects	Covariates				Interaction terms			
Cognitive outcome	**Cond**	**Baseline**	**Step**	**Age**	**IQ**	**B*Cond**	**Steps*Cond**	**Age*Cond**	**IQ*cond**
SPATIAL WORKING MEMORY: Corsi									
Accuracy	N	Sig. p<.001	N	N	N	Sig. p<.05	Sig. p<.05	N	N
Reaction time for correct responses	N	Sig. p<.01	N	N	N	N	-	N	N
Accuracy: crossing trials	N	Sig. p<.05	N	N	-	N	-	-	-
Accuracy: non-crossing trials	Sig. p<.05	N	N	Sig. p<.05	Sig. p<.05	N	-	N	N
EXECUTIVE FUNCTION : Stroop colour/word and Trail Making Test									
Stroop: interference	N	N	N	N	N	Sig. P<.05	N	N	N
Stroop: Reaction time of incongruent responses	N	N	N	Sig. P<.05	N	N	N	N	N
TMT A	N	N	Sig. P<.05	N	-	N	-	-	-
TMT B	N	Sig. p<.0001	N	N	N	N	-	Sig. p<.05	Trend p=.09
TMT B minus A	N	Sig. p<.0001	Sig. P<.01	N	Sig. p<.01	N	-	-	N

N indicates term included in final model but non-significant; - indicates term removed from final model for best fit (lowest AICc score); Cond=condition, B*cond=baseline*condition

5.13.2 Effects of 12-week intervention on health parameters

A tabulated summary of the effect of the intervention on indices of obesity and cardiometabolic health is shown in Table 5.12. The evidence suggests that within this overweight/obese sample, the majority of participants were within the healthy range for the cardiometabolic parameters at the start of the intervention.

- As expected, the baseline cardiometabolic and anthropometeric parameters were the strongest predictors of the corresponding post-intervention parameters.
- Baseline values showed significant (or a trend towards) interactions with condition for DBP and HOMA-IR. In each case, negligible group differences occurred when baseline and post-intervention were within the healthy range, and values that exceeded the healthy range were under-represented in the sample.
- Body fat percentage and fasting insulin were the only health parameters that were altered post-intervention (main effect of condition). After controlling for baseline values, body fat percentage was higher in NO-EX relative to the pedometer condition. Fasting insulin was significantly lower following NO-EX relative to the pedometer group.
- Despite the lack of differences between the pedometer and control group, the number of steps (post-intervention) was a significant predictor of fasting glucose, BMI and showed a trend for SBP. Those taking more steps had lower values for BMI and SBP. The finding that those achieving more steps had higher fasting glucose but this was not physiologically relevant since all values were within the healthy range.
- Post-intervention step-count also showed an interaction with fasting glucose indicating that the least active (lower step count) had higher fasting glucose in NO-EX. However, post-intervention step-count data is only available for NO-EX below 7000 steps/day so above this threshold no inferences can be made in relation to the pedometer condition.

Table 5.12 Tabulated summary of indices of health parameters

	Main effects	Covariates			Interaction terms		
Physiological parameters	**Condition**	**Baseline**	**Steps**	**Age**	**B*Cond**	**Steps*Cond**	**Age*Cond**
Indices of cardiometabolic health							
Fasting glucose	N	Sig. p<.05	Sig. p<.05	Sig. p<.05	N	Trend p=.06	N
Fasting insulin	Sig. P<.05	Sig. p<.0001	N	Sig. p<.01	N	-	-
HOMA-IR	N	Sig. p<.0001	N	Trend p=.09	Trend p=.09	-	-
Systolic blood pressure	N	Sig. p<.0001	Trend p=.07	N	N	-	-
Diastolic blood pressure	N	Sig. p<.0001	N	-	Sig. P<.05	-	N
Indices of obesity							
Body fat percentage	Sig. p<.05	Sig. p<.0001	N	-	Trend p=.09	-	-
BMI	N	Sig. p<.0001	Sig. p<.01	-	N	-	-
Waist circumference	N	Sig. p<.0001	N	N	N	-	-
Waist-hip ratio	N	Sig. p<.0001	N	-	N	-	-

N indicates term included in final model but non-significant; - indicates term removed from final model for best fit (lowest AICc score); Cond=condition, B*cond=baseline*condition

5.14 Discussion

The study reported in this chapter aimed to examine the impact of 12-weeks of increased daily step-count on measures of cognitive function, cardiometabolic health and obesity indices in an overweight/obese middle-aged adult sample relative to a no-exercise control. The intention had been to examine two differing step-count 'doses' against a control group, however the low number of participants completing the "high dose" of +6000 steps/day rendered this condition inadequate for statistical analysis. The decision was made to collapse the high (+6000 steps) and low (+3000 steps) dose pedometer groups into one condition. To account for the differing step counts achieved by the participants, post intervention step-count was included as a covariate in the analysis for all cognitive and health-related outcomes. Issues arising directly from this are discussed in the section 5.14.2.4.2.

5.14.1 Overview of findings

At first glance the findings appear to suggest there was no effect of the pedometer intervention, since there were few significant main effects of condition. However, exploration of the covariates and interactions suggest that post-intervention step-count was beneficial for a limited number of health parameters and cognitive function outcomes. Individuals exceeding the healthy ranges were potentially driving some of the main effects of condition (or baseline*condition interactions) but were under-represented in the sample.

5.14.1.1 Cognitive function outcomes

With regard to cognitive outcomes, the findings of most interest were the associations between increased step-count and better performance in measures of executive function, delayed verbal memory and spatial memory (immediate and delayed). Currently, there is no literature available for comparison in terms of the impact of step-count change (or objectively measured PA) on cognitive outcomes in obese adults. The only data examining the impact of a walking intervention on TMT and verbal memory performance is in the elderly (Maki; Kerr; Klusmann et al 2010) However, it is not appropriate to make comparisons to samples that are experiencing age-associated cognitive decline.

A main effect of intervention (after controlling for baseline score) was observed for Bakan task (false-positive responses) showing superior performance in the

pedometer condition. This appeared to be driven by an interaction with age as younger participants were making higher impulsive incorrect responses in the NO-EX condition only. Conversely, older individuals made fewer impulsive incorrect responses post-intervention in the pedometer condition only. This may indicate the younger participants in this sample were more impulsive than older participants. An unexpected finding was observed indicating superior post-intervention performance in NO-EX for the Corsi task (accuracy:non-crossing trials). Inspection of the Corsi data suggests NO-EX maintained their performance from baseline to post-testing, whereas a few individuals in the pedometer group showed a decline in performance, driving the average down. The non-exercise control group demonstrated some unexpected behaviour, as indicated by improved performance at post-test relative to baseline for Stroop interference, Bakan (reaction time for correct hits) and Corsi (total correct). In all cases, this was driven by 2 individuals in NO-EX with poor performance at baseline and improved post-test performance, perhaps highlighting change that was driven by an unmeasured confounding variable that had changed between test visits, such as differing motivation, concentration, fatigue or stress.

As expected, the strongest predictor of post-test cognitive performance was baseline performance. When this was controlled for in the analysis, minimal effects of the intervention were observed. Because the size of the control group was small and showed some unexpected behaviour, it is difficult to draw any conclusions about the efficacy of the pedometer intervention. This study failed to provide support for significant improvement in cognitive function outcomes following 12-weeks in a sample of overweight/obese adults. This may be interpreted in two ways: either the intervention of +3000 steps/day for 12 weeks was not sufficient to impact either health or cognitive function, or limitations to the methodology, analysis or sample characteristics were not conducive to detecting change.

5.14.1.2 Cardiometabolic health

Subtle improvements were observed in a limited number of cardiometabolic outcomes in response to the walking intervention, although the majority of the sample were within the healthy range at baseline which may have limited the capacity for change. High post-intervention step count was associated with lower blood pressure (SBP only) and reduced BMI. Although, two meta-analyses indicate improvements in cardiometabolic parameters (systolic and diastolic blood pressure, lipids and lipoproteins) following walking interventions these can occur irrespective of change in body composition (Kelley, Kelley, & Tran, 2001, 2004). With regard to blood pressure,

reductions within the healthy range are of clinical relevance as the association with cardiovascular risk has no lower threshold (McInnes, 2005). The raw data indicated that fasting insulin reduced in both conditions, however the analysis (once controlling for baseline insulin) determined that NO-EX had lower post-test values. The spread of data indicated that the pedometer group had more participants with high baseline fasting insulin, and it appears the statistical process of correcting for baseline variance washed out these effects. Post-intervention fasting glucose was identified as being significantly higher in NO-EX relative to the pedometer group, however as this was within the healthy range it does not have any clinical relevance. Typically associations between objectively measured step-count and glycaemic control have only been demonstrated in individuals with T2DM (Manjoo, Joseph, & Dasgupta, 2012) and with impaired glucose tolerance (as qualified by fasting glucose and 2-hr glucose) (Swartz et al., 2003a). The only participants with T2DM in the study presented in this chapter were removed from the analysis since they were outliers from fasting glucose and insulin, and the majority of the sample were within the healthy range. In a sample (~9300) with impaired glucose tolerance and elevated cardiovascular risk, every 2000 step/day increment at baseline was associated with a 10% reduction in risk for cardiovascular event over a 6-year follow-up period (Yates et al., 2014).

5.14.2 Possible explanations for null findings

5.14.2.1 Comorbid risk not present at baseline

Obesity status of the sample was confirmed, as qualified by general indices (body fat: females >40%, males >30%) and abdominal obesity (waist circumference >100cm), however, very few exhibited signs of compromised cardiometabolic health at baseline. The sample did not represent overweight/obese individuals exceeding the healthy range for fasting glucose, insulin and HOMA-IR. Subtle improvements in these parameters within an already healthy range are not clinically meaningful. Despite trying to recruit individuals with T2DM, only a limited number volunteered for the study and this was further impacted by attrition. As a consequence, no data from T2DM patients were included in the analysis. The sample also under-represented hypertensive individuals as only 2 completers were above the criteria for Grade 1: mild hypertension (SBP 140-159mmHg; DBP 90-99mmHg) (Chalmers et al., 1998). Therefore, if the hypothesis is that reduction in cardiometabolic parameters is the mechanistic link between obesity and cognitive function then we cannot expect to see

change in cognitive function in those that do not experience any change in these physiological parameters.

5.14.2.2 Compliance

The physical activity data (Actigraph accelerometer) collected over a 7-day period at the end of the intervention may not have been representative of average step-count achieved over the full duration (12 weeks) of the study. Objective measurement of step count attained, and therefore evidence of compliance, is not available for weeks 1-11 of the study. If, for example, participants failed to comply in the final week they would have been incorrectly identified as having a lower post-intervention step-count. Conversely, participants failing to comply during the study may have been motivated by the accelerometer in the final week, and so would have been identified as having high post-intervention step count. This may have had implications when exploring post-intervention step-count as a covariate in the analysis. It would have been preferable to use the accelerometers for every week of the study. However, due to the cost (~£250 per device) this was not feasible for this 12-week study.

While baseline and post-intervention step-count were objectively measured (7-day Actigraph GT3X), the intervention itself was guided by pedometer and self-report of daily step. Self-report is susceptible to social desirability bias and it is possible there may have been discrepancies between the step-count achieved and that which was reported. Objective evidence of this has been demonstrated in previous studies e.g. participants were not informed their pedometers had a function that stored the daily step count for 40 days (Fukuoka, Kamitani, Dracup, & Jong, 2011). In their 3-week pilot study, 7.3% of the sample consistently entered additional steps each night (online diary) to what was shown on the pedometer display in weeks 2 and 3. Whilst there is no evidence available on the prevalence of this in longer-term interventions, it is a factor that must be considered for this 12-week study. The pedometers used for this study (YAMAX SW-200) have been validated in overweight/obese adults and shown to have high correlation (r =.87) with output from Actigraph GT3X (Barreira et al., 2013). However, it is possible that some participants may have unknowingly under-or over achieved steps due to inaccuracy of device to detect actual steps. This typically occurs if the pedometer is not positioned correctly, and this is easily affected by clothing around and/or increased adiposity. A few participants requested to swap pedometers due to suspicion they were not registering step count accurately. One observation from drop-outs during the study was that a number cited the reason for leaving was frustration with a pedometer not accurately measuring steps. These were

merely subjective accounts and not supported by empirical evidence. However, if devices such as pedometers are to be used to guide and motivate physical activity adherence, we need to explore what circumstances compromise accuracy (i.e. placement, clothing, waist circumference).

5.14.2.3 Attrition

Despite extensive recruitment methods (Newspaper article in Yorkshire Evening Post, e-mail distribution lists and a poster campaign around Leeds) volunteer interest in the study was low. This study also suffered from high attrition rates with many participants dropping out in the first week (after completing all baseline tests). This raises concerns that this is not a desirable or feasible method of increasing PA levels for many adults. The attrition rates and refusal (in many cases) to initiate the +6000 step count (5 days per week) highlight that this is not immediately obtainable for some individuals. For individuals with a baseline of 4000 steps/day or more, a target of an additional 6000 steps, would take them to 10,000 steps per day. This is in accordance with Sidman et al. (2004) (previously described in **Error! Reference source not found.**) who observed low baseline step-count was predictive of reduced likelihood of meeting a total step goal of 10,000 steps per day. In this free-living intervention, the additional time required to meet the step goals had to fit in with work/life commitments for the participants. Informal comments from the participants indicated that trying to meet the step count targets on 5 days per week was difficult to manage. Based on a moderate pace (100 steps/min) the +6000 target translates to a time commitment of 60 minutes per day. The time required will be even higher for those that cannot maintain a pace of 100 steps/minute so this has implications use in populations with impaired mobility

5.14.2.4 Methodological Considerations of

5.14.2.4.1 Use of fingertip-capillary blood samples

Capillary blood samples were collected for assessment of fasting glucose, insulin and consequent calculation of HOMA-IR. The euglycemic-hyperinsulinemic clamp test is considered the gold standard for assessment of insulin sensitivity assessment. However, due to cost and invasive nature of this method it was not considered for this study. HOMA-IR has been shown to reliably reflect the insulin sensitivity derived from the euglycemic-hyperinsulinemic clamp (Bonora et al., 2000). However, the issue is the use of capillary blood as opposed to venous blood. High correspondence between capillary blood and venous blood has been demonstrated in fasted conditions as

Kuwa et al. (2001) obtained equivalent values of blood glucose in healthy participants from capillary blood (4.69±0.29 mmol/L) and venous blood (4.68± 0.33 mmol/L). Additionally, capillary samples are appropriate in fasted samples as no significant differences have been found glucose levels measured in venous blood and capillary blood (Yang, Chang, & Lin, 2012).

Fingertip-capillary sampling has been shown to be sensitive to changes in insulin following acute aerobic or resistance exercise (Balaguera-Cortes, Wallman, Fairchild, & Guelfi, 2011), or post-prandial responses to a standardised meal following four different exercise sessions (high-intensity interval training or continuous exercise) (Sim, Wallman, Fairchild, & Guelfi, 2014). Studies quantifying appetite- and metabolism-related peptides including insulin that have employed fingertip-capillary sampling have produced measures representative of the values reported using antecubital-venous samples (Cani et al., 2009; Green, Gonzalez, Thomas, Stevenson, & Rumbold, 2014). However, Green et al. (2014) directly compared insulin values from fingertip-capillary blood samples to antecubital-venous in a fasted state (time 0) and then every 30 minutes for two hours following a meal to measure agreement between the two methods. The authors found no evidence of systematic bias between antecubital-venous blood (302.4± 154.7 pmol/l per hour) and fingertip-capillary (236.2 ±113.0 pmol/l per hour). However, they did recommend caution as agreement between the two methods was worse at higher concentrations, and therefore quantification of insulin from capillary samples is not appropriate when other alternatives are available. The fingertip-capillary sampling in this study was conducted in fasted participants, and typically measured low values. Capillary blood contains a greater ratio of arterial blood than venous blood, and is therefore considered more representative of arterial blood (Merton, Jones, Lee, Johnston, & Holt, 2000). However, interstitial and intercellular fluid in capillary blood also means that capillary blood is not directly comparable to arterial blood. It must be taken into consideration that the insulin levels measured from capillary samples may not accurately reflect circulating insulin within the body. This has further implications for the calculation of HOMA-IR, which is already an estimation of hepatic insulin sensitivity (Radikova, 2003). HOMA-IR has shown high correlation (.88, $p<.0001$) with estimates obtained by euglycemic-hyperinsulinemic clamp (Matthews et al., 1985) but this is with blood obtained from venous samples. There is currently no data validating HOMA-IR estimated from fasted capillary blood so this must be interpreted with caution.

5.14.2.4.2 Step-count as a covariate

The analytical approach had to be adapted to compensate for the loss of an experimental condition and implications arising from this. Originally, step-count would not have been included as a covariate as there would have been two distinct groups (+3000 and +6000 steps/day). However, collapsing the two step target conditions into one the analysis had to control for the fact that some participants had completed double the step-count when compared to others over the course of 12 weeks. Including step-count as a covariate was an appropriate action to take, as confirmed by an independent statistician consulted for this study. However, it meant that anyone with missing step-count data was not included in the analysis. The statistical approach did not factor baseline step-count into the analysis. However, due to the exclusion criteria the sample did not include any individuals classed as active (≥10,000 steps/day) or high-active (>12,500). Within the pedometer group, 32% were classed as sedentary (>5,000 steps/day), 44% were low-active (500-7499 steps/day) and 24% were medium-active (7000-9999 steps/day) in accordance with step-count guidelines (Tudor-Locke & Bassett Jr, 2004). In a much larger sample, it would have been of interest to stratify by category and explore whether those with the lowest baseline step-count had greater benefit.

If funding permits, the use of accelerometers for the full duration of future studies is advisable for accurate assessment of daily step-count. However, the benefit of this extends beyond the assessment of compliance. Where a pedometer is limited to reporting step count only, an accelerometer allows for the data to be explored in terms of steps, bouts and intensity of activity. The participants for this study were given a step-count goal, however no restrictions were set regarding how this could have been achieved. Therefore, the daily target could have been obtained through one continuous bout (e.g. 3,000 steps), multiple smaller bouts (e.g. 500-1000 steps; ~10 mins), or accumulated throughout the day. As step-count is the only outcome, there is no indication of the intensity domain that any additional walking was performed in. A physical activity goal (e.g. 10,000 steps/day) per se may not be sufficient to drive health benefits, as there is evidence suggesting the way it is performed impacts on the success. The relative importance of step count, intensity and duration of physical activity when examining outcomes for vascular structure and function where compared following a 12-week pedometer intervention in sedentary older adults (>50years). Step count and moderate-intensity physical activity MPA (1952 to 5924 counts) were measured using Actigraph GT3X. Of all those that completed the study, there was no interaction between FMD% change over time in those that achieved a

daily 10,000 steps or >30 minutes of (MPA) accumulated in non-bouts) per day. However, subgroup analysis of those achieving >30 mins/day were stratified based on those achieving ≥20 mins/day through bouts (≥10 mins) to those that didn't perform bouts. Of participants achieving >30 minutes of accumulated MPA, those that achieved this through ≥20 mins/day in 10-minute bouts demonstrated significant improvement in FMD, whereas no change was observed in those that did not perform MPA in bouts. In this context, reaching the goal itself was not sufficient to reduce age-related endothelial dysfunction, but reaching that goal in bouts (>10 minutes) improved FMD. This has implications for the dosing of PA for specific health goals.

5.15 Conclusions

This research study aimed to examine the impact of two different step count goals, relative to a no-exercise control group, upon indices of cognitive performance, cardiometabolic health and obesity over a 12 week period. Due to attrition, and consequent collapse of the "high dose" (+6000 steps) and "low dose" (+3000 steps) conditions, a dose response could not be examined. All participants were entered as one "pedometer" condition, and post-intervention step count was included as a covariate in the analysis. The study significantly increased step-count post-intervention, and this was associated with better performance on executive function, verbal memory, spatial memory and spatial working memory. No further effects of increasing PA were observed on cognitive outcomes. The pedometer intervention had minimal impact on cardiometabolic health, however the majority of the sample were within the healthy range, thereby leaving limited capacity for improvement. Many of the participants reported difficulty attaining the target of +3,000 steps per day on 5 walk days per week. Although walking is cost effective and safe method to increase exercise, the step targets that are associated with health benefits (10,000 steps) have a high time-commitment which must be maintained on a daily basis. It has been suggested that the desired step-count goal is not achievable through daily activities and this could be supplemented by participation in higher intensity activities (Choi, Pak, & Choi, 2007).

Chapter 6:
General Discussion

Chapter 6 General Discussion

The final chapter summarises the key findings of this thesis in relation to the original thesis aims set out in Chapter 1. The original contribution of this work to the field of exercise and cognitive function in obesity is highlighted, and strengths and limitations of the work carried out are considered. The implications of the thesis findings for future research are discussed. There is currently a paucity of research regarding the effects of exercise (of varying regimes) on cognitive function in overweight/obese middle-aged adults. Consequently, evidence of cognitive tests that are sensitive to detect exercise-associated change are lacking in people of this demographic. Therefore, the work undertaken for this thesis was largely exploratory.

6.1 Overview of Thesis

The area of research examining the impact of exercise on cognitive function in obese adults at mid-life is in its infancy. Of the literature described in chapter 1, only 4 studies in total were conducted in middle-aged, obese adults (Drigny et al., 2015; Galioto et al., 2014; Langenberg et al., 2015;, Monleón et al., 2015). This confirmed the topic to be a novel and largely unexplored area of research, however, it may also be considered an obstacle when designing the studies as there was very limited relevant material to draw from. The studies presented in this thesis comprised of one cross-sectional examination of cognitive function data in relation to PA and health parameters, and two pre-post exercise intervention studies.

The literature described in section 1.2.4 indicates a paucity of research examining the relationship between physical activity (PA) and cognitive function in middle-aged obese adults. Furthermore, only 2 studies conducted in obese adults used objective measures of PA (section 1.2.5). Both studies examined the relationship between objectively measured PA and cognition in pre-bariatric (morbidly obese) adults (Galioto et al., 2014; Langenberg et al., 2015), and provided rationale for study 1. The data for study 1 was gathered from baseline data for Study 2 and Study 3 and helped to identify cognitive tests that were sensitive (or not sensitive) to habitual PA.

The primary aim of the thesis was to examine whether improvement in cognitive function could occur following an exercise regimen. Chapter 1 (section 1.2.2) indicated that increased physical activity and/or cardiorespiratory fitness (CRF) translates to improved cognitive function in non-obese adults, yet this has largely

been unexplored in overweight/obese adults. However, it is not known what aspects of exercise (volume or intensity) yield optimal improvements, or the physiological adaptations that are required to translate to cognitive change. Studies 2 and 3 employed two differing protocols of exercise/PA.

The original thesis aims were:

i. *To explore the relationship between objectively measured physical activity and cognitive function in a sample of overweight/obese and middle-aged adults.*

ii. *To compare the impact of medium-term heavy-intensity exercise regimes (interval and continuous) on indices of cognitive function and cardiovascular health. Change over time was examined relative to baseline cognitive performance, IQ and age*

iii. *To examine the impact of a medium-term light-intensity "free-living" pedometer programme on indices of cognitive function and cardiometabolic health. Change over time was examined relative to baseline cognitive performance, IQ and age.*

6.2 Key findings

Study 1 (n=63) aimed to examine the relationship between objectively measured physical activity with multiple cognitive test outcomes in a sample of low-active, overweight/obese, middle-aged adults. The relationship between habitual PA and cognitive function has not been examined in obese individuals using objective measures of PA. Therefore, the work undertaken for this thesis was largely exploratory. The cross-sectional exploration of the relationship between objectively measured PA and cognitive function (over multiple domains) indicated that the greatest predictors of cognitive function were age and IQ, with minimal contribution from the physical activity and body composition composites. The PCs made a limited contribution to variance in cognitive function. Attention, as measured by performance on the Bakan task, was negatively associated with adiposity and sedentary behaviour composites (PC2 and PC3 respectively). However, spatial memory (VSLT) and spatial working memory (Corsi) indicated a favourable impact on performance with increasing sedentary behaviour (PC3). The sedentary/low-active profile of the sample

indicated that the vast majority of participants were not meeting the guidelines (150 accumulated minutes of MPA per week). Additionally, only a very small minority were undertaking any VPA, which consequently compromised the quality of the principal component containing this theoretically relevant variable.

Study 2 (n=28) aimed to compare the impact of 12-weeks high-intensity exercise regimes (interval and continuous) on indices of cardiovascular fitness and cognitive function in middle-aged, overweight/obese females relative to a no-exercise control group. The impact of increasing participation in high-intensity exercise over a 12-week period showed a limited number of favourable training effects on executive function and spatial memory. This occurred alongside minimal improvements on cardiorespiratory fitness. Manipulation of the INT regime presents us with great opportunity to selectively target systemic health factors associated with cognitive decline, and optimise cerebrovascular adaptation.

Study 3 (n=33) aimed to examine the impact of increasing habitual activity through pedometer “step-count” targets over 12-weeks on indices of cardiometabolic health and cognitive function. Findings indicate that post-intervention step-count was associated with executive function, spatial working memory, spatial memory and verbal memory.

Collectively, these studies have shown that IQ, age and baseline cognitive ability have a far greater impact on cognitive function, and this is over and above any contribution from exercise or health parameters. This is not an unexpected finding, but it does have implications for the dialogue surrounding obesity research (6.4.1). There was no evidence of cognitive impairment or poor performance in the sample of low-active and overweight/obese adults studied for this thesis. Conversely, inspection of the raw data indicated ceiling effects for many participants at baseline, and this was maintained at subsequent test visits (perhaps limiting the ability to assess change).

The objective measurement of physical activity confirmed that participants studied for this thesis were sedentary to low-active. According to the literature described in Chapter 1, the combination of a sedentary/low active lifestyle with indices of obesity mean this sample are at elevated risk for obesity-associated comorbidities (hypertension, CVD, diabetes) and decrements in cognitive performance relative to age-matched healthy-weight counterparts. However, the sample studied for this thesis indicated that most fell within the healthy ranges for indices of cardiometabolic

health. These findings are therefore not generalisable to individuals of this demographic with presence of obesity-driven comorbidity.

6.2.1 Cognitive domains (and tests) sensitive to exercise-associated change

The spatial working memory (Corsi) task was shown to be most sensitive across the three studies to the effects of exercise, and interaction with covariates such as age and IQ. Accuracy on this task was favourably impacted by post-intervention step count, and also following the INT regime relative to the other conditions. This task was shown to be sensitive to variation in IQ and also age (within adults 30-60 years old). Tests of executive function were only administered in studies 2 and 3, but in both cases detected exercise-associated change. The Trail Making Test detected differences according to post-intervention step count, whereas the ToH task showed training effects following the INT regime relative to the other conditions. The VVLT showed limited sensitivity within studies 2 and 3, observed through trends, for favourable effect of step-count on delayed recall and training effects following the CON regime on immediate learning (total acquisition) relative to the other conditions. The VSLT showed limited sensitivity within studies 2 and 3, observed through trends, for favourable impact of post-intervention step-count and training effects following the INT regimes. Attention (Bakan task) seemed to be highly sensitive to age within the two intervention studies, however, it did not seem to be impacted by the exercise regimes themselves. It was observed that the tests with more challenging aspects were able to detect differences, and it is likely that any cognitive changes that may be evident at mid-life would be subtle in a sample that were not experiencing obesity-associated comorbidity. If baseline cognitive performance is high at baseline, there is little scope for improvement driven by exercise over a 12-week time frame. All tests administered for this thesis were shown to be sensitive to age and IQ in the expected direction.

6.2.1.1 Influence of age and IQ

The resounding finding was that age and IQ had the greatest association with cognitive function outcomes across the 3 studies. However, an interesting effect is observed between Studies 2 and 3. When considering the same cognitive tests that were used for both studies 2 and 3, age (and interactions with condition) was largely unrelated to cognitive outcomes in Study 2 (INT/CON), yet was implicated in a larger number of outcomes in Study 3. In Study 2, increasing age showed a negative

association with performance on one outcome on Corsi task, but only in crossing-trials which are more challenging than non-crossing trials. It is possible that this sample were not demonstrating any detectable age-associated decline, as all participants (except for one age 51 years old) were between the ages of 30 to 50 years. Study 3 had a large cluster of participants between the ages of 50-60 years, and age was associated with performance on Bakan, TMT, and to lesser extent Corsi and VSLT. It is possible that some participants within this study were starting to show age-associated cognitive decline. A similar pattern emerges for IQ between studies 2 and 3, in that it is largely unrelated to cognitive outcomes in Study 2 (INT/CON), yet implicated in a larger number of outcomes in Study 3. This finding is of interest as it may indicate that IQ is starting to play a protective role in the ageing participants of the pedometer group. It is possible, this collectively shows the older members are starting to experience age-related decline.

6.2.1.2 Baseline cognitive performance

Baseline cognitive performance was the greatest predictor of performance on subsequent test visits across Studies 2 and 3. In study 2, it was evident that those with poor baseline cognitive performance had superior performance at subsequent testing following the INT regime on tests of executive function (ToH), spatial working memory (Corsi), and spatial memory (VSLT) in Study 2. However, in Study 3 an effect is observed where those with poor baseline performance show superior performance in the NO-EX condition at subsequent testing for attention (Bakan), spatial working memory (Corsi) and Stroop interference, relative to the pedometer group. The extant literature reveals a multitude of plausible mechanisms through which obesity-driven comorbidities can lead to brain health, and conversely how exercise may favourably impact these. However, if IQ and baseline cognitive function have the greatest impact of cognitive function, might it be argued that education or cognitive stimulation is a more potent stimulus for neurocognitive protection.

6.2.2 Preservation versus improved cognitive function?

From the perspective of the primary outcome of cognitive function, the success of an intervention was evaluated based on whether cognitive function had improved over a 12-week period (Study 2 and Study 3). But the question remains as to whether the appropriate goal in middle-aged obese adults is an improvement in cognitive function or should it be preservation of cognitive function over a longer period of time. A wealth of research provides support for detectable improvement in cognitive function

following exercise in older adults. Yet these samples are experiencing age-associated cognitive decline, with greater capacity to “improve”. It is likely that in middle-aged adults, any changes would be subtle, and therefore difficult to detect.

6.2.3 Physiological adaptation following exercise intervention

Firstly, a limited number of volunteers for study 2 and study 3 presented with obesity-associated comorbidity or compromised cardiometabolic health. A vast number of physiological parameters are associated with cognitive function, as described in section 1.2.6.3, such as inflammation, glucose hormeostasis, blood pressure and lipids. This translates to a reduction in vascular inflammation, endothelial damage and improves vascular compliance. Only 4 participants in Study 3 were insulin resistant, as indicated by HOMA-IR and 6 participants were hypertensive. Of the sample for Study 2, 3 participants presented as being hypertensive. Based on the hypothesis that change in cognitive function would be driven by physiological adaptation to exercise and reduction in systemic risk factors, it is possible that greater effects would be observed in samples with poorer baseline health. However, improved cognitive function has been observed following exercise interventions in healthy adults (section 1.2.2). Such changes have been observed alongside structural brain changes. Exercise regimes may be developed to target optimal adaptation within the brain for the structures that support cognition.

6.2.4 Sedentary time: cognitively stimulating versus passive

Study 1 observed an unusual finding, that prolonged sedentary time was associated with better performance on spatial memory and spatial working memory tasks. One thing to consider when investigating the impact of sedentary behaviour on cognitive function is whether a cognitively stimulating/demanding task is performed during that time or not. The participants were recruited from the area surrounding the University of Leeds, with many volunteers being staff, including professors, lecturers and PhD students. It is possible that performing cognitively stimulating or demanding tasks during time spent sedentary has a protective effect against any cognitive harm potentially caused by high levels of sedentariness.

The context of sedentary time may be very important with relation to cognitive function outcomes. It has been shown that sedentary behaviour in the form of passive TV viewing was associated with poorer executive function outcomes in 2179 healthy adults (Kesse-Guyot et al., 2012). A negative association was observed between TV

watching and Trail Making Test (TMT) performance. Longitudinal studies in middle-aged and sedentary adults (n=5437) indicate that high levels of TV viewing at mid-life were predictive of poorer Mini-Mental State Examination scores at a 5-year follow-up (Wang et al., 2006). Future research should attempt to classify whether sedentary time is spent doing cognitively stimulating or unstimulating tasks.

One question for debate is whether cognitively stimulating training would superior to exercise in preserving cognitive decline alone or in combination with exercise. Evidence suggests that combined exercise with cognitive training may be the optimal method to preserve/enhance cognitive function. Functional and structural changes in the human brain have been observed following either exercise (Hillman et al., 2008) or cognitive training (Lövden et al., 2012; Stine-Morrow, 2011). However, very few studies have combined both interventions to compare the effects of exercise and cognitive training on cognitive function (Hotting & Roder, 2012). The first study to compare a combination of aerobic exercise and cognitive training against the individual interventions or no training (control group) was by Fabre et al. (2002). This study indicated the combination of aerobic endurance training plus cognitive training targeting various cognitive functions (e.g. memory, attention, spatial skills) was superior in improving cognitive function in older adults.

More recently in middle-aged (40-55 years) and sedentary adults, Holzschneider et al. (2012) examined the combined effects of combined a physical exercise and spatial memory training on spatial memory functions both at the behavioural and neural level. Spatial learning skills and functional brain activation (fMRI) were measured during a spatial maze learning task before and after the 6-month interventions. One condition completed aerobic endurance training (‘cycling’) whereas the control condition completed a non-endurance stretching/coordination programme. In the final month (month 5) all participants had six cognitive training sessions; either spatial training (‘spatial training’) or a non-spatial visualperceptual control training (‘perceptual training’). Results indicated that irrespective of the exercise training condition, participants of the spatial learning groups showed the largest improvement in maze task performance relative to the perceptual learning groups. This finding was supported by a positive correlation between the brain activation level associated with the spatial task and the level of cardiovascular fitness (VO2peak values) in participants who had received cardiovascular training and spatial cognitive training. This indicates that exercise alone may not be sufficient to translate to functional changes in brain networks, particularly for spatial learning and that a combination with

cognitive training may be optimal. Furthermore, the cognitive training had more pronounced effects of post-test cognitive performance than the exercise training alone.

A positive effect of cognitive interventions has been demonstrated in various domains, including working memory (Dahlin et al., 2008]), executive functions (Persson & Reuter-Lorenz, 2008]), processing speed (Edwards et al., 2005), and reasoning (Boron et al., 2007]). If the main goal is to improve/preserve cognitive function then it is likely that exercise interventions alone are not sufficient to drive substantial effect and future research should focus on combined exercise and cognitive training. However, it is known that on a neural level that exercise can increase hippocampal volume, increase cerebral blood flow, and improve functional connectivity. These changes are thought to translate to improved cognitive function. Therefore, exploration of the types of exercise that yield optimal structural brain changes to support a cognitive training programme would be highly worthwhile. This type of research is in its infancy, but the findings reported by Drigny et al., 2014, indicate that HIIT may be an exciting avenue to explore with regard to changes within the brain.

6.3 Limitations of methodology

6.3.1 Cognitive test selection

To provide rationale for cognitive test selection for this thesis, information had to be gathered from two areas of research. Tests were chosen that were sensitive to detect differences between obese and non-obese samples or had detected a change in cognitive function following an exercise regimen. As indicated in section 1.1.3 and 1.2.2 of the literature review, there was a wide choice of valid tests and no general consensus or indication whether any specific tests would be the optimal choice. A further complication is that with the inclusion of physiological parameters another layer is added to the rigmarole of cognitive test selection. Particularly as cognitive domains and tests are known to be sensitive to specific health parameters (i.e. verbal memory and insulin sensitivity). There is also conflict between selecting a wide range of tests/domains for exploratory purposes, or focus on one specific domain and a narrow selection of tests.

6.3.2 Serial cognitive testing and order effects

Studies 2 and 3 employed a repeated measures design which raises the possibility that practice effects could explain any improvement in cognitive function over time as participants became more familiar with the tests. To reduce the potential influence of practice effects participants completed a practise version of the cognitive test battery 1-week prior to the baseline cognitive tests, and this practice data was not included in the statistical analysis. Furthermore, counterbalanced versions of the test batteries were administered at pre, mid and post-testing. There was a fixed time-frame of six weeks between each test session so this would have also reduced the influence of practice effects on outcomes between visits. The order of the cognitive testing within each battery remained the same at all testing visits, so it is possible that this may have influenced specific tests. The battery for Study 2 took 44 minutes to complete, and the battery for Study 3 lasted 38 minutes. It is possible that fluctuations in fatigue or motivation may have influenced specific tests, particularly at the start and end of the test battery. There is also the possibility that certain tests may influence performance on the subsequent test. For example, the Bakan task (6-minutes) was widely reported to be fatiguing which may have impacted test performance on the test that immediately followed. However, because a number of the individual tests had a delayed component with a fixed time-frame for completion it was not possible to counterbalance the order of tests within each battery.

6.3.3 Recruitment

Recruitment of participants (or lack of) had a huge impact on data collection during this 4-year thesis. Recruitment methods included campus based posters and leaflets, campus based e-mail distribution lists, poster and leaflet campaigns around all areas of Leeds, talks (Diabetes UK Leeds support group) and newspaper articles in the Yorkshire Evening Post. Despite extensive recruitments methods, interest in the studies was lower than expected. Of those that expressed initial interest, the majority had to be excluded based on medication use for comorbidities and depression, see CONSORT diagrams in sections 4.3.1.2 and 5.5.3. Many participants also fell below the minimum BMI threshold. It might be considered that the exclusion criteria may have impacted on recruitment as a large proportion with obesity do have obesity-associated comorbidities and associated medication. Further research could be more inclusive but stratify data based on comorbidity or medication use.

Another observation was that once the study information had been sent out to interested volunteers, many did not respond again to further contact. Based on the information they had received they had decided not to take part in the study. It would be helpful to know what components of the study were perceived as off-putting to the general public. It must be taken into consideration the impact that a study would have on participants in terms of time commitment, invasiveness of procedures, interest in the topic or benefits to participants. The studies were not able to offer monetary compensation for participation in the studies. In addition, each study was 12-weeks long and testing required participants to attend the University of Leeds campus for lengthy test sessions (90-minutes) on multiple occasions throughout the study duration.

6.3.4 Compliance

As the physical activity component of study 3 was performed in a free-living environment, compliance to the protocol cannot be guaranteed. Participants returned self-report information on their daily pedometer step count total each week. Due to issues with cost of devices, it was not possible to use accelerometers to objectively measure the targets reached throughout the 12-week intervention. The use of objective measures precludes issues of compliance to step count and is highly recommended for these types of studies. Compliance to the training regime was not an issue for Study 2 as the INT and CON sessions were supervised by researchers, and the exercise work-rates were controlled by the equipment. We could confirm that that every participant performed the exercise that was prescribed to them. However, for both studies 2 and 3, it was part of the requirements that participants did not make any changes to their normal dietary patterns, particularly concerning weight loss attempts through calorie restriction. We had no evidence to support whether participants made any dietary changes or complied with instructions to keep the diet unchanged. Food diaries may have provided interesting data on this, however these are still vulnerable to the inaccuracies of self-report data. An unexpected finding was observed in Study 2 (section 4.11.3.3.2), in that for all groups body fat increased over the 12-week intervention. The increase in exercise does not lead to an increase in body fat unless there is a compensatory eating mechanism.

6.3.5 Control group

The control group (n=10) were added retrospectively, and due to recruitment difficulties the same group acted as a comparison condition for both intervention studies. For both Study 2 and 3, raw data indicated improvements in a number of cognitive outcomes for the exercise conditions. However, after controlling for baseline performance, this statistical approach was largely unable to detect differences in post-intervention performance between the experimental conditions and the no-exercise control group. The average scores from the control group demonstrated improved performance from baseline to post-intervention in attention (Bakan) and spatial working memory (Corsi) outcomes. Inspection of the raw data revealed that this effect was driven by 2 individuals who had poor performance at baseline and showed marked improvement at mid-point, which was maintained at post-testing. Due to the low number of cases, the behaviour of these 2 individuals resulted in a group mean that showed an improvement in performance.

6.4 Recommendations

Individuals who are both sedentary and obese are at elevated risk for many chronic CVD outcomes, and accelerated age-related cognitive decline. Although this relationship is not understood, it is suggested that regular exercise may preserve cognitive function through reduction of systemic CVD risk, and also direct effects on brain structure and function. The area of research examining the impact of exercise on cognitive function in obese individuals is in its infancy, and it is therefore unknown what physiological parameters should be targets for intervention. Targets for intervention will be dependent on the baseline cardiovascular or metabolic profile of the individuals undertaking exercise, and this can differ widely within an obese sample.

Additionally, a large body of the research examining the relationship between obesity and cognitive function fails to adequately control for cardiorespiratory fitness, CVD risk and other psychosocial factors which are known to impact on cognitive function. It seems that in obesity research, there is increasing evidence to suggest that these confounding variables have greater predictive power of cognitive function than the presence of adiposity itself. Therefore, failure to control for all the things known to impact on health and cognitive function may contribute to a type of ‘Semmelweis reflex’ in obesity research (Bálint & Bálint, 2009). This is where an established norm

is held in the scientific community in the face of contrary new evidence. It is apparent from the extant literature read as part of this thesis, the concept that obesity may impact on cognitive function independent of other factors is heavily entrenched in the literature and widely accepted. This is despite emerging evidence that once other factors are controlled for (education, subclinical CVD measures, CRF) the relationships between obesity and cognitive function are attenuated. The most appropriate course of action is to control for all known factors that impact on cognitive function, however this is largely unfeasible for a lot of researchers due to cost and time constraints. This would require full medical assessment of cardiovascular health (vascular function, blood pressure, cardiac function), blood samples (lipids, glucose, insulin, inflammatory markers), CRF test and also measurement of psychosocial factors (stress, depression, esteem), education and IQ. The research undertaken for this thesis also could not meet these requirements, such that many theoretically important factors were not measured. As researchers, consideration of the participants must be made regarding the number of time-consuming and potentially invasive procedures involved in a study. This may also have a direct impact on the recruitment of volunteers and attrition rates over a medium-term intervention with repeated test phases.

6.4.1 Obesity stigma

The existence of several obesity paradoxes in health research may have theoretical relevance to cognitive function research. Discussed in Chapter 1are the concepts of “fat but fit” and “healthy obesity” where obesity is not a risk factor for mortality in physically fit individuals, and where a sizeable proportion of obese adults have normal cardiometabolic risk profiles, respectively (Karandish & Shirani, 2015; McAuley & Blair, 2011). It seems that in some individuals, obesity does translate to poorer health and/or cognitive dysfunction, but this is certainly not the case for all. The process of targeting only obese individuals for exercise intervention may be psychologically harmful (Graham & Edwards, 2013). It is known that known that fitness levels are strongly associated with mortality, irrespective of body size (Sui et al., 2007). The process of only targeting obese/overweight individuals for intervention reaffirms obesity stigma and fails to address the core need for improved fitness (health) as opposed to weight. With regard to public health promotion, improved fitness must be encouraged for all. There is a growing body of research drawing attention the fact that targeting obese individuals for exercise interventions may inadvertently be causing more harm than good (Azevedo & Vartanian, 2015; Graham & Edwards, 2013; Pearl,

Dovidio, Puhl, & Brownell, 2015). The focus must be shifted away from weight, and towards exercise for health and enjoyment (Leone & Ward, 2013).

The primary goal of “tackling obesity” has been placed on weight (fat) loss through diets, exercise, medication or surgery, with the emphasis on body size and not health. This reinforces that weight loss is the key component of the success of an intervention, but a large proportion are unable to maintain a lower body weight over time (Karandish & Shirani, 2015). There is growing concern that the focus on weight predisposes some individuals to negative consequences such as repeated cycles of weight loss and regain, eating disorders, reducing self-esteem, and weight stigmatization and discrimination (Bacon & Aphramor, 2011; Mann et al., 2007; Montani, Viecelli, Prévot, & Dulloo, 2006). The Health at Every Size (HAES) paradigm, shifts the focus from weight loss/control to health promotion irrespective of body size (Robison, 2005). It is recommended that in order for health promotion to be truly effective in obesity, body acceptance must be encouraged and size diversity embraced. Intentionally or unintentionally singling out individuals based on weight contributes to stigma, and the interventions may do more harm than good (Azevedo & Vartanian, 2015). There is evidence to suggest that personal experiences of weight stigmatisation and internalised weight bias are associated with reduced exercise motivation and self-efficacy (Pearl, Puhl, & Dovidio, 2014).

6.4.2 Exercise for enjoyment

When comparing the perceived benefits and barriers to exercise between obese and non-obese women it was found obese participants were twice as likely to agree that they only exercise for weight loss (Leone & Ward, 2013). It was posited by the authors that this may indicate that obese women believe the long term benefits of exercise are only attained once weight loss has been achieved. Furthermore, obese women were more likely to report lack of enjoyment as a barrier to exercise. From informal discussion with the participants volunteering for the thesis studies, nearly all reported that their motivation for joining the exercise study was to lose weight. Exercise is certainly beneficial for health, but the optimal type/profile of this is under debate. One size does not fit all. While INT seems beneficial for vascular health, equivocal results are found for metabolism/fat loss/etc between HIIT and MICT. It may be that depending on the health parameter under examination, the optimal “type” of exercise may vary according to health, and the type of adaptation required. This will also differ on the health status of the individual undertaking exercise. This also does not take into account stages of change – it does not matter if HIIT is the perfect exercise

prescription for someone, if they are not able to adopt and adhere to this type of exercise. Promote for enjoyment, and build up efficacy, as exercise should not just be viewed as a mechanism to lose weight.

6.4.3 Implications for scientific community

When considering the ethical issues relating to public health approaches to obesity there have been frequent calls for interventions to target the whole population (not just obese) and shift the focus onto health promotion (Azevedo & Vartanian, 2015). This has implications for the scientific community and obesity research, which typically recruits obese individuals and healthy weight controls as a comparison group. The future of research "in obese" should not target obese individuals but include people of all body sizes, and stratify groups by measured health parameters as opposed to weight. This will become complicated in individuals with more than one comorbidity, however, it is known that aggregated risk factors interact with each other so it is not good practice to fail to control for this.

6.4.4 Translating to real-world application

Research studies go through rigorous exclusion/inclusion criteria prior to study commencement – to prevent people with elevated risk of harm from participating in something that could bring on an event (cardiac, stroke). Also, during exercise testing in a lab people are monitored closely ECG, BP check, life-support trained. The general public hearing about a new HIIT, may not even know if they are of elevated risk (undiagnosed issues) or if they are aware, may not understand the magnitude of the implications of them participating in heavy intensity exercise. The high level of control over exercise parameters in a lab is necessary to isolate the most relevant mechanisms for physiological adaptation. The equipment allows us to examine work-rates and accurately measure the metabolic strain that is induced. Exercise prescription with this level of accuracy is not possible for the general public. If our study results were to be translated to a public health message suggesting intervals at 70% delta VO_{2max} with recovery bouts at 120% LT were beneficial for health/cognition/etc, then no-one would be able to implement this accurately. The general public do not have the opportunity to attend a laboratory for monitored maximal exercise testing by health practitioners, so that the work-rates corresponding to parameters can be calculated. Therefore, it may be more helpful to examine exercise strategies that are easy for the public to understand and adopt. This thesis

used one heavily controlled lab study, and one in a free-living environment. The pedometer step count targets were easy to adopt by the participants.

6.5 Final conclusions

This thesis aimed to explore the relationship between cognitive function and exercise in obese, middle aged adults. The cross-sectional research (study 1) indicated that age and IQ had far greater impact on the cognitive function outcomes relative to the physical activity or body composition principal components. The primary agenda was to explore whether exercise could translate to improvements in cognitive function over a medium-term period of time (3 months). Two intervention studies yielded a low number of exercise-associated post-intervention improvements in cognitive function, predominantly in executive function and working spatial memory tasks. The majority of the sample were metabolically healthy obese adults, and minimal physiological adaptations were observed (CRF, BP) over the 12-week interventions. The rationale for both studies was based on the hypothesis that interventions inducing a greater improvement in health would translate to greater improvements in cognitive function. It is possible that in both cases, the exercise interventions were not sufficient to drive physiological adaptation required that would be required to translate to cognitive function outcomes. Furthermore, high baseline cognitive function and IQ had the greatest association with cognitive test performance. This research would have benefitted greatly from larger sample sizes that were more heterogeneous in terms of intelligence and health.

From the perspective of improving cognitive function, future research should incorporate exercise training with cognitive training. The components of exercise that yield optimal structural and functional brain changes should be explored. In terms of systemic adaptation to exercise in obese samples, the focus should be on improving health parameters (CRF, BP and insulin sensitivity) as opposed to fat loss. In order to promote exercise adoption and adherence, heavy focus should be placed on exercise for enjoyment. Public health messages and the scientific community must make a concerted effort not to alienate overweight/obese individuals by targeting obese individuals as the sole recipient of exercise interventions or health advice. Exercise is beneficial for all, and low cardiorespiratory fitness is a greater predictor of mortality than excess fat (section 1.1.1.1). To aid recruitment for “obesity research” studies should be advertised for individuals of all body sizes, with markers of obesity

and comorbidities used to either stratify samples or included as covariates in statistical analyses.

6.6 References

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6.7 Appendices

Appendix 6.1 Initial Contact Questionnaire

Initial Contact Questionnaire

Name ……..... Date ___ / ___ / ___

Contact telephone no: ……..……..…….....

Email .....

WHAT IS YOUR DATE OF BIRTH? ____ / ____ /____ Age ……..

- WHAT IS YOUR APPROXIMATE :
  - Height .....
  - Weight …….
- IS ENGLISH YOUR FIRST LANGUAGE?
  - Yes ☐ Details: ……..
  - No ☐
- DO YOU SMOKE?
  - Yes ☐ Given up ☐
  - No ☐

  Details:……
- DO YOU EXERCISE?
  - Yes ☐ Type/Regularity (must be ≤ 2) .
  - No ☐

  Details:……
- ESTIMATED HOURS A DAY SPENT WALKING? (e.g to and from work)

  ……
- ARE YOU CURRENTLY SUFFERING FROM ANY ILLNESS OR CHRONIC CONDITION?
  - Yes ☐ Type / How often ……...
  - No ☐

IF YES, DETAILS:……..……....

- ARE YOU CURRENTLY TAKING ANY MEDICATION
    - Yes ☐ Type / How often ……..……..
    - No ☐

IF YES DETAILS:……...……...…….....….

- HAVE YOU BEEN DIAGNOSED WITH DEPRESSION OR TAKEN ANTIDEPRESSANTS?
    - Yes ☐ Details ……....…...
    - No ☐

- HAVE YOU BEEN DIAGNOSED WITH TYPE 1 OR TYPE 2 DIABETES?
    - Yes ☐ Details .....……....…...
    - No ☐

- HAVE YOU BEEN DIAGNOSED WITH ISCHAEMIC HEART DISEASE (ISCHAEMIA)?
    - Yes ☐ Details ……....…...
    - No ☐

- HAVE YOU BEEN DIAGNOSED WITH ANGINA?
    - Yes ☐ Details ……..…...
    - No ☐

- HAVE YOU EXPERIENCED UNCONTROLLED CARDIAC DYSRHYTHMIAS?
    - Yes ☐ Details ……..
    - No ☐

- DO YOU HAVE A CARDIAC PACEMAKER FITTED?
    - Yes ☐ Details ……..
    - No ☐

- HAVE YOU BEEN DIAGNOSED WITH UNCONTROLLED HYPERTENSION?
    - Yes ☐ Details ……..
    - No ☐

- HAVE YOU BEEN DIAGNOSED WITH A NEUROLOGICAL DISORDER?
    - Yes ☐ Details ……..
    - No ☐

- HAVE YOU SUFFERED A STROKE?
  - Yes ☐ Details ……..
  - No ☐

- HAVE YOU SUFFERED FROM A MUSCULOSKELETAL INJURY OR IMPAIRMENT IN THE LAST 6 MONTHS?
  - Yes ☐ Details ……..
  - No ☐

- HAVE YOU UNDERGONE ANY SURGERY IN THE LAST 6 MONTHS?
  - Yes ☐ Details ……..
  - No ☐

- HAVE YOU UNDERGONE ANY BARIATRIC SURGERY IN THE LAST 5 YEARS?
  - Yes ☐ Details ……..
  - No ☐

- DO YOU HAVE ANY SURGICAL PROCEDURES PLANNED FOR THE NEXT 6 MONTHS?
  - Yes ☐ Details ……..
  - No ☐

- HAVE YOU HAD OR ARE YOU EXPERIENCING ANY MENOPAUSAL SYMPTOMS (e.g hot flushes or night sweats)?
  - Yes ☐ Details ……..
  - No ☐

- ARE YOU TAKING ANY HORMONAL CONTRACEPTION?
  - Yes ☐ Name ……..
  - No ☐ Details ……...

Invited for Visit 1 Yes / No Date ____ / ____ /____ Time …….

Appendix 6.2 AHA/ACSM Health/Fitness Facility Preparticipation Screening Questionnaire

AHA/ACSM Health/Fitness Facility Preparticipation Screening Questionnaire

Assess your health needs by marking all *true* statements.

History

You have had:

___ A heart attack
___ Heart surgery
___ Cardiac catheterization
___ Coronary angioplasty (PTCA)
___ Pacemaker/implantable cardiac defibrillator/rhythm disturbance
___ Heart valve disease
___ Heart failure
___ Heart transplantation
___ Congenital heart disease

Symptoms

___ You experience chest discomfort with exertion.
___ You experience unreasonable breathlessness.
___ You experience dizziness, fainting, blackouts.
___ You take heart medications.

*If you marked any of the statements in this section, consult your physician or other appropriate healthcare provider before engaging in exercise. You may need to use a facility with a **medically qualified staff**.*

Other health issues

___ You have diabetes
___ You have or asthma other lung disease.
___ You have burning or cramping in your lower legs when walking short distances.
___ You have musculoskeletal problems that limit your physical activity.
___ You have concerns about the safety of exercise.
___ You take prescription medication(s).
___ You are pregnant.

Cardiovascular risk factors

___ You are a man older than 45 years.
___ You are a woman older than 55 years, you have had a hysterectomy, or you are postmenopausal.
___ You smoke, or quite within the previous 6 mo.
___ Your BP is greater than 140/90.
___ You don't know your BP.
___ You take BP medication.
___ Your blood cholesterol level is >200 mg/dL.
___ You don't know your cholesterol level.
___ You have a close blood relative who had a heart attack before age 55 (father or brother) or age 65 (mother or sister).
___ You are physically inactive (i.e., you get less than 30 min. of physical activity on at least 3 days per week).
___ You are more than 20 pounds overweight.

*If you marked two or more of the statements in this section, you should consult your physician or other appropriate healthcare provider before engaging in exercise. You might benefit by using a facility with a **professionally qualified exercise staff** to guide your exercise program.*

___ None of the above is true.

You should be able to exercise safely without consulting your physician or other healthcare provider in a self-guided program or almost any facility that meets your exercise program needs.

Balady et al. (1998). AHA/ACSM Joint Statement: Recommendations for Cardiovascular Screening, Staffing, and Emergency Policies at Health/Fitness Facilities. *Medicine & Science in Sports & Exercise, 30*(6). (Also in: *ACSM's Guidelines for Exercise Testing and Prescription*, 7th Edition, 2005. Lippincott Williams and Wilkins http://www.lww.com)

www.acsm-msse.org/pt/pt-core/template-journal/msse/media/0698c.htm

Appendix 6.3 Participant Information Sheet: Study 2

UNIVERSITY OF LEEDS

The Impact of differing exercise regimes upon cardiac function and mental performance in female participants with a body mass index (BMI) of at least 30

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

The purpose of the study is to examine the effects of (i) everyday physical activity and (ii) different types of exercise regimes on heart and blood vessel function and mental performance (e.g. memory, reaction time, and problem solving skills) in women with a body mass index equal to or greater than 30. If exercise regimes that might be easier to achieve because they are conducted in an intermittent manner (short bursts) can improve heart and blood vessel health, plus positively change weight and brain function, then these regimes can be utilised more widely.

Some results from the study will be used towards an educational qualification by a member of the research team.

Why have I been chosen?

You are invited to participate in the study because you are a woman aged between 35-50 years, reporting good health and a Body Mass Index (BMI) of at least 30kg/m^2. BMI is a number calculated from your weight and height that provides a reliable indicator of body fatness for most people. It is calculated by dividing your weight in kilograms by the square of your height in metres.

For example, if you weigh 81 Kg and are 1.64m tall, BMI would be calculated as follows: $BMI = \frac{81\ kg}{(1.64m\ \text{X}\ 1.64m)}$

We are hoping to recruit approximately 100 female participants from the community. You have either responded to an advertisement, been recruited by word of mouth, or you have previously volunteered to take part in a research study at the University and indicated that you were happy to be contacted about other future studies.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect your legal rights or your selection in any way. If you do decide to withdraw we will ask you if we can include all data collected from you up until this point.

What will happen to me if I take part?

Initially, you will be asked to attend three “experimental” sessions to complete the following tests on separate days.

At the first session we will outline the study and all procedures in detail with you. You will complete a Recruitment Information Questionnaire (RIQ) to confirm all the inclusion/ exclusion criteria and ensure you are suitable for this study. You will complete a Physical Activity Readiness Questionnaire (PAR-Q) which we will review and determine whether you are fit to perform the exercise component of this study. You will also complete the National Adult Reading Test (NART) which is a method used in clinical settings to assess intelligence levels

Following simple measures of body weight and height, we will measure your body fat percentage using a technique called bioimpedance which requires you to stand on a machine, dressed but in your bare feet and to hold two hand-grips. This machine measures the amount of fat and muscle you have in your body by passing a small electric current through your body and measuring the resistance. This is completely safe, provided that you do not have a cardiac pacemaker fitted, and you will not be able to feel anything. The bioimpedance machine is very similar to those which you might find in a commercial gym.

You will be asked to complete a cycling test on a stationary bicycle under the supervision of the investigator and a medic. This test involves cycling at progressively higher intensities you can no longer continue while we monitor your heart rate and breathing using ECG and a gas collection system. An ECG is an interpretation of the electrical activity of the heart over a period of time. It is a non-invasive procedure that captures the signals externally through skin electrodes

The gas collection system simply measures the air you breathe in and out to see how much oxygen your body uses. The test takes between 6 and 12 minutes and is a test often undertaken by patients who have recently had heart attacks or are about to have surgery. This test will also be used as a screening tool for ECG abnormalities that may be evident before and during exercise. If any unusual findings are noted you will not be asked to complete the test or the exercise will be stopped. You will be given information to take to your GP at this point. You will also be asked to practise completing the cognitive tests (tests of mental performance) so that you know what to expect on the actual cognitive test days.

The second laboratory visit will involve several measures of the health of arteries.

The speed of the pulse as it travels along the blood vessels will be measured using a device called the SphygmoCor. This device takes non-invasive measures of blood pressure. This involves placing a pen-like device over the blood vessels in the neck, wrist, arm and foot. We will also look at your heart using an ultrasound machine. This is the same type of machine that looks at babies in the womb and is very safe. We will ask you to wear a t-shirt that has been cut-off about mid-torso so that you can take off your bra but be completely covered. A medical examiner (sonographer) will place some gel on your breast bone and just under your left breast. He will then place a probe onto the skin at these sites to look at the health of your heart. A female researcher will be present and you will be provided with a customised t-shirt so that the breast will be covered. For the blood vessel function you will be lying down on your back and we will inflate a blood pressure cuff around your lower arm for a period of 5 minutes. This is a safe procedure but will feel uncomfortable towards the end of the 5 minutes. This discomfort will disappear when the cuff is released. We will hold a probe against the crook of your arm during this test to assess function using ultrasound. You will then rest for 10-15 minutes. After which, you will be given a dose of glyceryl trinitrate (GTN). One of the researchers will spray a small amount of this substance under your tongue. This allows your blood vessels to relax. During this time the same artery in your arm will be imaged using ultrasound.

In the third laboratory visit you will complete short battery of cognitive tests, which will last approximately 44 minutes in total. This battery will consist of computerised tests of both verbal and spatial memory plus tests of vigilance and attention (which you will have already practiced at the screening visit).

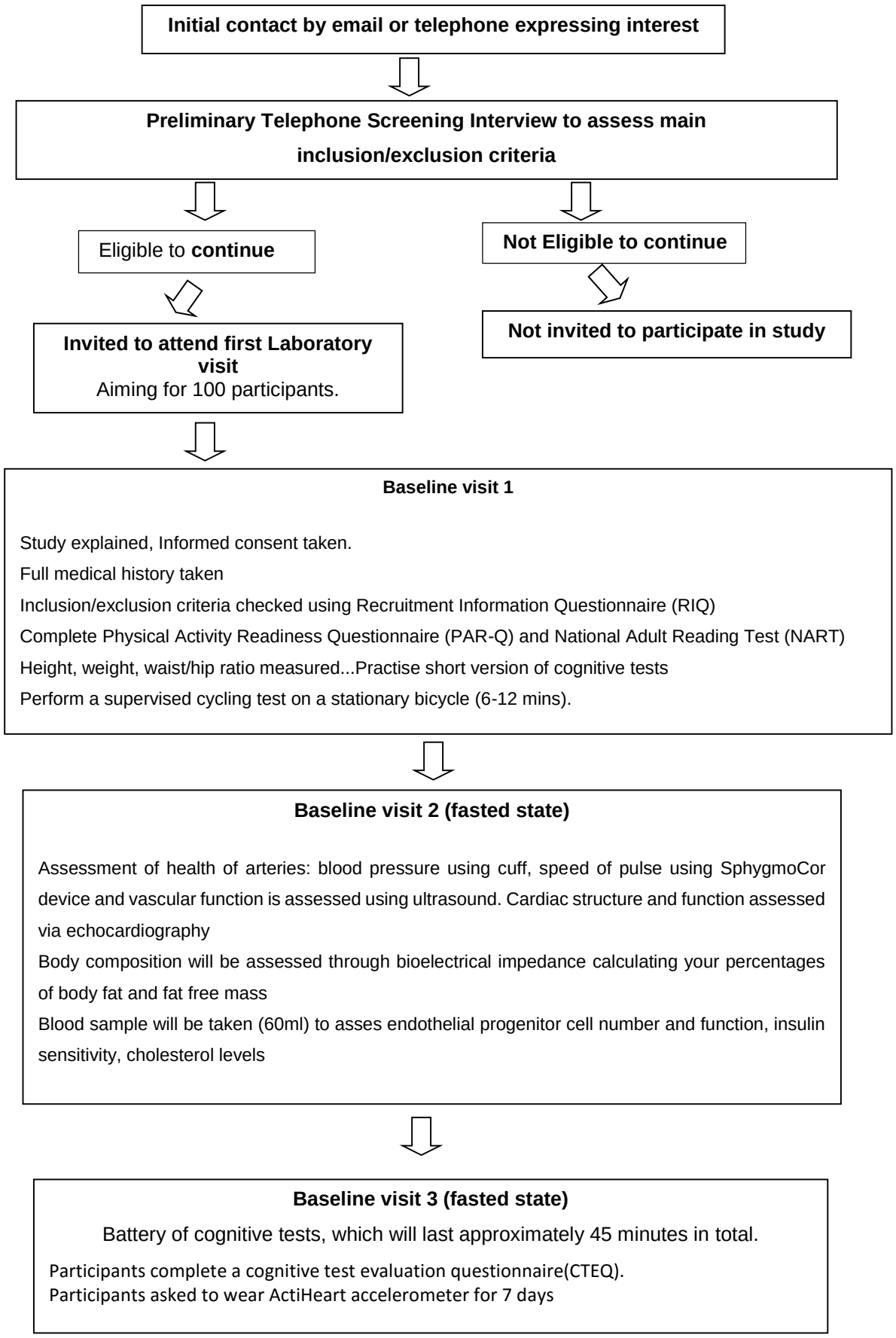
After completing the cognitive tests you will be asked to complete a short questionnaire on your experience of completing the tests (e.g. how well do you think you performed in these tests?). Finally a blood sample will be taken by the medic or a phlebotomist (60ml which is about 4 tablespoons). This blood sample will be used to assess your vascular health by calculating the number and function of a special type of blood cells that are related to your cardiovascular health.

We will then give you an ActiHeart accelerometer to wear for a period of one week in order to assess movement counts and sedentary behaviour. After these seven days using the accelerometer you will be invited back to the laboratory to discuss participation in the exercise training component of the study.

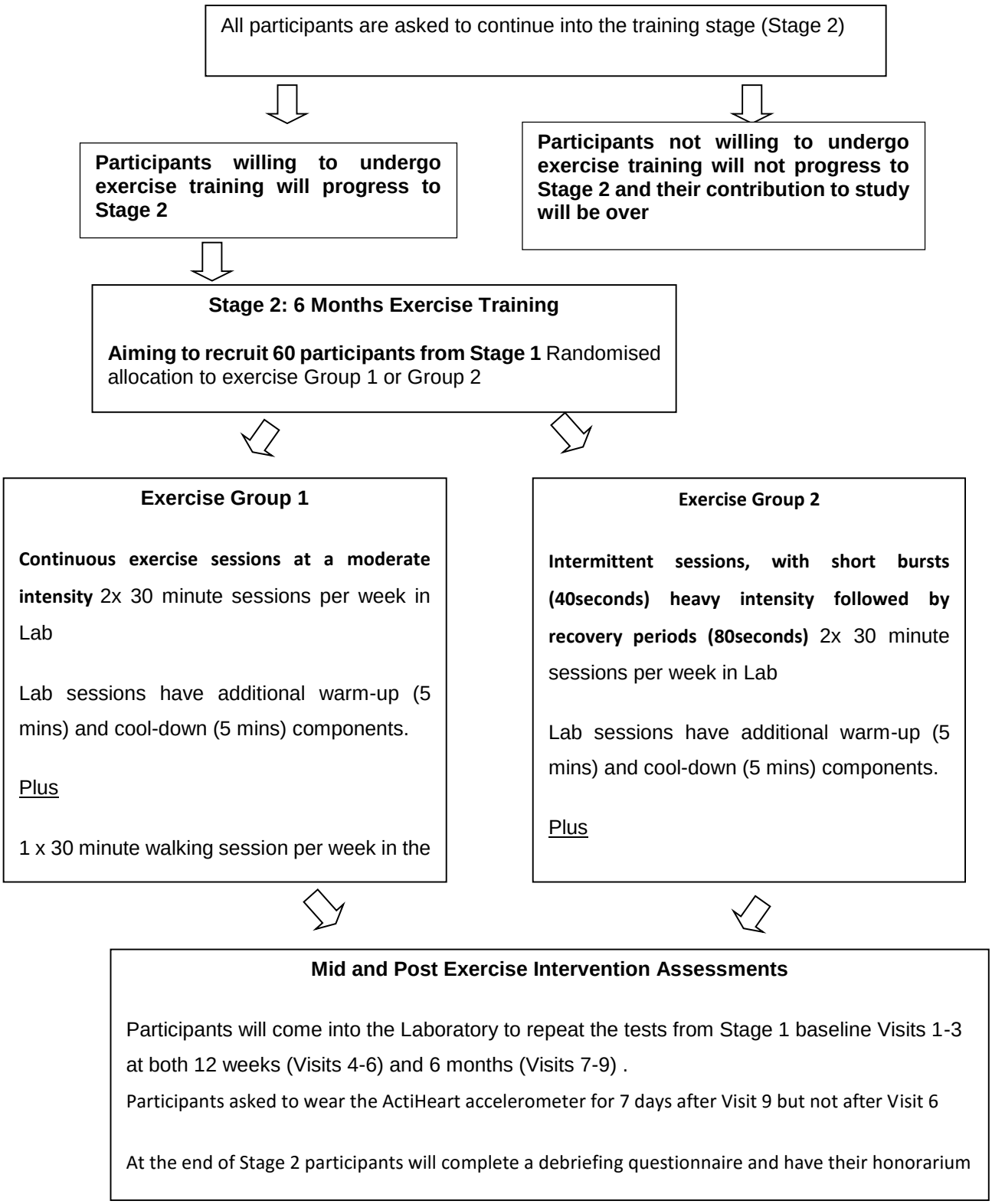
Following discussion of the exercise training intervention, we will then ask you to attend two exercise sessions per week at the University for six months. There will be different times to choose from. These sessions will be 30-40 minutes long and involve cycling on a stationary cycle. You will have a personal trainer for this session and we will build up to the 30 minutes. You will either be cycling continuously at a low exercise load or in short bursts of 40 seconds, followed by 80 seconds rest. Water will be available and there are private shower facilities next to the laboratory. We will ask you to complete one 20 minute brisk walk per week at home. In your first and midpoint training session a small drop of blood will be taken from your finger every 3-5minutes to evaluate a blood marker that allows us to assess how hard you are exercising at. We are also asking for volunteers to have 60ml of their blood taken before and after the first and last training session but you do not have to do this part if you don't want to.

At the end of the six months the measures we took during the first three visits to the laboratory will be repeated.

The following diagram explains Stage 1 of the study:



The following diagram explains Stage 2 of the study:



What do I have to do?

If you decide to take part we will ask you to continue your lifestyle as normal. The only restrictions that we would wish you to follow would be to refrain from exercise, caffeine and alcohol for 12 hours prior to each laboratory visit, and not to eat in the two hours before visiting the laboratory. As well, we ask that you not participate in other studies that involve blood collection at the same time as you are undertaking this study and that you do not donate blood during this period. If you have to attend hospital for any reason during the study you would need to inform Dr Karen Birch or Dr Ali Khalil.

What are the possible disadvantages and risks of taking part?

There is almost always a small risk to undertaking any exercise task. More so if you have not been physically active for a significant period of time. There is a very small risk of muscle injury during the performance tests. You will have proper warm up and cool down activities that will minimise any potential risks to your well-being. Side effects such as muscle soreness are a normal response to undertaking exercise. This should be very minimal because of the warm up and cool down that you will undertake. Very rarely you might feel faint after the exercise sessions. We will monitor you closely after the exercise and make sure you cool down correctly. Fainting usually happens when people just stop exercising suddenly. We do not let this happen in our laboratory. In healthy adults, having a cardiovascular event (e.g. heart attack) is very rare. To minimise this risk you will go through a pre-screening process before any exercise is performed. You may experience a headache or dizziness following the GTN dose, although many people do not have any side effects. We will measure your blood pressure after the assessment and make sure you feel well before being allowed to leave the laboratory.

What are the possible benefits of taking part?

You may feel better both physically and mentally following this exercise training study. You may lose some weight and you may find that you feel fitter and more able to cope physically with daily life. There may be some direct benefits to the health of your heart and lungs. You participation will hopefully be helping the body of research knowledge in this area, which may help people in the future. Finally, some of the testing procedures may reveal aspects of your cardiovascular fitness and health that you may find interesting and useful.

What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, you may complain to the University Secretary. If you wish to make a complaint then please ask a member of the research team how to proceed.

Will my taking part in the study be kept confidential?

Yes, any information which is collected about you during the course of the research will be kept strictly confidential. Once you decide to take part you will be given a subject number and this number will be used on all of the paperwork associated with the research. In this way no-one will be able to identify who the results belong to, and the master copy of names and subject numbers will be kept separately from the result sheets, in a locked cabinet by Dr Karen Birch and Dr Ali Khalil. Your name and address will not be associated with any data that is used in scientific reports or publications.

What will happen to the results of the research study?

When the study is completed the results will be analysed and used in the write-up of academic research publications. Remember that your own results are confidential and that your name will not be associated with any information published from this study. All of the data will be kept for 5 years and then destroyed.

Who is organising and funding the research?

This research is being organised by Dr Karen Birch of the Centre for Sport and Exercise Sciences and Professor Louise Dye of The Institute of Psychological Sciences. The funding for this research has been made available from the University of Leeds

Will I receive anything for taking part?

Upon completion of the study, a small payment to cover some of the travel costs will be paid to each participant to compensate you for the time that you have invested in

the study. If you decide to withdraw before completing the study you will be compensated in accordance with the number of visits that you have completed (at the rate of £10 per visit).

Contact for further information.

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Appendix 6.4 Consent form: Study 2

UNIVERSITY OF LEEDS

INFORMED CONSENT FORM

The Impact of differing exercise regimes upon cardiac function and mental performance in female participants with a body mass index (BMI) of at least 30

Plea
Init

1. I confirm that I have read and understood the Participant Information Sheet dated 16/04/2012 (version 4) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.

3. I have been informed that Visit 3 of the baseline visits and the post-exercise training laboratory visit will involve a 60 ml blood sample being taken

4. I understand that data collected during the study, may be looked at by individuals from the University research team, collaborators on the research project and the University of Leeds for the purposes of research governance. All data will be anonymised with the exception of the recruitment questionnaires containing personal data. I give permission for these individuals to have access to my data.

5. I agree to take part in the above study…….....

Participant's name…… Date ____ / ____ /_____

Signature …….....

Researcher's name……Date ____ / ____ /_____

Signature …….....

Appendix 6.5 Participant Information Sheet: Study 3

UNIVERSITY OF LEEDS

Impact of differing walking dose upon cognitive function in people with a body mass index (BMI) of at least 25.

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

The purpose of this study is to investigate the impact of two different doses of physical activity (achieved through daily number of steps) upon indices of body size, blood pressure, mental performance (e.g. memory, reaction time, and problem solving skills) and insulin sensitivity in sedentary people with a body mass index equal to or greater than 25.
Some results from the study will be used towards an educational qualification by a member of the research team. This study is supervised by Dr Clare Lawton and Dr Karen Birch (see page 7).

Why have I been chosen?

You are invited to participate in the study because you are:
1) Aged between 30-60 years
2) Reporting good health OR diagnosis of Type 2 Diabetes Mellitus (including use of diabetic medication)
3) Reporting a sedentary or low-active lifestyle
4) Have a Body Mass Index (BMI) of at least 25kg/m^2. BMI is a number calculated from your weight and height that provides a reliable indicator of body fatness for most people. It is calculated by dividing your weight in kilograms by the square of your height in metres.

For example, if you weigh 81 Kg and are 1.64m tall, BMI would be calculated as follows: $BMI = \frac{81\ kg}{(1.64m\ \mathrm{X}\ 1.64m)}$ → *BMI = 30.1*

We are hoping to recruit approximately 108 participants from the community to participate in this 12-week physical activity study. You have either responded to an advertisement, been recruited by word of mouth, or you have previously volunteered to take part in a research study at the University and indicated that you were happy to be contacted about other future studies.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect your legal rights or

your selection in any way. If you do decide to withdraw we will ask you if we can include all data collected from you up until this point.

What will happen to me if I take part?

There will be four visits to the lab in total. Initially, you will be asked to attend two "experimental" sessions to complete the following tests on separate days before starting the 12-week walking component of the study.

Visit 1: 60-90 mins

At the first session we will outline the study and all procedures in detail with you. You will complete a Recruitment Information Questionnaire (RIQ) to check your medical history, confirm all the inclusion/exclusion criteria and ensure you are suitable for this study. You will complete a Physical Activity Readiness Questionnaire (PAR-Q) which we will review and determine whether you are fit to perform the exercise component of this study. You will complete the Wechsler adult intelligence scale (WAIS-III) which is a method used in clinical settings to assess intelligence levels. You will also complete the positive and negative affect scale (PANAS-X) to assess mood, and the Perceived Stress Scale (PSS) to assess current levels of perceived stress. Height and weight will also be taken to confirm BMI.

We will then give you an ActiHeart accelerometer to wear for a period of one week in order to assess your physical activity level. This is a small, light device worn around the hip on a belt provided during your waking hours, and should not cause you any inconvenience. After seven days using the accelerometer you will be invited back to the laboratory to complete the official cognitive test.

Visit 2: 60 mins

You will also be asked to practise completing the cognitive tests (tests of mental performance) so that you know what to expect on the actual cognitive test days.

Visit 3: 60-90 mins (1 week after completing visit 2)

The third laboratory visit is a fasted visit which we will schedule for a morning appointment. This means after eating your evening meal the night before you do not have any breakfast or drink anything other than water before you attend this visit.

We will first of all take simple measures of body weight and height, waist circumference and hip circumference. We will measure your body fat percentage using a technique called bioimpedance which requires you to stand on a machine, dressed but in your bare feet and to hold two hand-grips. This machine measures the amount of fat and muscle you have in your body by passing a small electric current through your body and measuring the resistance. This is completely safe, provided that you do not have a cardiac pacemaker fitted, and you will not be able to feel anything. The bioimpedance machine is very similar to those which you might find in a commercial gym. Resting blood pressure will be taken using a standard automated cuff on your left arm. Three measurements will be taken with a minutes rest between each measurement.

We will also measure your blood glucose and insulin levels using a capillary diabetic kit, you will be shown a step-by-step guide of this procedure before you decide to participate in this research.
You will then complete the battery of cognitive tests, which will last approximately 38 minutes in total. This battery will consist of computerised tests of both verbal and spatial memory plus tests of vigilance and attention (which you will have already practiced at the screening visit).

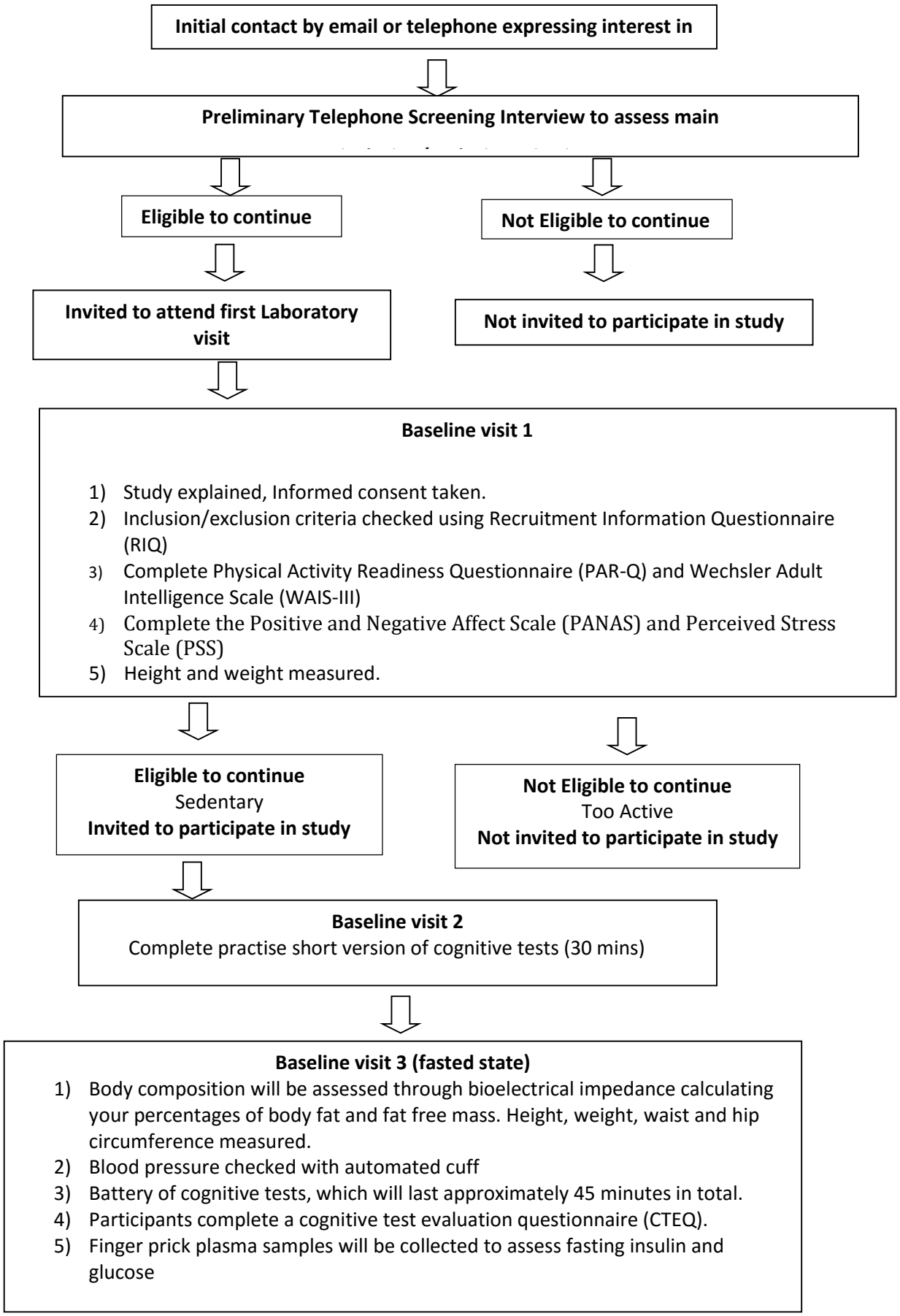
After completing the cognitive tests you will be asked to complete a short questionnaire on your experience of completing the tests (e.g. how well do you think you performed in these tests?).

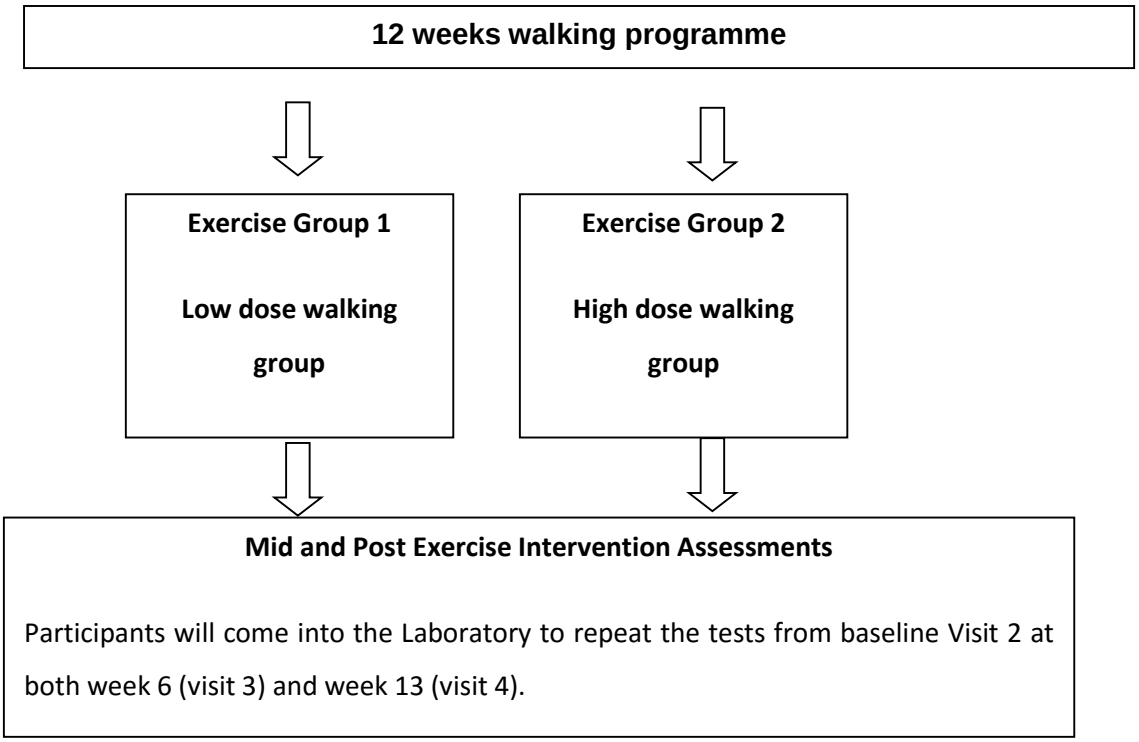
Walking programme

Following discussion of the physical activity intervention, we will then ask you to reach a target number of steps per day on 5 days per week for the duration of the study. This target number will be selected for you, and depending on which group you are randomly assigned to will either be a high or a low dose. You will be given a pedometer to track your daily number of steps and a weekly log sheet. We ask you to write your daily number of steps in the log sheet every day and we will arrange to collect this from you at the end of each week. If you would prefer we can send this to you by e-mail and you can fill this out and e-mail it back to us. We would also like permission to phone you once a week at a time convenient for you. This call is to check how you are getting on, as it is very important that you are achieving your prescribed number of steps on your 5 walk days each week. If you are having problems reaching your targets, or experiencing any health problems then it is important you talk to us about this so we may help you. In this call we can also answer any questions you may have and hopefully boost your motivation each week!

The tests from visit 3 will be repeated half-way through the study in week 6 (visit 4) and at the end of week 12 (visit 5). This only requires one visit at mid and one visit at post study, each lasting 60-90 minutes. You will also be asked to wear the accelerometer the week after completing the study, week 13, to assess movement counts.

The following diagram explains Stage 1 of the study:





What do I have to do?

You will be asked to attend the laboratory for five experimental sessions to be assessed for body composition, blood pressure, mental performance and insulin resistance. You will then be provided with a pedometer and asked to reach a target number of daily steps on 5 days per week, for 12 week duration. The tests you completed before starting the study will be repeated at week 6 and after you have completed the study. We ask that you do not change your diet in any way. The only restrictions that we would wish you to follow would be to refrain from exercise, caffeine and alcohol for 12 hours prior to each laboratory visit, and not to eat in the two hours before visiting the laboratory. If you have to attend hospital for any reason during the study you would need to inform one of the investigators (contact details on page 7).

What are the possible disadvantages and risks of taking part?

The finger-prick blood sample collection is a low-risk procedure, but some may find this slightly painful. Amy Weeks has been trained in the finger prick technique, has first aid training and will be following a standardised procedure to minimise discomfort and any risk associated with this procedure. There is almost always a small risk to undertaking any exercise task. More so if you have not been physically active for a significant period of time. Very rarely you might feel faint after walking sessions if you attempt too much in one go. We will start you off with a manageable target and phone weekly to see how you are getting on. There is a chance in T2 diabetic patients of developing foot ulcers if care and attention in not paid to the feet. We will advise you on appropriate footwear and to look out for any symptoms of lost feeling in the feet. We also advise you to pay attention to any blisters, bruises or cuts on your feet and if there is any cause for concern to contact a doctor or podiatrist immediately and discontinue the walking study. Finally, the blood pressure measures may show that you have a high blood pressure, which you may have not previously known about. In this case we will advise you to see your doctor to have this checked.

What are the possible benefits of taking part?

You may feel better both physically and mentally following this walking study. You may lose some weight and you may find that you feel fitter and more able to cope physically with daily life. There may be some direct health benefits such as improved blood pressure or insulin sensitivity. You participation will hopefully be helping the body of research knowledge in this area, which may help people in the future. Finally, some of the testing procedures may reveal aspects of your health that you may find interesting and useful.

What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, you should contact Dr Clare Lawton or Dr Karen Birch) who will investigate your complaint. If you remain unhappy and wish to make a formal complaint then this can be done through the university complains procedure.

Will my taking part in the study be kept confidential?

Yes, any information which is collected about you during the course of the research will be kept strictly confidential. Once you decide to take part you will be given a subject number and this number will be used on all of the paperwork associated with the research. In this way no-one will be able to identify who the results belong to, and the master copy of names and subject numbers will be kept separately from the result sheets, in a locked cabinet by Dr Clare Lawton or Dr Karen Birch. Your name and address will not be associated with any data that is used in scientific reports or publications.

What will happen to the results of the research study?

When the study is completed the results will be analysed and used in the write-up of academic research publications. Remember that your own results are confidential and that your name will not be associated with any information published from this study. All of the data will be kept for 5 years and then destroyed.

Who has reviewed this research?

All research is looked at by an independent group of people called a research ethics committee, to protect your interests. This study has been reviewed by the research ethics committee of the Institute of Psychological Sciences (reference number: 14-0070)

Who is organising and funding the research?

This research is being organised by Dr Clare Lawton of The Institute of Psychological Sciences and Dr Karen Birch of the Centre for Sport and Exercise Sciences. The research is funded as part of an educational award (PhD) by the ESRC and NHS. It is a collaboration between the University of Leeds and Salford Royal Hospital NHS Trust.

Will I receive anything for taking part?

Upon completion of the study, a small payment (up to maximum of £15) to cover some of the travel costs can be paid to each participant upon request. Bus tickets or documentation of miles driven must be provided and this will be processed by an external finance office before a payment can be made. All those that complete all aspects of the study will be entered into a prize draw for your chance to win £50 of Love2shop vouchers.

Contact for further information.

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Appendix 6.6 Consent form: Study 3

UNIVERSITY OF LEEDS

INFORMED CONSENT FORM

Impact of differing walking dose upon cognitive function in people with a body mass index (BMI) of at least 25.

Please Initial

6. I confirm that I have read and understood the Participant Information Sheet dated 28/03/14 (version 4) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. _____

7. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. _____
8. I have been informed that Visit 2,3 and 4 will involve a finger prick blood sample being taken _____

9. I understand that data collected during the study, may be looked at by individuals from the University research team, collaborators on the research project and the University of Leeds for the purposes of research governance. All data will be anonymised with the exception of the recruitment questionnaires containing personal data. I give permission for these individuals to have access to my data. _____

10. I agree to take part in the above study.....

11. I give/do not give permission for my contact details to be kept securely on file for potential future studies (please delete as appropriate)

Participant's name…… Date ____ / ____ /_____

Signature ……

Researcher's name……Date ____ / ____ /_____

Signature……

Appendix 6.7 Recruitment Information Questionnaire

Date of contact _____ /_____ /_____ Researcher …….

How did you find out about the study? Contacted by us ☐

Poster advert ☐

Word of Mouth ☐

Other ☐

CONTACT INFORMATION

Name ……

Address ……

……

……

Contact phone number ……

E-mail ……

Dept ……

Date of Birth ____ / ____ /____ Age …….

Measured height……. Measured weight…….

Measured BMI ……

GENERAL INFORMATION

Occupation Employed ☐ Unemployed ☐

Retired ☐ Housewife ☐

Student ☐ Other ☐

Hours of work - Full time/ Part time

Night shifts - Yes/No Details …….

Holidays planned or booked over next 6 months? Yes/No

Dates ……

HEALTH

How would you rate your general health…….

Have you ever been told you have any of the following?

Myocardial Infarction	Yes/No
Atherosclerosis	Yes/No
Heart Disease	Yes/No
Coronary Thrombosis	Yes/No
Rheumatic Heart	Yes/No
Heart Attack	Yes/No
Aneurism	Yes/No
Coronary Occlusion	Yes/No
Angina	Yes/No
Cardiac Dysrhythmias	Yes/No
Heart Murmur	Yes/No
Stroke	Yes/No
Transient Ischaemic Attack	Yes/No
Hypertension	Yes/No

If you answered Yes to hypertension, are you taking any medication for this? Please give details:

……
……

Do you have or have you had any medical conditions? (i.e. heart condition, asthma, diabetes)

……..

……

Current medications

……

Do you have a cardiac pacemaker fitted? Yes/No

Do you suffer from any neurological disorders? If so please give details:

……
……

Have you suffered a musculoskeletal impairment or injury in the past 6 months? If so please give details:

……
……

Have you had any surgical procedures within the last 6 months? If so please give details:

……
……

Have you ever smoked? No, never smoked ☐

Yes ☐

Given up ☐ How long ago?.....

How many units of alcohol do you usually drink per week?

……..

N.B. 1 small (125mls) glass of wine or half a pint of lager or 1 shot of spirits = 1 unit

EXERCISE

Do you do regular exercise? **Yes / No**

If yes, how many times a week do you exercise? One to four ☐

More than four ☐

What type of exercise do you do?

……..

If none, are you planning to start doing regular exercise in the next 4 months?

Details……
……

PREGNANCY

Are you currently pregnant or planning a pregnancy this year? Yes / No

Have you had a baby or have you been pregnant in the last 6 months? Yes/ No

Date of delivery (if applicable) ___ / ___ / ___

Have you breast fed in the last 6 months? Yes / No

MENOPAUSAL SYMPTOMS

Do you think you have reached the menopause (the menopause means not having had a period for 12 months of more)

……..

Are you taking/ have you taken hormone replacement therapy (HRT)?.....

What was the date of your last period?

.....

How many periods have you had in the last 12 months?……..

Are you experiencing hot flushes? Yes / No How often

……..

Are you experiencing night sweats? Yes / No How often

……

Has your weight varied within the last 3 months? Yes / No

If yes by how much? .....

Are you currently on any form of a weight loss diet? Yes / No

Details……

.....

OTHER INFORMATION

Can we keep this information on file and contact you about future studies? Yes / No

Inclusion visit arranged for Date _____ /_____ /_____

ADDITIONAL NOTES

Appendix 6.8 Wechsler Abbreviated Scale of Intelligence

wasi™ WECHSLER *ABBREVIATED* SCALE OF INTELLIGENCE™

Record Form

Name _____ ID _____

Address/School _____ Grade/ Highest Education _____

Examiner _____

	Year	Month	Day
Date of Testing			
Date of Birth			
Age			

Subtest Scores

Subtest	Raw Score	*T* Score
Vocabulary		
Block Design		
Similarities		
Matrix Reasoning		

Sums of *T* Scores: Verbal | Performance | 4–Subtest | 2–Subtest | Full Scale

Profile of Subtest Scores

Verbal		Performance	
V	S	BD	MR

80 75 70 65 60 55 50 45 40 35 30 25 20

Profile of IQ Scores

VIQ	PIQ	FSIQ

160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50

WASI IQ Scores

	Sum of *T* Scores	IQ	Percentile	___% Confidence Interval
Verb.				–
Perf.				–
Full–4				–
Full–2				–

Prediction Intervals

WISC–III		WAIS–III	
90%	68%	90%	68%
–	–	–	–

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0154981532

10 11 12 A B C D E

1. Vocabulary

Start Point
Ages 6–8: Item 5
Ages 9–89: Item 9

Reverse Rule
All Ages: Administer Items 1–4 in forward sequence if score of 0 or 1 on Item 5 or 6.

Ages 9–89: Administer Items 5–8 in reverse sequence if score of 0 or 1 on Item 9 or 10.

Discontinue Rule
After 5 consecutive scores of 0

Stop Point
Ages 6–8: After Item 30
Ages 9–11: After Item 34
Ages 12–16: After Item 38
Ages 17–89: No stop point

Scoring Rule
Items 1–4: 0 or 1
Items 5–42: 0, 1, or 2

Item	Response	Score
		(0 or 1)
1. Fish		
2. Shovel		
3. Map		
4. Shell		
		(0, 1, 2)
6–8 5. Shirt		
6. Shoe		
7. Flashlight		
8. Car		
9–89 9. Bird		
10. Calendar		
11. Number		
12. Bell		
13. Lunch		
14. Police		
15. Vacation		
16. Pet		
17. Balloon		
18. Transform		
19. Alligator		

Continue

1. Vocabulary *(Continued)*

Item	Response	Score (0, 1, 2)
20. Cart		
21. Blame		
22. Dance		
23. Purpose		
24. Entertain		
25. Famous		
26. Reveal		
27. Decade		
28. Tradition		
29. Rejoice		
30. Enthusiastic		
31. Improvise		
32. Impulse		
33. Haste		
34. Trend		
35. Intermittent		
36. Devout		
37. Impertinent		
38. Niche		
39. Presumptuous		
40. Formidable		
41. Ruminate		
42. Panacea		

STOP

STOP

STOP

Maximum Raw Score
Ages 6–8: 56
Ages 9–11: 64
Ages 12–16: 72
Ages 17–89: 80

Total Raw Score

3. Similarities *(Continued)*

	Item	Response	Score (0, 1, 2)
	23.	Peace–War	
9–11 STOP	24.	Capitalism–Socialism	
	25.	Tradition–Habit	
	26.	Freedom–Law	

Maximum Raw Score
Ages 6–8: 36
Ages 9–11: 44
Ages 12–89: 48

Total Raw Score ____

4. Matrix Reasoning

Start Point
Administer Sample Items A and B first.
Ages 6–8: Item 1
Ages 9–11: Item 5
Ages 12–44: Item 7
Ages 45–79: Item 5
Ages 80–89: Item 1

Reverse Rule
Ages 9–11 and **Ages 45–79:** Administer Items 1–4 in reverse sequence if score of 0 on Item 5 or 6.
Ages 12–44: Administer Items 1–6 in reverse sequence if score of 0 on Item 7 or 8.

Discontinue Rule
After 4 consecutive scores of 0 or after 4 scores of 0 on 5 consecutive items

Stop Point
Ages 6–8: After Item 28
Ages 9–11: After Item 32
Ages 12–44: No stop point
Ages 45–79: After Item 32
Ages 80–89: After Item 28

Scoring Rule
Items 1–35: 0 or 1

Item	Response Options (Circle One)	Score (0 or 1)
A.	1 **2** 3 4 5 DK	
B.	1 2 3 4 **5** DK	
6–8 80–89 1.	1 **2** 3 4 5 DK	
2.	1 2 3 **4** 5 DK	
3.	1 **2** 3 4 5 DK	
4.	1 2 3 **4** 5 DK	
9–11 45–79 5.	1 2 **3** 4 5 DK	
6.	**1** 2 3 4 5 DK	
12–44 7.	**1** 2 3 4 5 DK	
8.	1 2 **3** 4 5 DK	
9.	1 2 3 4 **5** DK	
10.	1 2 3 4 **5** DK	
11.	1 2 3 4 **5** DK	
12.	1 **2** 3 4 5 DK	
13.	1 2 **3** 4 5 DK	
14.	**1** 2 3 4 5 DK	
15.	1 **2** 3 4 5 DK	
16.	1 2 3 **4** 5 DK	
17.	1 2 **3** 4 5 DK	

Item	Response Options (Circle One)	Score (0 or 1)
18.	**1** 2 3 4 5 DK	
19.	**1** 2 3 4 5 DK	
20.	1 2 3 **4** 5 DK	
21.	1 2 3 4 **5** DK	
22.	1 2 3 4 **5** DK	
23.	1 **2** 3 4 5 DK	
24.	1 **2** 3 4 5 DK	
25.	**1** 2 3 4 5 DK	
26.	1 2 3 4 **5** DK	
27.	1 2 3 **4** 5 DK	
6–8 80–89 STOP 28.	1 2 **3** 4 5 DK	
29.	1 2 **3** 4 5 DK	
30.	1 2 3 **4** 5 DK	
31.	**1** 2 3 4 5 DK	
9–11 45–79 STOP 32.	1 2 3 **4** 5 DK	
33.	1 **2** 3 4 5 DK	
34.	1 2 **3** 4 5 DK	
35.	1 2 3 4 **5** DK	

Maximum Raw Score
Ages 6–8: 28
Ages 9–11: 32
Ages 12–44: 35
Ages 45–79: 32
Ages 80–89: 28

Total Raw Score ____

Appendix 6.9 Actigraph accelerometer wear time log

Participant ID **Accelerometer no.**

Instructions for wearing the accelerometer and log sheet

- *Please wear the accelerometer every day starting from the morning after you collect it from the trial enrolment session.*
- *Please do not get the accelerometer wet. Remove it for swimming, having a bath or shower and record on this log sheet. Please remember to put it back on again after you have taken it off.*
- *You do not need to wear the accelerometer while you sleep. Take it off before going to bed and record the time. It's a good idea to leave it somewhere where you can see it first thing in the morning. Every morning, remember to put it on as soon as you wake up.*
- *The accelerometer should be worn on the hip bone and can be worn underneath or on top of your clothing. It should fit tightly but comfortably around the body.*

	Time put on	Time taken off	Reason for taking off	How much time spent	
				Swimming (minutes)	Cycling (minutes)
		E.g 7.30pm	E.g. shower	E.g. 20 mins	E.g. 0 mins
Day 1 (on waking)					
(bed time)					
Day 2 (on waking)					
(bed time)					
Day 3 (on waking)					
(bed time)					

	Time put on	Time taken off	Reason for taking off	How much time spent	
				Swimming (minutes)	Cycling (minutes)
Day 4 (on waking)	→				
(bed time)					
Day 5 (on waking)	→				
(bed time)					
Day 6 (on waking)	→				
(bed time)					
Day 7 (on waking)	→				
(bed time)					

Appendix 6.10 SOP for creating 16 word VVLT lists

Use the file “New words for MRC database with words from stories deleted”. This is on the N drive in Unilever 07, main study, cog tests. This file has 9 worksheets. One of these is the “source” worksheet which contains all the words. You will notice that despite the name of this file, this worksheet still contains words which are in the story recall version.

The remaining worksheets in this file contain words which are categorised according to 3 properties: concreteness, familiarity, and imageability. The worksheets are named according to the properties of the words in worksheet. For example, the worksheet named “HHH” contains words which are high in concreteness, high in familiarity, and high in imageability. As another example, the worksheet LHL contains words which are low in concreteness, high in familiarity, and low in imageability, and so on and so forth.

For the 16 word VVLT lists 480 words are needed. There are 10 VVLT versions, each which contain 3 word lists (named ‘A’ ‘B’ and ‘C’). Each word list requires 16 words. Therefore, there are 48 (3x16) words in each VVLT version, and 480 words (10x48) in total. Each of the word lists need to be matched for various properties which could affect recall, such as concreteness, imageability, familiarity, and word length. In order to do this certain words need to be selected from certain worksheets (e.g. HHH or HLH etc.). Follow the instructions below to select the words.

For each 16 word word list:

- 4 words must be selected from worksheet HHH.
  1 word must be 4 letters
  1 word must be 5 letters
  1 word must be 4 or 5 letters
  1 word must be 6 or 7 letters.

  (* there are only 39 5 letter words so of the “1 must come from 4 or 5” a maximum of 9 will come from the 5 letter words. In addition, there are only 11 seven letter words so of the “1 word must be 6 or 7 letters” a maximum of 11 7 letter words can be used)

- 3 words must be selected from worksheet HLH.
  2 words must be 4 or 5 letters (there are only 58 4 or 5 letter words so use 2 words which are 6 letters).
  1 word must be 6 or 7 letters (again, there are only 28 6 or 7 letter words so use 2 words which are 8 letters)

- 1 word must be selected from worksheet LHH.
  Use a word with any number of letters.

- 4 words must be selected from worksheet LHL.
  2 words must come from 4 letters (there are only 57 4 letter words, so use 3 words which are 5 letters).
  1 word must be 5 or 6 letters.
  1 word must be 7 or 8 letters

- 4 words must come from worksheet LLL
  1 word must be 4 letters
  1 word must be 5 letters
  1 word must be 6 letters
  1 word must be 7 or 8 letters.

Appendix 6.11 Versions for Visual Verbal Learning Test

Version 1			Version 2		
List A	**List B**	**List C**	**List A**	**List B**	**List C**
BOOK	NOSE	GRASS	CITY	HALL	EDGE
EARTH	METAL	STEP	MOUTH	VOICE	PAPER
ROOM	SNOW	FILM	STAND	ROUND	SWEET
PERSON	BRIDGE	SUMMER	DOCTOR	CHURCH	SPRING
HOLE	POOL	KING	GOLD	DUST	CAMP
COAST	MARCH	FRAME	BLOCK	CHAIN	CROSS
PATIENT	PLATFORM	SHOULDER	FOREST	ISLAND	MARKET
LOVE	VOTE	READ	HAPPY	SPACE	SPEAK
FAIR	AREA	KIND	DROP	BUSY	SICK
BEST	COOL	MOVE	FAST	CARE	TELL
SHORT	EVENT	WHOLE	THING	PEACE	THINK
DISTANCE	RESPECT	FEELING	READING	PURPOSE	SUCCESS
FLOW	LACK	RATE	GAIN	DUTY	JOIN
BRIEF	IDEAL	LEVEL	PHASE	POWER	MINOR
CHOOSE	FACTOR	LATTER	METHOD	REVIEW	IMPACT
SESSION	ATTEMPT	CONTENT	JUSTICE	FAILURE	BALANCE

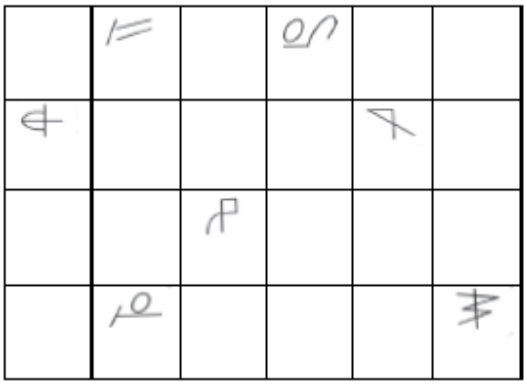
Version 3			Version 4		
List A	**List B**	**List A**	**List B**	**List A**	**List B**
NEWS	NINE	PAGE	**List A**	**List B**	**List C**
COLOUR	DRINK	FIGHT	BLUE	BODY	COLD
NOTE	PAIN	SHOP	WOOD	WIND	TRIP
BEDROOM	BROTHER	COLLEGE	HEAT	HILL	LADY
ARMY	BAND	BILL	FAMILY	LEADER	LETTER
DANCE	ENEMY	FLOOR	RIFLE	SCALE	SPOKE
CATTLE	COLUMN	CORNER	FELT	FORT	HERO
GENERAL	SILENCE	PRETTY	MACHINE	OFFICER	PAYMENT
NICE	SAVE	TALK	DEATH	DOZEN	EIGHT
NONE	SLOW	TURN	ABLE	AWAY	BORN
CLEAN	CLOSE	GUESS	CALL	COST	DONE
INTEREST	OCCASION	RELIGION	EFFORT	FUTURE	GROWTH
POOR	RULE	TASK	SCIENCE	SERVICE	SOCIETY
CARRY	LEARN	SCENE	LESS	NEXT	RISK
JUNIOR	MOTION	SOCIAL	CLAIM	ISSUE	MORAL
COMMAND	CULTURE	EXTREME	BELIEF	BITTER	BUDGET

Version 5			Version 6		
List A	**List B**	**List C**	**List A**	**List B**	**List C**
SEAT	SONG	SPOT	DARK	DATE	DEAD
KNIFE	LIGHT	MONEY	BLOOD	CHAIR	CHILD
MUSIC	NIGHT	PARTY	LAKE	LAND	LINE
CIRCLE	COFFEE	DINNER	NOTICE	SEASON	SQUARE
FLESH	GROUP	MOTOR	JURY	PICK	TEAM
CLAY	CELL	CASE	BEACH	TRIAL	POINT
COUSIN	ESTATE	FIGURE	STATION	OPENING	VILLAGE
EAST	HELL	NAME	WROTE	THICK	HEAVY
EASY	FEAR	FINE	FACT	HEAR	REAL
FIRM	FREE	GIVE	GROW	LEFT	WANT
PROUD	QUIET	REACH	EXTRA	SENSE	USUAL
ABILITY	CONTROL	FREEDOM	BUSINESS	INCREASE	PERSONAL
WISH	VIEW	UNIT	BEAT	DEAR	EVER
SPITE	STYLE	THEME	APART	BREAK	LEAST
CENTRE	CRISIS	ENOUGH	EXTENT	LISTEN	SPIRIT
FUNCTION	MAJORITY	RESEARCH	BENEFIT	CENTURY	MEASURE

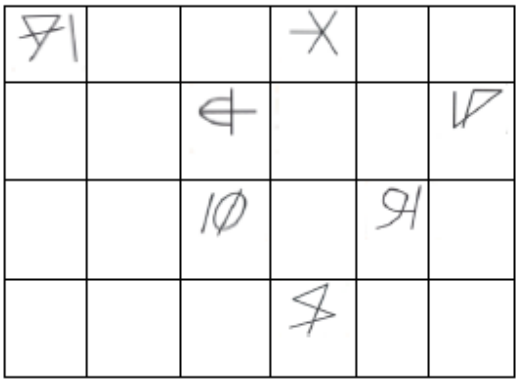
Practice version		
List A	**List B**	**List C**
FOOT	TEST	WALL
GLASS	HEART	HUMAN
COVER	FRONT	TASTE
PICTURE	STUDENT	WEATHER
BASE	DRAW	FILE
TEXT	RACE	MARK
PROPERTY	VALLEY	YELLOW
DEEP	LORD	PAIR
TYPE	WEST	WIDE
CLEAR	WRONG	RESULT
AFRAID	AMOUNT	CAREER
QUALITY	TROUBLE	WORKING
RISE	SEEK	TILL
WORTH	VALUE	TRUST
SYMBOL	UNIQUE	WONDER
PORTION	REALITY	PRIMARY

Appendix 6.12 Visual Spatial Learning Test versions

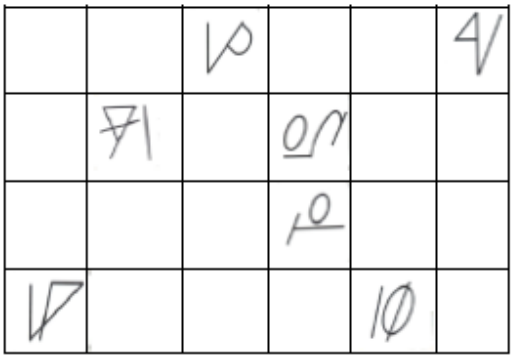
Version 1



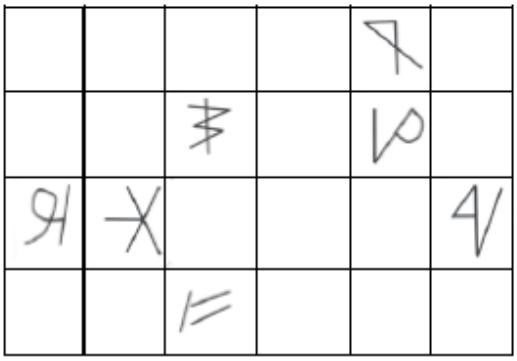
Version 2



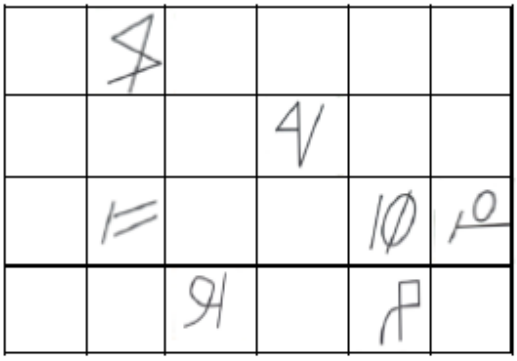
Version 3



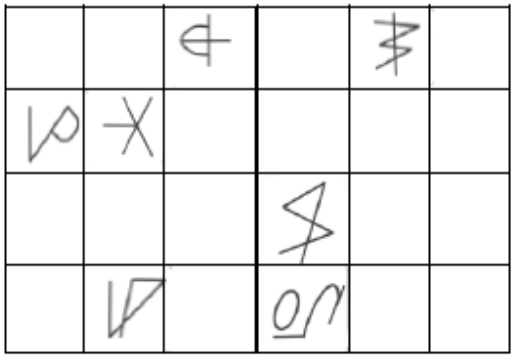
Version 4



Version 5



Version 6



Practice Version

Appendix 6.13 Cognitive Test Evaluation Questionnaire

Subject number: **Subject Initials:** **Visit:** **Date:**

1. How much time pressure did you feel due to the rate/pace of the tests?

Not very much _____ Very much

2. How difficult did you find these tests today?

Not at all difficult _____ Extremely difficult

3. How much did you concentrate during these tests?

A small amount _____ A large amount

4. How hard did you try in these tests?

Not at all hard _____ Extremely hard

5. How well do you think you performed in these tests?

Not at all well _____ Extremely well

6. How frustrating did you find these tests today?

Not at all frustrating _____ Extremely frustrating

7. Please number the following tests from the battery you have just completed indicating how difficult you found them? (1 = easiest test, 8 = hardest test)

Visual Spatial Learning Test (Pattern memory test on board) _____

Visual Verbal Learning Test (Word list memory test) _____

Corsi block tapping test (Red square sequences) _____

Stroop Task (Colour/word test) _____

Bakan Test (3 odd or 3 even numbers in a row) _____

Word Recognition test (Delayed word list memory task) _____

Delayed Visual Spatial Learning (Delayed pattern memory test) _____

Trail Making Test (Joining circles with letters/numbers) _____

Appendix 6.14 Blood Pressure: Standard Operating Procedure v2 30/09/2009

1. Staff

In order to perform blood pressure (BP) testing on volunteers, staff must first read the Omron M7 manual.

This is a low risk procedure and is commonly used for self monitoring of blood pressure.

2. Volunteers

All volunteers must be well informed of the study and its requirements via the Study Information Sheet. Participants should also be given a verbal explanation and have signed the associated consent form (see appendices 1 and 2 for examples of a typical study information sheet and consent form for a study using blood pressure measures with mandatory information highlighted).

3. Equipment

Omron Digital Automatic Blood Pressure Monitor M7.

4. Testing

1. Please note that BP should be measured after the participant has spent 10 minutes resting.
2. Explain to the volunteer clearly and confidently what you are going to do and show them the equipment you will be using.
3. Allow the volunteer to ask any questions and talk through any concerns.
4. Explain to the volunteer that, in the event of receiving a high BP result, it is recommended that they speak to their GP. Participants receiving a high BP score should also be told that this could be a result of 'white coat syndrome' whereby BP is elevated due to anxiety levels related to undergoing the BP measure. However, participants should be made aware that it is important that all cases of high BP be investigated further by their GP.
5. Ask the volunteer to sit comfortably at a table with their feet flat and the floor and their arm resting on the table.
6. Ask participants to relax their arm and turn their palm upward.
7. Fit the cuff to the participant's arm ensuring that it is at heart height during measurement.
8. Press the on/off button on the Omron M7 – wait for zero and the heart symbol to appear before continuing.
9. Ask the participant to sit still and not move or speak during the measurement process.
10. Press the start button.
11. Wait for the cuff to automatically inflate.
12. Wait for the cuff to then automatically deflate.
13. Record the values of blood pressure from the display (note: the top number is systolic BP and the number underneath is the diastolic BP).
14. Ideally the first reading should be corroborated with a second reading (with a 3rd reading taken in case of a discrepancy between the first and second readings).
15. When you have finished testing BP, press on/off button to turn off the power (*note*: power automatically switches off after 5 minutes).
16. When you have finished using the BP monitor, slightly fold the air tube and insert it into the cuff (<u>do not</u> disconnect the air tube).
17. Put the cuff and main unit in the storage case.
18. Provide the participant with a copy of his/her BP result (see Appendix 3 for an example).
19. Participants with high BP should again be told to discuss this further with their GP.

Appendix 6.15 Multiple linear regression analyses of relationship between delayed verbal memory and health parameters

		Delayed verbal memory (n=62)				
Model		**B**	**SE B**	**β**	**t**	**Sig**
1						
	Constant	-0.18	3.61		-0.05	.96
	Age	0.01	0.05	0.03	0.22	.83
	IQ	0.06	0.03	0.27	2.11	.04
2						
	Constant	3.09	4.75		0.65	.52
	Age	-0.01	0.05	-0.03	-0.18	.86
	IQ	0.04	0.03	0.19	1.38	.17
	SBP	-0.00	0.03	-0.02	-0.16	.88
	PC1	-0.17	0.35	-0.06	-0.49	.63
	PC2	-0.60	0.40	-0.21	-1.47	.15
	PC3	0.29	0.35	0.11	0.83	.41
	PC4	0.08	0.35	0.03	0.22	.83

Model 1: adjusted R^2 = .07; F(2,61)=2.33, ns
Model 2: adjusted R^2 = .12; F(7,61)=1.06, ns

Appendix 6.16 Multiple linear regression analyses of relationship between proactive interference and health parameters

		Proactive Interference (n=62)				
Model		**B**	**SE B**	**β**	**t**	**Sig**
1						
	Constant	5.86	3.22		1.82	.07
	Age	-0.07	0.04	-0.19	-1.51	.14
	IQ	-0.01	0.02	-0.06	-.46	.65
2						
	Constant	6.87	4.30		1.60	.12
	Age	-0.05	0.05	-0.15	-1.06	.30
	IQ	-0.00	0.03	-0.02	-0.16	.88
	SBP	-0.02	0.02	-0.12	-0.82	.42
	PC1	0.03	0.32	0.01	0.09	.93
	PC2	0.14	0.37	0.05	0.38	.71
	PC3	-0.18	0.32	-0.08	-0.58	.57
	PC4	-0.06	0.32	-0.03	-0.19	.85

Model 1: adjusted R^2 = .04; F(2,61) = 1.32, ns
Model 2: adjusted R^2 = .06; F(7,61) = .50, ns

Appendix 6.17 Multiple linear regression analyses of relationship between retroactive interference and health parameters

		Retroactive Interference (n=61)				
Model		**B**	**SE B**	**β**	**t**	**Sig**
1[1]						
	Constant	-3.25	2.93		-1.11	.27
	Age	0.10	.04	0.32	2.60	.01
	IQ	0.01	.02	0.06	0.50	.62
2[2]	Constant	-2.18	3.91		-0.56	.58
	Age	0.11	0.04	0.34	2.46	.02
	IQ	0.02	0.02	0.09	0.63	.54
	SBP	-0.01	0.02	-0.09	-0.65	.52
	PC1	-0.19	0.29	-0.08	-0.64	.52
	PC2	-0.00	0.33	-0.00	-0.01	.99
	PC3	-0.31	0.29	-0.14	-1.09	.28
	PC4	0.06	0.29	0.03	0.21	.84

Model 1: adjusted R^2 = .08; $F(2,60) = 3.67$, $p < .05$
Model 2: adjusted R^2 = .05; $F(7,60) = 1.27$, ns

Appendix 6.18 Multiple linear regression analyses of relationship between VSLT designs and health parameters

		VSLT designs (n=55)				
Model		**B**	**SE B**	**β**	**t**	**Sig**
1[1]	Constant	14.58	3.78		3.85	.00
	Age	-0.11	0.05	-0.27	-2.10	.04
	IQ	0.07	0.03	0.32	2.48	.02
2[2]	Constant	18.91	4.83		3.92	.00
	Age	-0.12	0.06	-0.30	-2.14	.04
	IQ	0.06	0.03	0.27	1.96	.06
	SBP	-0.02	0.03	-0.11	-0.78	.44
	PC1	-0.02	0.36	-0.01	-0.05	.96
	PC2	-0.58	0.43	-0.19	-1.34	.19
	PC3	0.19	0.38	0.07	0.49	.63
	PC4	0.18	0.36	0.07	0.50	.62

Model 1: adjusted R^2 = .13; F(2,54) = 4.85, p< .01
Model 2: adjusted R^2 = .16; F(7,54) = 1.77, ns

Appendix 6.19 Multiple linear regression analyses of relationship between VSLT locations and health parameters

		VSLT locations (n=55)				
Model		**B**	**SE B**	**β**	**t**	**Sig**
1						
	Constant	16.57	6.07		2.73	.01
	Age	-0.18	0.08	-0.29	-2.17	.03
	IQ	0.06	0.04	0.17	1.28	.21
2						
	Constant	15.44	7.82		1.97	.05
	Age	-0.19	0.09	-0.31	-2.14	.04
	IQ	0.04	0.05	0.13	0.90	.37
	SBP	0.03	0.04	0.09	0.63	.53
	PC1	0.20	0.59	0.05	0.33	.74
	PC2	-0.23	0.70	-0.05	-0.33	.75
	PC3	0.77	0.61	0.18	1.27	.21
	PC4	0.12	0.58	0.03	0.22	.83

Model 1: adjusted R^2 = .07; F(2,54) = 2.94, p= .06
Model 2: adjusted R^2 = .10;; F(7,54) = 1.10, ns

Appendix 6.20 Multiple linear regression analyses of relationship between VSLT designs/locations and health parameters

		VSLT designs/locations (n=55)				
Model		**B**	**SE B**	**β**	**t**	**Sig**
1	Constant	9.49	7.33		1.30	.20
	Age	-0.26	0.10	-0.33	-2.61	.01
	IQ	0.11	0.05	0.26	2.08	.04
2						
	Constant	9.88	9.42		1.05	.30
	Age	-0.30	0.11	-0.39	-2.73	.01
	IQ	0.09	0.06	0.21	1.49	.14
	SBP	0.03	0.05	0.09	0.65	.52
	PC1	-0.05	0.71	-0.01	-0.08	.94
	PC2	-0.74	0.85	-0.13	-0.87	.39
	PC3	0.91	0.74	0.17	1.23	.22
	PC4	0.21	0.69	0.04	0.31	.76

Model 1: adjusted R^2 = .13; ΔR^2 = .17; F(2,54) = 5.12, p< .01
Model 2: adjusted R^2 = .14; ΔR^2 = .04; F(7,54) = 1.71, ns

Appendix 6.21 Multiple linear regression analyses of relationship between Bakan false positives and health parameters

		Bakan false positives (n=63)				
Model		**B**	**SE B**	**β**	**t**	**Sig**
1[1]	Constant	9.14	4.06		2.25	.03
	Age	-0.07	0.05	-0.16	-1.24	.22
	IQ	-0.02	0.03	-0.09	-0.74	.46
2[2]	Constant	8.59	5.17		1.66	.10
	Age	-0.07	0.06	-0.17	-1.24	.22
	IQ	-0.01	0.03	-0.06	-0.44	.66
	SBP	0.00	0.03	-0.01	-0.06	.95
	PC1	0.27	0.38	0.09	0.71	.48
	PC2	-0.34	0.44	-0.11	-0.79	.44
	PC3	-0.83	0.38	-0.28	-2.17	.03
	PC4	-0.02	0.38	-0.01	-0.05	.96

Model 1: adjusted R^2 = .03; F(2,62) = 1.12, ns
Model 2: adjusted R^2 = .14; F(7,62) = 1.23, ns

Appendix 6.22 SAS PROC mixed models for the Visual Verbal Learning Test (VVLT)

	Total Acquisition	Delayed recall	Recognition List A	Retroactive Interference	Proactive Interference
Main effect terms					
Visit	F(1,20)=1.61, ns	F(1,21)=1.14, ns	F(1,20)=0.62, ns	F(1,21)=2.29, ns	F(1,20)=0.02, ns
condition	F(2,21)=2.75, p= .09	F(2,21)=1.33, ns	F(2,21)=0.53, ns	F(2,22)= 0.78, ns	F(2,22)=0.63, ns
Covariate					
Baseline	F(1,21)=28.1, p<.0001	F(1,21)=20.7, p<.001	F(1,21)=4.39, p< .05	F(1,22)=3.09, p = .09	F(1,22)=0.23, ns
Age					
IQ					
Interaction terms					
Baseline*visit	F(1,20)=1.12, ns	F(1,21)=1.14, ns	F(1,20)=0.21, ns	F(1,21)=1.47, ns	F(1,20)=2.64, ns
Baseline*condition	F(2,21)=2.5, ns	F(2,21)=1.76, ns	F(2,21)=0.40, ns	F2,22)= 1.32, ns	F(2,22)=0.91, ns
Visit*condition	F(2,20)=0.25, ns	F(2,21)=1.76, ns	F(2,20)=0.61, ns	F(2,21)=0.70, ns	F(2,22)=0.59, ns
Age*condition					
IQ*condition					

Where no F value is presented this interaction or covariate was not retained in the final model

Appendix 6.23 SAS PROC mixed models for the Visual Spatial Learning Test (VSLT)

	Designs	Locations	Immediate Designs/Locations	Delayed designs/locations
Main effect terms Visit condition	 F(1,22)=0.03, ns F(2,22)=0.61, ns	 F(1,21)=7.94, p< .01 F(2,22)=0.93, ns	 F(1,22)=4.18, p< .05 F92,22)=0.02, ns	 F(1,22)= 2.40, ns F(2,22)=2.09, ns
Covariate Baseline Age IQ	F(1,22)=15.09, p< .001	F1,22)=5.2, p< .05	F(1,22)=4.20, p< .05	F(1,21)=14.71, p< .001
Interaction terms Baseline*visit Baseline*condition Visit*condition Age*condition IQ*condition	 F(1,22)=0.00, ns F(2,22)=0.50, ns F(2,22)=3.01, p= .07	 F(1,21)=6.80, p< .05 F(2,22)=0.57, ns F(2,21)=1.11, ns	 F(1,22)=4.65, p< .05 F(2,22)=0.05, ns F2,22)=1.71, ns	 F(1,21)=1.91, ns F(2,22)=2.89, p= .08 F(2,21)=0.56, ns

Where no F value is presented this interaction or covariate was not retained in the final model

Appendix 6.24 SAS PROC mixed models for the Bakan Rapid Visual Information Processing Task

	Correct hits	Reaction time of correct hits	False-positive responses	Missed responses
Main effect terms				
Visit	F(1,20)=1.06, ns	F(1,20)=0.55, ns	F(1,18)=0.26, ns	F(1,21)=3.78, p= .07
condition	F(2,21)= 2.00, ns	F(2,21)=1.26, ns	F(2,21)=9.76, p< .001	F(2,22)=0.48, ns
Covariate				
Baseline	F(1,21)=120.32, p< .001	F(1,21)=15.56, p<.001	F(1,21)=5.07, p< .05	F(1,22)=81.61, p< .001
Age			F(1,21)=10.05, p< .01	
IQ				
Interaction terms				
Baseline*visit	F(1,20)=0.14, ns	F(1,20)=0.66, ns	F(1,18)=0.02, ns	F(1,21)=0.77, ns
Baseline*condition	F(2,21)=1.60, ns	F(2,21)=1.26, ns	F(2,21)=2.66, p= .09	F(2,22)=0.36, ns
Visit*condition	F(2,20)=0.03, ns	F(2,20)=1.11, ns	F(2,18)=1.81, ns	F(2,21)= 0.00, ns
Age*condition				
IQ*condition				

Where no F value is presented this interaction or covariate was not retained in the final model

Appendix 6.25 SAS PROC mixed models for the Corsi spatial working memory task

	Total correct responses	Reaction time of correct responses	Correct responses: crossing trials	Correct responses: non-crossing trials
Main effect terms				
Visit	F(1,21)=3.56, p< .07	F(1,21)=0.00, ns	F(1,22)=0.10, ns	F(1,21)=0.00, ns
condition	F(2,21)=5.44, p< .01	F(2,20)=1.96, ns	F(2,20)=0.25, ns,	F(2,22)=1.85, ns
Covariate				
Baseline	F(1,21)=92.76, p<.001	F(1,20)=27.3, p<.001	F(1,20)=16.51, p<.001	F(1,22)=12.58, p<.01
Age			F(1,20)=3.42, p= .07	
IQ	F(1,21)=9.71, p<.01	F(1,20)=5.58, p< .05	F(1,20)=4.73, p< .05	
Interaction terms				
Baseline*visit	F(1,21)=3.85, p= .06	F(1,21)=0.11, ns	F(1,22)=0.06, ns	F(1,21)=0.13, ns
Baseline*condition	F(2,21)=5.97, p< .01	F(2,20)=2.09, ns	F(2,20)=0.26, ns	F(2,22)=2.12, ns
Visit*condition	F(2,21)=0.16, ns	F(2,21)=2.41, ns	F(2,22)=0.56, ns	F(2,21)=0.19, ns
Age*condition				
IQ*condition				

Where no F value is presented this interaction or covariate was not retained in the final model

Appendix 6.26 SAS PROC mixed models for the Tower of Hanoi task

	errors	Time to solve task
Main effect terms		
Visit	F(1,19)=0.42, ns	F(1,20)=6.38, p< .05
condition	F(2,21)=0.31, ns	F(2,21)=3.25, p= .06
Covariate		
Baseline	F(1,21)=10.19, p<.01	F(1,21)=69.19, p<.001
Age		F(1,15)=0.11, ns
IQ		F(1,15)=0.22, ns
Interaction terms		
Baseline*visit	F(1,19)=0.06, ns	F(1,20)=10.57, p< .01
Baseline*condition	F(2,22)=0.03, ns	F(2,21)=6.25, p< .01
Visit*condition	F(2,20)=0.06, ns	F(2,20)=2.88, p= .08
Age*condition		F(2,15)=0.08, ns
IQ*condition		F(2,15)=0.19, ns

Where no F value is presented this interaction or covariate was not retained in the final model

Appendix 6.27 SAS PROC mixed models for Grooved pegboard task

	Completion time: non-dominant hand	**Completion time: non-dominant hand**
Main effect terms Visit condition	 F(1,21)=3.03, ns F(2,21)=7.60, p< .01	 F(1,20)=0.01, ns F(2,21)=4.82, p< .05
Covariate Baseline Age IQ	F(1,21)=146.83, p<.001	F(1,21)=80.96, p<.001
Interaction terms Baseline*visit Baseline*condition Visit*condition Age*condition IQ*condition	 F(1,21)=2.76, ns F(2,21)=7.74, p< .01 F(2,21)=1.93, ns	 F(1,20)=0.03, ns F(2,21)=4.59, p< .05 F(2,20)=1.54, ns

Where no F value is presented this interaction or covariate was not retained in the final model

Appendix 6.28 SAS PROC mixed models for indices of cardiovascular health

	Absolute VO_2 max	Relative VO_2 max	Lactate Threshold	Percentage LT at VO_{2max}	Mean arterial pressure
Main effect terms					
condition	F(2,16)=0.94, ns	F(2,18)=2.26, ns	F2,19)=0.31, ns	F(2,18)=0.26, ns	F(2,18)=8.15, p<.01
Covariate					
Baseline	F(1,16)=180.79, p<.0001	F(2,18)=130.82, p<.0001	F(1,19)=14.04, p<.001	F(1,18)=4.23, p<.05	F(1,18)=39.84, p<.001
Age			F(1,19)=0.05, ns	F(1,18)=0.42, ns	F(1,18)=3.31, p=.08
Interaction terms					
Baseline*condition	F(2,16)=0.00, ns	F(2,18)=1.95, ns	F(2,19)=0.83, ns	F(2,18)=0.20, ns	F(2,18)=4.77, p<.05
Age*condition	F2,16)=0.67, ns		F(2,19)=0.04, ns	F(2,18)=0.17, ns	F(2,18)=1.38, ns

Where no F value is presented this interaction or covariate was not retained in the final model

Appendix 6.29 SAS PROC mixed models for indices of obesity

	Percentage body fat	BMI	Waist circumference	Waist-hip ratio
Main effect terms				
Visit	F(1,20)=3.10. p= .09	F(1,19)=0.76, ns	F(1,19)=0.81, ns	F(1,21)=3.15, p= .09
condition	F(2,22)=1.07, ns	F(2,20)=0.18, ns	F(2,21)=0.44, ns	F(2,22)=0.80, ns
Covariate				
Baseline	F(1,22)=77.79, p<.001	F(1,20)=958.53, p<.0001	F(1,21)=399.40, p< .001	F(1,22)=105.43, p<.001
Age				
Interaction terms				
Baseline*visit	F(1,20)=2.45, ns	F(1,19)=0.60, ns	F(1,19)=0.89, ns	F(1,21)=3.66, p= .07
Baseline*condition	F(2,22)=1.07, ns	F(2,20)=0.17, ns	F(2,21)=0.42, ns	F(2,22)=0.88, ns
Visit*condition	F(2,20)=1.15, ns	F(2,19)=3.67, p< .05	F(2,19)=1.99, ns	F(2,21)=3.82, p< .05
Age*condition				

Where no F value is presented this interaction or covariate was not retained in the final model

Appendix 6.30Standard Operating Procedure: Finger-prick capillary blood sample

SOP for Finger Prick Blood Glucose analysis using YSI and Insulin analysis using ELISA

Note: This SOP is an amendment to the IPSEC approved SOP 202 (Finger Prick Blood Glucose Testing) – version 4 (19 June 2007) and adds information specific to finger prick sample collection for YSI (glucose) and ELISA (Insulin) analyses.

1. Staff

In order to perform finger prick blood glucose (FPBG) and finger prick blood insulin (FPBI) testing on volunteers, staff must have read the YSI Blood Glucose Analyser operating manual, the Unistik 3 and Microvette CB 300 manuals and the SOP for the ALPCO insulin ELISA kit. In-house training includes familiarisation with the testing equipment and observing the procedure as carried out by a competent/experienced member of staff (minimum of 2 separate FPBG/FPBI events). Staff should practise the procedure on themselves or a colleague prior to taking samples from a volunteer. Subsequent training involves supervised practise (FPBG/ FPBI testing under the supervision of a competent/experienced member of staff). Supervised practise should take place on at least 2 occasions (until the member of staff feels competent to undertake this procedure). Following this the competence of the staff member should be confirmed by an appropriate assessor and this must be documented in the HARU training log (See Appendix 1). A competent/experienced assessor is defined as someone who has performed finger prick blood glucose testing successfully and without incident on at least 10 occasions following in-house training.

2. Volunteers

All volunteers must be well informed of the study and its requirements (via the Participant Information Sheet and verbal explanation) and have signed the associated consent form. (See appendices 2 and 3 for examples of a typical Participant Information Sheet and consent form for a study using finger prick blood sampling with mandatory information highlighted).

3. Preparation of Room/Test Area.

The room must be clean and tidy. The desk/table should be cleaned with a 2% solution of Virkon. All equipment and study paperwork should be prepared and checked in advance. The meter and lancing device should be cleaned with a 2% solution of Virkon and all equipment placed in a clean kidney dish.

Equipment blood sampling:

- Unistik 3 extra single use safety
- Microvette CB 300 tubes (Sarstedt)
- Sterets
- Gauze
- Sterile scissors
- Liquid nitrogen

Equipment blood analysis:

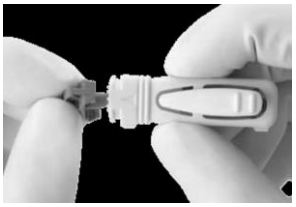
- YSI blood glucose analyser & YSI kit box
- ALPCO insulin ELISA kit
- Precision pipettes with disposable tips capable of dispensing 25-100 µl
- Repeating or multi-channel pipette capable of dispensing 100 µl
- Volumetric container and pipettes for reagent preparation
- Distilled or deionized water
- Microplate washer or wash bottle
- Orbital microplate shaker capable of 700-900 rpm
- Microplate reader with 450 and 620-650 nm filter

4. Testing

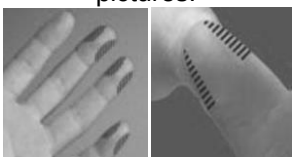
4.1 Blood sampling and storage

Wash testing site with soap and warm water and make sure it is completely dry before testing. Explain to the volunteer clearly and confidently what you are going to do and show them the equipment you will be using.
Allow the volunteer to ask any questions and talk through any concerns

1. Hold the Unistik 3 body and twist off the grey lancet cap until you feel it separate from the yellow body. Don't pull, just twist. Dispose of the grey cap in the bin.

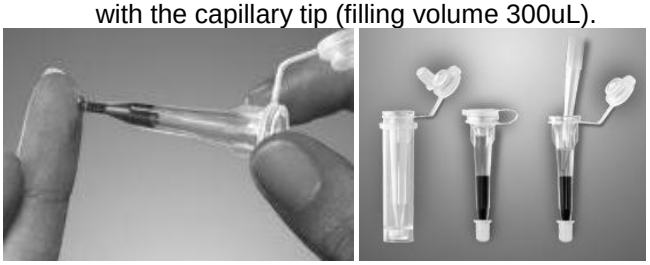


2. Choose a site as indicated by the shaded areas on pictures.



3. Hold the Unistik device firmly against the chosen site and press the release button. To obtain a drop of blood, massage the sample site, taking care not to squeeze too hard at the site

4. Remove the conically shaped inner tube of the Microvette from the carrier tube. Hold the Microvette in a horizontal or slightly inclined position and collect the blood sample with the capillary tip (filling volume 300uL).



5. When filled, detach the small stopper attached to the cap and push the stopper firmly onto the tip of the tube.

6. Replace the cap to close the tube.

7. Give the volunteer a Steret and piece of gauze to clean the sample site.

8. Place the collection tube into the carrier tube. Mix the sample thoroughly by gently inverting the Microvette

9. Measure Blood Glucose using the YSI Blood Glucose Analyser (see 4.2)

10. Centrifuge the remaining sample for insulin analysis (2000x g/ 5 min / 20°C) to generate plasma. Wear gloves!

11. Take 150µL of the clarified plasma and freeze in liquid nitrogen for transport to Leeds Dental Institute. Store the samples at -80°C until insulin analysis using ELISA (see 4.3). Liquid nitrogen should be collected in a 'dewar' flask using appropriate protective clothing (gloves and face protection). The nitrogen should never be used or taken in an enclosed space (e.g. a lift) because of the risk of suffocation.

4.2 Measuring Blood Glucose using the YSI Blood Glucose Analyser

The YSI kit box is kept in the fridge between G39 & G40.

1. The YSI will be in Standby mode. To exit standby press **standby**, then **2** then **enter**.

2. Firstly run the buffer solution and the internal standard through the system. You do this by pressing **Menu** and then **1 - service**. Cycle the buffer first by pressing **2-buffer**. This will cycle the buffer solution. Make sure that the buffer flows to the waste bottle. Cycle the internal standard next by pressing **3-cal**. Make sure the internal standard flows to the sample chamber.

3. You then need to check the probe response. Enter the diagnostics menu by pressing **Menu** then **3-diagnostics**. To see the probe response press **3-probe**. The number displayed on the screen is the baseline current (Ib). Press **1-flush**. Buffer will be flushed. The baseline reading should be <5nA. Then press **2-calibrator**. The cal pump will cycle and some of the standard will be aspirated. The plateau (pL) reading should be >8nA above the baseline Ib current. If there is not at least an 8nA difference between the two readings, do not run the instrument.

4. Place the unit into run mode by pressing the **Menu** then the **Run** key. It will flush buffer and the baseline will be checked for <5nA and stability. The instrument is then calibrated and a report printed and the screen will display 'ready for sample'.

5. Check the membranes are OK by using a small amount of YSI 2363 Potassium Ferrocyanide solution as a sample. Press **sample** and when the sipper has stopped hold the tube so only 3mm of the sipper is in the sample. Press **sample** again. The acceptable range is between 0 – 5.

6. Do a linearity test using a small amount of YSI 1531 glucose standard. Press **sample** and when the sipper has stopped hold the tube so only 3mm of the sipper is in the sample. Press **sample** again. The acceptable range is between 47.5 to 52.5mM.

7. If any of the above readings are outside the limits press **Calibrate** to re-calibrate the unit and then test them again.

8. The machine is now ready to use. To test a sample, press **sample** and when the sipper has stopped hold the tube so only 3mm of the sipper is in the sample. Press **sample** again. Write down the result or make a note on the printout of the volunteer ID.

NB. In run mode, the YSI calibrates itself every 15 minutes or every 5 samples. It will sometimes self –calibrate several times until a stable calibration is established.

9. Once you have finished testing take the unit out of run mode by pressing **Run,** then **2** then **enter**. Put the unit back into standby mode by pressing **menu** and then **standby**

4.3 Measuring Blood Insulin using the ALPCO insulin ELISA kit

REAGENT PREPARTION AND STORAGE CONDITIONS

- The kit should be stored at 2-8°C. The kit is stable until the expiry date on the box label.
- All reagents must reach room temperature prior to preparation and subsequent use in the assay.

Diabetes Controls (Levels 1 and 2) are provided in a lyophilized form. Dilute each control with 0.6 ml of deionized water. Close the vial with the rubber stopper and cap, then gently swirl the vial and allow it to stand for 30 minutes prior to use. The contents of the vial should be in solution with no visible particulates. The reconstituted controls are stable for 7 days stored at 2-8°C. For longer term storage the controls should be stored at <-20°C in aliquots for up to 6 months (repeated freeze/thaw cycles should be avoided). The concentration ranges of the controls are provided on the Certificate of Analysis enclosed with each kit; however, it is recommended that each laboratory establishes its own acceptable ranges.

Wash Buffer (21X) is diluted with 20 parts deionized water. For example, to prepare Working Strength
Wash Buffer, dilute 20 ml of Wash Buffer (21X) with 400 ml of deionized water. Working Strength Wash
Buffer is stable for 30 days at room temperature (18-25°C).

ASSAY PROCEDURE

Bring all reagents to room temperature prior to use. Briefly vortex all reagents before use. A standard curve must be included with each assay and/or with each plate, if more than one plate is run at a time.
All standards, controls, and samples should be run in duplicate.

1. Designate enough microplate strips for the standards, controls, and desired number of samples. The remaining strips should be stored in the tightly sealed foil pouch containing the desiccant and stored at 2-8°C.
2. **Pipette 25 µl** of each standard, reconstituted Control (see *Reagent Preparation),* or sample into their respective wells.
3. **Pipette 100 µl** of Detection Antibody into each well.
4. Cover microplate with a plate sealer and **incubate for 1 hour,** shaking at 700-900 rpm on an orbital microplate shaker at room temperature (18-25°C).
5. Decant the contents of the wells and **wash the microplate 6 times** with at least 350 µl of Working Strength Wash Buffer (see *Reagent Preparation)* using a microplate washer. Alternatively, use a wash bottle to fill the wells, and then discard the liquid, inverting and firmly tapping the microplate on absorbent paper towels between washes. After the final wash with either the microplate washer or wash bottle, remove any residual Wash Buffer and bubbles from the wells by inverting and firmly tapping the microplate on absorbent paper towels. (See *Microplate Locking Diagram* below.)
6. **Pipette 100 µl** of TMB Substrate into each well.
7. Cover microplate with a plate sealer and **incubate for 15 minutes** at room temperature (18-25°C) on an orbital microplate shaker (700-900 rpm).
8. **Pipette 100 µl** of Stop Solution into each well. Gently mix the wells to stop the reaction. Remove bubbles before reading with microplate reader.
9. Place the microplate in a microplate reader capable of reading the absorbance at 450 nm with a reference wavelength of 620-650 nm. The microplate should be analyzed within 30 minutes following the addition of the Stop Solution.

80-INSHU-E01.1, E10.1 SHORT PROTOCOL:

Insulin ELISA

Pipette 25 µl of Standards, Controls, and Samples
↓
Pipette 100 µl Detection Antibody
↓
Incubate 1 hour (700-900 rpm) @ RT
Wash 6X
↓
Pipette 100 µl TMB Substrate
↓
Incubate 15 minutes (700-900 rpm) @ RT
↓
Pipette 100 µl Stop Solution, gently shake
↓
Read @ 450 / 620-650 nm within 30 minutes

CALCULATION OF RESULTS

The Varioscan Flash plate reader should be programmed to quantify the absorbance data ained using a 4 parameter logistic (pl) fit.

Appendix 6.31 Pedometer log sheets

Instructions for wearing the pedometer and log sheet

Please wear the pedometer every day during the study

- The pedometer should be worn on the hip bone and can be worn underneath or on top of your clothing.
- At the start of each day, hold down the reset button until the display shows 0. Then wear you pedometer as usual, this will count the number of steps you are taking.
- **For step count take final reading at the end of each day when you take the pedometer off before bed. Write down the total number of steps for each day on this sheet. A new sheet will be provided for you every week.**
- Please do not get the pedometer wet. Remove it for swimming, having a bath or shower and record on this log sheet. Please remember to put it back on again after you have taken it off.
- You do not need to wear the pedometer while you sleep. Take it off before going to bed and record the time. It's a good idea to leave it somewhere where you can see it first thing in the morning. Every morning, remember to put it on as soon as you wake up.
- You do not have to achieve your target increase of steps in one go, this can made up over the day bit by bit.

At baseline your average step count was X,XXX over the seven days.

Your target number of steps to achieve on your 3 chosen walk days is X,XXX. This equates to approximately 30 extra minutes of walking on each walk day. It is ok to be slightly below this, and it is absolutely fine to go over this amount. Just write down the step count at the end of each day. You can select which are walk days and rest days.

Week 1	Date	Walk day or Rest day?	Time put on	Time taken off	Total Step Count
Day 1					
Day 2					
Day 3					
Day 4					
Day 5					
Day 6					
Day 7					

Appendix 6.32SAS PROC mixed models for the Visual Verbal Learning Test (VVLT)

	Total Acquisition	Delayed recall	Recognition List A	Retroactive Interference	Proactive Interference
Main effect terms					
Condition	F(1,15)=0.26, ns	F(1,21)=0.73, ns	F(1,21)=1.09, ns	F(1,16)=0.28, ns	F(1,19)=0.003, ns
Covariate					
Baseline	F(1,22)=22.30, p<.001	F(1,21)=41.83, p<.0001	F(1,21)=18.10, p<.001	F(1,16)=1.64, ns	F(1,19)=2.49, ns
Steps	F(1,15)=1.04, ns	F(1,21)=3.11, p=.09	F(1,21)=0.14, ns	F(1,16)=1.63, ns	F(1,19)=1.25, ns
Age	F(1,15)=0.02, ns			F(1,16)=0.73, ns	F(1,19)=0.36, ns
IQ	F(1,15)=0.14, ns	F(1,21)=3.14, p=.09	F(1,21)=3.81, p=.06	F(1,16)=0.01, ns	
Interaction terms					
Baseline*condition	F(1,15)=2.95, ns	F(1,21)=3.11, ns	F(1,21)=0.66, ns	F(1,16)=0.97, ns	F(1,19)=1.92, ns
Steps*condition					
Age*condition	F(1,15)=0.55, ns				F(1,19)=0.36, ns
IQ*condition	F(1,15)=0.45, ns				

Where no F value is presented this interaction or covariate was not retained in the final model

Appendix 6.33 SAS PROC mixed models for the Visual Spatial Learning Test (VSLT)

	Designs	Locations	Immediate Designs/Locations	Delayed designs/locations
Main effect terms				
condition	F(1,19)=1.73, ns	F(1,16)=0.28, ns	F(1,16)=1.04, ns	F(1,16)=0.05, ns
Covariate				
Baseline	F(1,19)=2.06, ns	F(1,16)=0.01, ns	F(1,16)=0.06, ns	F(1,16)=0.65, ns
Steps	F(1,19)=3.64, p=.07	F(1,16)=2.17, ns	F(1,16)=1.24, ns	F(1,16)=3.65, p=.07
Age		F(1,16)=1.83, ns	F(1,16)=1.13, ns	F(1,16)=3.66, p=.07
IQ				
Interaction terms				
Baseline*condition	F(1,19)=1.63, ns	F(1,16)=0.13, ns	F(1,16)=0.72, ns	F(1,16)=0.05, ns
Steps*condition				
Age*condition				
IQ*condition				

Where no F value is presented this interaction or covariate was not retained in the final model

Appendix 6.34 SAS PROC mixed models for the Bakan Rapid Visual Information Processing Task

	Correct hits	Reaction time of correct hits	False-positive responses	Missed responses
Main effect terms				
condition	F(1,19)=2.36, ns	F(1,17)=0.22, ns	F(1,19)=7.92, p<.01	F(1,18)=2.84, ns
Covariate				
Baseline	F(1,19)=64.65, p<.0001	F(1,17)=5.08, p<.05	F(1,19)=0.59, ns	F(1,18)=59.64, p<.0001
Steps	F(1,19)=0.16, ns	F(1,17)=0.03, ns	F(1,19)=2.47, ns	F(1,18)= 0.13, ns
Age		F(1,17)=0.01, ns		F(1,18)=0.69, ns
IQ		F(1,17)=0.02, ns		F(1,18)=1.99, ns
Interaction terms				
Baseline*condition	F(1,19)=0.95, ns	F(1,17)=4.55, p<.05	F(1,19)=2.47, ns	F(1,18)=0.68, ns
Steps*condition				
Age*condition	F(2,19)=14.32, p<.001	F(1,17)=1.40, ns	F(2,19)=2.75, p=.09	F(1,18)=16.87, p<.001
IQ*condition	F(2,19)=6.14, p<.01	F(1,17)=0.55, ns		F(1,18)=8.46, p<.01

Where no F value is presented this interaction or covariate was not retained in the final model

Appendix 6.35 SAS PROC mixed models for the Corsi spatial working memory task

	Total correct responses	Reaction time of correct responses	Correct responses: crossing trials	Correct responses: non-crossing trials
Main effect terms				
condition	F(1,18)=0.00, ns	F(1,18)=0.02, ns	F(1,21)=0.02, ns	F(1,17)=5.03, p<.05
Covariate				
Baseline	F(1,18)=20,14, p<.001	F(1,18)=10.21, p<.01	F(1,21)=4.98, p<.05	F(1,17)=0.20, ns
Steps	F(1,18)=2.82, ns	F(1,18)=0.90, ns	F(1,21)=0.47, ns	F(1,17)=0.92, ns
Age	F(1,18)=0.87, ns	F(1,18)=0.02, ns	F(1,21)=0.43, ns	F(1,17)=5.07, p<.05
IQ	F(1,18)=1.75, ns	F(1,18)=0.12, ns		F(1,17)=5.39, p<.05
Interaction terms				
Baseline*condition	F(1,18)=5.82, p<.05	F(1,18)=0.33, ns	F(1,21)=0.00, ns	F(1,17)=1.22, ns
Steps*condition	F(1,18)=6.58, p<.05			
Age*condition	F(1,18)=0.50, ns	F(1,18)=0.23, ns		F(1,17)= 1.50, ns
IQ*condition	F(1,18)=0.29, ns	F(1,18)=0.32, ns		F(1,17)=1.74, ns

Where no F value is presented this interaction or covariate was not retained in the final model

Appendix 6.36 SAS PROC mixed models for executive function outcomes

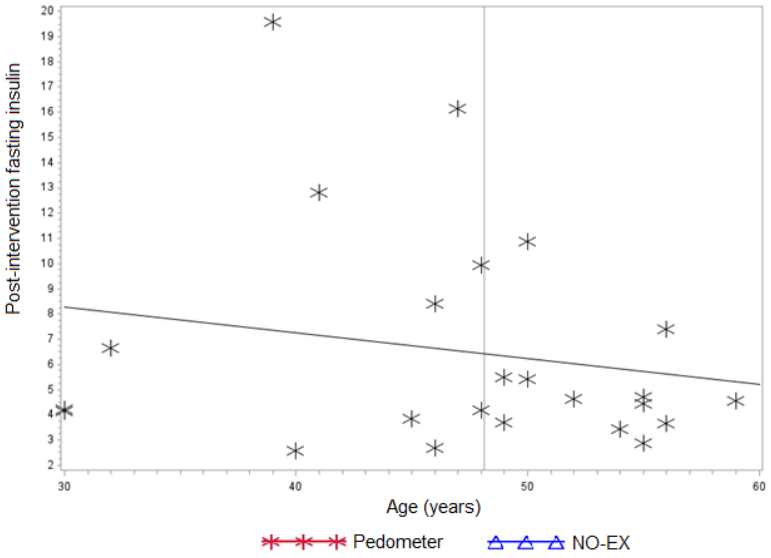
	RT Incongruent	Stroop Interference	TMT A	TMT B	TMT BminusA
Main effect terms					
condition	F(1,16)=1.73, ns	F(1,17)=0.30, ns	F(1,19)=0.00, ns	F(1,16)=0.90, ns	F(1,16)=2.09, ns
Covariate					
Baseline	F(1,16)=0.30, ns	F(1,17)= 0.23, ns	F(1,19)= 1.49, ns	F(1,16)=19.30, p<.001	F(1,16)=47.63, p<.0001
Steps	F(1,16)=0.72, ns	F(1,17)= 0.12, ns	F(1,19)=6.85, p<.017	F(1,16)=1.64, ns	F(1,16)=10.39, p<.01
Age	F(1,16)=6.02, p<.05	F(1,17)=2.67, ns	F(1,19)=0.37, ns	F(1,16)=1.74, ns	F(1,16)=3.10, ns
IQ	F(1,16)=1.35, ns	F(1,17)=0.10, ns		F(1,16)=2.85, ns	F(1,16)=8.05, p<.01
Interaction terms					
Baseline*condition	F(1,16)=2.86, ns	F(1,17)= 5.67, p<.05	F(1,19)=0.18, ns	F(1,16)=0.27, ns	F(1,16)=0.42, ns
Steps*condition	F(1,16)=0.97, ns	F(1,17)= 0.52, ns			
Age*condition	F(1,16)=0.35, ns	F(1,17)=0.40, ns		F(1,16)=6.87, p<.05	
IQ*condition	F(1,16)=0.45, ns	F(1,17)=0.20, ns		F(1,16)=3.26, p=.09	F(1,16)=1.54, ns

Where no F value is presented this interaction or covariate was not retained in the final model

Appendix 6.37 SAS PROC mixed models for indices of cardiometabolic health

	Fasting glucose	Fasting insulin	HOMA-IR	Systolic blood pressure	Diastolic blood pressure
Main effect terms					
Condition	F(1,17)=2.70, ns	F(1,17)=4.47, p<.05	F(1,16)=2.63, ns	F(1,23)=0.24, ns	F(1,21)=2.70, ns
Covariate					
Baseline	F(1,17)=4.38, p=.05	F(1,17)=79.86, p<.0001	F(1,16)=76.38, p<.0001	F(1,23)=39.54, p<.0001	F(1,21)=21.53, p<.0001
Steps	F(1,17)=5.76, p<.05	F(1,17)=2.28, ns	F(1,16)=0.00, ns	F(1,23)=3.41, p=.07	F(2,21)=0.00, ns
Age	F(1,17)=6.94, p<.05	F(1,17)=9.18, p<.01	F(1,16)=3.16, p=.09		
Interaction terms					
Baseline*condition	F(1,17)=0.77, ns	F(1,17)=1.02, ns	F(1,16)=3.25, p=.09	F(1,23)=0.09, ns	F(1,21)=4.88, p<.05
Steps*condition	F(1,17)=4.04, p=.06				
Age*condition	F(1,17)=1.51, ns				F(2,21) =0.70, ns

Where no F value is presented this interaction or covariate was not retained in the final model



Appendix 6.38 Age (horizontal axis) plotted against fasting insulin

Appendix 6.39 SAS PROC mixed models for indices of obesity

	Percentage body fat	BMI	Waist circumference	Waist-hip ratio
Main effect terms				
Condition	F(1,22)=4.37, p<.05	F(1,23)=2.29, ns	F(1,21)=0.04, ns	F(1,24)=0.12, ns
Covariate				
Baseline	F(1,22)=524.72, p<.0001	F(1,23)=1325.12, p<.0001	F(1,21)=199.7, p<.0001	F(1,24)=68.42, p<.0001
Steps	F(1,22)=0.19, ns	F(1,23)=8.33, p<.01	F(1,21)=0.06, ns	F(1,24)=0.12, ns
Age			F(1,21)=0.03, ns	
Interaction terms				
Baseline*condition	F(1,22)=3.12, p=.09	F(1,23)=1.63, ns	F(1,21)=0.00, ns	F(1,24)=0.12, ns
Steps*condition				
Age*condition				

Where no F value is presented this interaction or covariate was not retained in the final model