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Modifiable Risk Factors for Cognitive Decline in People with Type 2 Diabetes

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Declaration

I, Anniek Jarmila Sluiman, declare that this thesis is of my own composition and the work presented here has not been submitted for any other degree or professional qualification.

The Edinburgh Type 2 Diabetes Study, which provided the data for all analyses presented here, had already completed the baseline clinics by the time I joined the study, but I was responsible for the collection of data at the year 10 follow-up clinic in 2016/2017. Therefore, all of the baseline clinical variables and the baseline cognitive test data used for the purpose of the analyses presented in this thesis were collected, cleaned and (in some cases) manipulated through the efforts of other members of the research team. Cardiac, cerebral and microvascular events and data on mortality were collected and updated throughout the 10 years of follow-up through efforts of other members of the research team, although I was involved in the data collection of new events at year 10 with other members of the research team. All of the statistical analyses on the basis of this data were performed by myself.

Signed: 

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Abstract

Introduction: Type 2 diabetes is a known risk factor for cognitive decline and dementia and continues to be one of the most common non-communicable diseases in the world. Obesity, a hallmark of type 2 diabetes is often associated with general inactivity and chronic increased levels of systemic inflammation. The literature suggests that obesity, along with systemic inflammation and inactivity levels are associated with cognitive decline and dementia in the general population. There is uncertainty as to what effect (if any) obesity, systemic inflammation and activity levels have on people with diabetes.

Aims: To determine whether systemic inflammation, obesity and physical (in) activity levels are associated with cognitive decline and/or dementia in older people with type 2 diabetes.

Methods: The Edinburgh Type 2 Diabetes Study (ET2DS) is a representative prospective cohort of 1066 men and women living in Scotland, aged 60-75 years at baseline. Cognitive data was gathered by means of a comprehensive cognitive test battery, at baseline and at year 10 follow-up. Other data on medical history, vascular events, circulating biomarkers, physiological examination and activity levels was also gathered at each phase of data collection. Criteria were developed to determine probable cases of dementia at year 10 follow-up. Principal component analysis (PCA) was used to derive a latent general cognition variable '*g*' using imputed data to provide a summary score of the different cognitive tests. Multivariable regression analysis was used to assess the association of risk factor variables with general cognition, cognitive decline and dementia. Statistical models adopted the correction method, where baseline cognitive ability was used to correct for follow-up cognitive ability, in order to provide an indication of the association of a risk factor on cognitive decline. Logistic multivariable regression models were used to explore the effect of risk factors on incident dementia. Adjustment variables included a wide range of demographic, vascular-related and diabetes-related risk factors.

Results: In the ET2DS, associations were found between waist to hip ratio (WHR) and cognitive decline (standardised beta= -0.076; p=0.020), in fully adjusted models but not with body mass index (BMI). Waist circumference (WC) was found to be associated with cognitive decline (standardised beta= 0.059; p= 0.032), however in fully adjusted models this association was no longer statistically significant. Findings supported a possible association of higher plasma fibrinogen (standardised beta= -0.059; p=0.032) and IL-6 (standardised beta= -0.064; p=0.018) with cognitive decline, however in fully adjusted models this association was no longer statistically significant.

Physical activity and sedentary behaviour were shown to be associated with a decline in cognitive ability (standardised beta= 0.171; p<0.001, standardised beta= -0.135; p<0.001, respectively), in fully adjusted models.

Obesity-related variables associated with incident dementia included BMI (OR 0.95; 95% CI 0.90- 0.99; p<0.05), WC (OR 0.97; 95% CI 0.95-0.99; p<0.05) and percentage body fat (OR 0.94; 95% CI 0.90-0.98; p<0.01). Baseline inflammation marker IL-6 was identified as a possible risk factor for incident dementia (OR 1.56; 95% CI 1.08- 2.27; p < 0.05). Physical activity and sedentary behaviour were also associated with dementia prevalence at year 10 (OR 0.53; 95% CI 0.36 - 0.78; p<0.001, OR 2.01; 95% CI 1.31 – 3.08; p<0.001, respectively).

Conclusions: Specific measures of obesity, inflammation and activity level were associated with cognitive decline and risk of dementia, in older people with type 2 diabetes. Care must be taken when interpreting these results as causal relationships cannot be inferred and further work must take place to confirm the directionality of these associations. These results, in the context of other work, may be used to reveal possible underlying biological mechanisms of diabetes related cognitive decline and dementia and guide work on preventative therapies or interventions for this disease.

Lay Abstract

Type 2 diabetes is a disease that affects many people worldwide and has been shown to increase the risk of dementia and cognitive decline, namely the slowing thinking skills such as memory and information processing. People who are overweight, often as a result of lack of exercise, are more likely to develop diabetes and obesity has been shown to increase inflammation in the body. There is uncertainty as to what the main risk factor is for cognitive decline and dementia. The aim of this study was to find if level of obesity, physical activity and inflammation are associated with cognitive decline and dementia in older people with diabetes.

The Edinburgh type 2 diabetes study uses information collected over a period of 10 years from a large group of men and women aged 60-75 years, with type 2 diabetes, living in Scotland. Cognitive ability was measured by psychological tests that look at memory, information processing, problem solving ability and other thinking skills, and was measured both at the start of the study and after 10 years. Other medical information on lifestyle such as smoking, diseases such as heart attacks, and medications was also collected. A questionnaire on weekly exercise was used, and measurements such as body mass index and waist to hip ratio, both of which giving indications as to how much fat is stored in the body and how it is distributed, were recorded. After 10 years the number of people who developed dementia were recorded. By using statistical techniques, associations between obesity and cognitive decline were modelled as were the associations between obesity and people who developed dementia. The analysis was carried out in such a way that it was possible to see to what extent level of inflammation influenced the relationships between obesity and cognitive decline or dementia in the group.

The main finding of this study was that body shape (waist to hip ratio) was associated with cognitive decline to a greater extent than total body fat (body mass index) in people with type 2 diabetes, and that inflammation did not influence this relationship. Another finding was that, a specific inflammation marker called IL6 was shown to be associated with cognitive decline. Level of exercise was also shown to be related to cognitive ability. Surprisingly, dementia appears to be associated with a lower body mass index and lower levels of exercise. This may be due to the slow progression of dementia, and that many people that had developed dementia after 10 years may already have had symptoms such as weight loss at the start of the study. More work is needed to find out if any of these risk factors cause dementia or cognitive decline, as the results of the present study cannot be used to reveal causal relationships. This would be important as it may help in developing strategies to prevent dementia and cognitive decline in people with diabetes who are already at a higher risk than the general population.

Table of Contents

Chapter 1: Introduction 17

1.1 Diabetes Mellitus *17*

1.2 Intelligence and cognition *19*

1.3 Age related cognitive decline *21*

1.4 Cognitive Impairment and Dementia *21*

1.5 Neural mechanisms of cognitive ageing and dementia *24*

1.6 Diabetes related dementia and cognitive decline *25*

1.7 Risk factors *27*

1.7.1 Risk factors for cognitive decline in the general population *27*

1.7.2 Risk factors for cognitive decline in people with diabetes *28*

Chapter 2: Aims and Objectives 31

2.1 Aims *31*

2.2 Objectives *32*

Chapter 3: A systematic literature review on physical inactivity, sedentary behaviour and obesity as risk factors for cognitive decline in people with type 2 diabetes. 33

3.1 Background *33*

3.2 Aim *34*

3.3 Methods *34*

3.3.1 Eligibility criteria *34*

Types of studies *34*

Types of participants *35*

Report/publication characteristics *36*

3.3.2 Search strategy *36*

3.3.3 Selection of studies *37*

3.3.4 Data extraction and management *38*

3.3.5 Risk of bias tool *38*

3.4. Results *39*

3.4.1 Studies identified *39*

3.4.2 Characteristics, risk of bias and findings of studies *42*

Characteristics of studies *58*
Risk of Bias *58*
3.4.2.1 Findings: Obesity and cognitive ability *59*
3.4.2.2 Findings: Obesity and cognitive decline *63*
3.4.2.3 Findings: Physical activity and cognitive ability *64*
3.4.2.4 Findings: Physical activity and cognitive decline *65*
3.5. Discussion *66*
3.5.1 Notable features of the studies *67*
3.5.2 Strengths and limitations of this review *70*
3.5.3 Future research *72*
3.6 Conclusions *72*
Chapter 4: Methods 74
4.1 The Edinburgh Type 2 Diabetes study *74*
4.2 The ET2DS population *75*
4.3 Ethical approvals *76*
4.4 Participant follow-up at year 10 ..... *76*
4.5 Clinical data collection *77*
4.5.1 Demographics *78*
4.5.2 Medical history and diabetes *79*
4.5.3 Physiological examination *79*
4.5.4 Blood and urine samples *80*
4.5.5 Physical activity questionnaire *80*
4.5.6 Cognitive examination *81*
4.6 Record linkage and Events *87*
4.6.1 Vascular events *87*
4.6.2 Incident dementia events *88*
4.6.3 Diabetic Retinopathy *90*
4.7 Data management and cleaning *91*
4.8 Missing HbA1c data *92*
4.9 Data analysis *92*
4.9.1 Clinical and physiological variables *93*
4.9.2 Preparation of cognitive variables prior to analyses *94*
4.9.3 Statistical analysis *97*

Chapter 5: Results 101

5.1 CHARACTERISTICS OF BASELINE STUDY POPULATION AND 10-YEAR FOLLOW-UP 101

5.1.1 Baseline characteristics 101

5.1.2 Missing data 105

5.1.3 Representativeness 105

5.1.4 Ten year follow-up attendance and attrition 106

5.1.5 Baseline characteristics of 10-year follow-up population versus non-attenders 108

5.1.6 Baseline cognitive status of total study population and those attending 10-year follow-up 113

5.1.7 Change in cognitive scores from baseline to year 10 in those attending follow-up 116

5.1.8 Baseline characteristics of people with incident dementia by year 10 116

5.1.9 Baseline cognitive ability of people with incident dementia at year 10 121

5.2 INTER-CORRELATIONS AND RISK FACTOR ASSOCIATIONS OF OBESITY AND SYSTEMIC INFLAMMATION MARKERS 123

5.2.1 Inter-correlations of obesity measures and association with other risk factors at baseline . 123

5.2.2 Inter-correlations of inflammatory markers and associations with obesity measures 127

5.2.3 The association between systemic inflammatory markers and cognitive ability at baseline 128

5.2.4 Associations between obesity measures and cognitive ability at baseline 131

5.3 OBESITY, INFLAMMATION AND COGNITIVE CHANGE 132

5.3.1 The association between BMI and cognitive decline 132

5.3.2 The association between WHR and cognitive decline 136

5.3.3 The association between systemic inflammatory markers and cognitive decline 138

5.3.4 The association between BMI and cognitive decline when adjusting for inflammation 141

5.3.5 The association between WHR and cognitive decline in total population and in men and women separately 144

5.3.6 The association between WHR and cognitive decline when adjusting for inflammation 144

5.3.7 The association between waist circumference (WC) and cognitive decline when adjusting for inflammation 147

5.3.8 Summary of analysis 149

5.4 OBESITY, INFLAMMATION AND DEMENTIA 149

5.4.1 The association between inflammation and Dementia 149

5.4.2 The association between Obesity and Dementia 152

5.4.3 Summary of dementia analyses 156

5.5 PHYSICAL ACTIVITY, SEDENTARY BEHAVIOUR, COGNITIVE CHANGE AND DEMENTIA 156

5.5.1 Follow-up characteristics of the attending population 156

5.5.2 Follow-up characteristics of the clinic visit and home visit attending population 160

5.5.3 Inter-correlations of (in) activity measures *164*
5.5.4 Physical activity, sedentary behaviour and decline in general cognition *164*
5.5.5 Association of physical activity and sedentary behaviour with prevalent dementia at year 10 ..... *167*
5.5.6 Summary of analysis *167*
Chapter 6: Discussion 169
6.1 Main results *169*
6.1.1 Inflammation *169*
6.1.2 Obesity *171*
6.1.3 Physical activity *174*
6.1.4 Biological Mechanism *175*
6.2 Strengths of the Study *176*
6.3 Limitations of the study *179*
6.4 Comparison to other work *187*
6.5 Conclusions and Further work *191*
References: 194
Appendices: 205

List of Tables

TABLE 1. STUDIES EXPLORING THE CROSS-SECTIONAL ASSOCIATION BETWEEN OBESITY AND COGNITIVE ABILITY 43
TABLE 2. STUDIES EXPLORING THE LONGITUDINAL ASSOCIATION BETWEEN OBESITY AND COGNITIVE DECLINE 49
TABLE 3. STUDIES EXPLORING THE CROSS-SECTIONAL ASSOCIATION BETWEEN PHYSICAL ACTIVITY AND COGNITIVE ABILITY 51
TABLE 4. STUDIES EXPLORING THE LONGITUDINAL ASSOCIATION BETWEEN PHYSICAL ACTIVITY AND COGNITIVE DECLINE . 55
TABLE 5. (A) RISK OF BIAS IN REPORTING IN THE CROSS -SECTIONAL STUDIES 56
TABLE 5. (B) RISK OF BIAS IN REPORTING IN THE LONGITUDINAL STUDIES 57
TABLE 6. THE LOADING SCORES OF THE COGNITIVE TESTS ON THE UN-ROTATED COMPONENT 'G' 96
TABLE 7. BASELINE CHARACTERISTICS OF THE ET2DS AND THE PERCENTAGE OF MISSING DATA..... 103
TABLE 8. REASONS FOR NON-ATTENDANCE AT YEAR 10 FOLLOW-UP 108
TABLE 9. BASELINE CHARACTERISTICS OF ATTENDERS AND NON-ATTENDERS OF THE ET2DS AT YEAR 10 110
TABLE 10. (A) INTER-CORRELATIONS OF COGNITIVE TEST SCORES AT BASELINE..... 114
TABLE 10. (B) INTER-CORRELATIONS OF COGNITIVE TEST SCORES AT YEAR 10..... 114
TABLE 11. BASELINE COGNITIVE TEST SCORES FOR TOTAL POPULATION AND FOR 10 YEAR FOLLOW-UP POPULATION ... 115
TABLE 12. COGNITIVE TEST SCORES OF ATTENDERS AT FOLLOW-UP AT BASELINE AND YEAR 10 FOLLOW-UP..... 117
TABLE 13. BASELINE DEMOGRAPHIC CHARACTERISTICS OF DEMENTIA PATIENTS AND SAMPLE WITHOUT DEMENTIA AT YEAR 10..... 118
TABLE 14. BASELINE COGNITIVE TEST SCORES IN DEMENTIA PATIENTS AND SAMPLE WITHOUT DEMENTIA AT YEAR 10 FOLLOW UP 122
TABLE 15. (A) INTER-CORRELATIONS OF OBESITY MEASURES AT BASELINE..... 124
TABLE 15. (B) INTER-CORRELATIONS OF OBESITY MEASURES AT YEAR 10 FOLLOW-UP 124
TABLE 16. ASSOCIATIONS BETWEEN BMI AND WHR WITH BASELINE RISK FACTORS 125
TABLE 17. INTER-CORRELATIONS OF INFLAMMATORY BIOMARKERS AT BASELINE..... 127
TABLE 18. ASSOCIATIONS BETWEEN BMI AND WHR WITH POTENTIAL MEDIATING INFLAMMATORY RISK FACTORS AT BASELINE..... 128
TABLE 19. THE ASSOCIATION BETWEEN INFLAMMATORY MARKERS AND COGNITIVE STATUS AS MEASURED BY INDIVIDUAL COGNITIVE TESTS AND *G* AT BASELINE..... 130
TABLE 20. CROSS-SECTIONAL ASSOCIATIONS BETWEEN BMI AND WHR AND COGNITIVE TEST SCORES AT BASELINE.... 132
TABLE 21. THE CUT-POINTS AND DISTRIBUTION OF AGE AND SEX PER BMI QUINTILE..... 133
TABLE 22. THE ASSOCIATION BETWEEN BMI AND COGNITIVE DECLINE AS MEASURED BY INDIVIDUAL COGNITIVE TESTS AND *G* AT YEAR 10 FOLLOW-UP..... 135
TABLE 23. THE ASSOCIATION BETWEEN WHR AND COGNITIVE DECLINE AS MEASURED BY INDIVIDUAL COGNITIVE TESTS AND *G* AT YEAR 10 FOLLOW-UP 137
TABLE 24. THE ASSOCIATION BETWEEN INFLAMMATORY MARKERS AND COGNITIVE DECLINE AS MEASURED BY INDIVIDUAL COGNITIVE TESTS AND *G* AT YEAR 10 FOLLOW-UP..... 139
TABLE 25. (A) THE ASSOCIATION BETWEEN BMI AND COGNITIVE DECLINE AS MEASURED BY INDIVIDUAL COGNITIVE TESTS AND *G*, ADJUSTING FOR SYSTEMIC INFLAMMATION AFTER VASCULAR COVARIATES 142
TABLE 25. (B) THE ASSOCIATION BETWEEN BMI AND COGNITIVE DECLINE AS MEASURED BY INDIVIDUAL COGNITIVE TESTS AND *G*, ADJUSTING FOR SYSTEMIC INFLAMMATION BEFORE VASCULAR COVARIATES 143
TABLE 26. THE ASSOCIATION BETWEEN WHR AND COGNITIVE DECLINE AS MEASURED BY INDIVIDUAL COGNITIVE TESTS AND *G*, ADJUSTING FOR SYSTEMIC INFLAMMATION 146
TABLE 27. THE ASSOCIATION BETWEEN WC AND COGNITIVE DECLINE AS MEASURED BY INDIVIDUAL COGNITIVE TESTS AND *G*, ADJUSTING FOR SYSTEMIC INFLAMMATION 148
TABLE 28. THE ASSOCIATION BETWEEN IL-6, TNF A, CRP AND FIBRINOGEN AT BASELINE AND DEMENTIA AT YEAR 10 FOLLOW-UP..... 151

TABLE 29. THE ASSOCIATION BETWEEN BMI, WHR, WC AND % BODY FAT AT BASELINE AND DEMENTIA AT YEAR 10 FOLLOW-UP 155
TABLE 30. CHARACTERISTICS OF THE ET2DS AT FOLLOW-UP AND THE PERCENTAGE OF MISSING DATA 158
TABLE 31. FOLLOW-UP CHARACTERISTICS OF THE ET2DS AT YEAR 10 WHO RECEIVED A CLINIC OR HOME VISIT 162
TABLE 32. INTER-CORRELATIONS OF ACTIVITY AND OBESITY MEASURES AT FOLLOW-UP 164
TABLE 33. THE CROSS-SECTIONAL ASSOCIATION BETWEEN PHYSICAL ACTIVITY AND SEDENTARY TIME SCORE AND *G* AT YEAR 10 FOLLOW-UP 166
TABLE 34. THE CROSS-SECTIONAL ASSOCIATION BETWEEN PHYSICAL ACTIVITY AND SEDENTARY TIME SCORE AND DEMENTIA AT YEAR 10 FOLLOW-UP 168

List of Figures

FIGURE 1. SEARCH TERMS FOR SYSTEMATIC REVIEW. 37
FIGURE 2. THE MODIFIED RISK OF BIAS TOOL 39
FIGURE 3. THE SYSTEMATIC SELECTION PROCESS USED TO IDENTIFY PUBLICATIONS INCLUDED IN THIS REVIEW AFTER THE REMOVAL OF ALL DUPLICATES. 41
FIGURE 4. ATTENDERS OF THE YEAR 10 FOLLOW UP OF THE ET2DS 107
FIGURE 5. BASELINE BMI CATEGORISED BY QUINTILE PLOTTED AGAINST FOLLOW-UP 'G' 133
FIGURE 6. BASELINE BMI CATEGORISED BY QUINTILE PLOTTED AGAINST FOLLOW-UP DEMENTIA 152

List of Abbreviations

AD *Alzheimer's disease*

BMI *Body mass index*

BVFT *Borkowski Verbal Fluency Test*

CI *Confidence interval*

CRP *C-reactive protein*

CVD *Cardiovascular disease*

DR *Diabetic retinopathy*

DST *Digit Symbol Coding Task*

ET2DS *Edinburgh Type 2 Diabetes Study*

FA *Factor analysis*

Faces *Faces test*

fMRI *Functional magnetic resonance imaging*

HADS *Hospital Anxiety and Depression Scale*

IL-6 *Interleukin-6*

LM *Logical Memory*

LNS *Letter-Number Sequencing*

MCI *Mild cognitive impairment*

MeSH *Medical Subject Headings*

MHVS *Mill Hill Vocabulary Scale*

MI *Myocardial infarction*

MMSE *Mini-Mental-State Examination*

MR *Matrix Reasoning*

NART *National Adult Reading Test*

OR *Odds ratio*

PCA *Principle component analysis*

RCT *Randomised controlled trial*

SD *Standard deviation*

SE *Standard error*

SES *Socioeconomic status*

SOP *Standardised operating procedure*

TIA *Transient ischaemic attack*

TMT-A *Trail-Making Test A*

TMT-B *Trail-Making Test B*

TNF-α *Tumor necrosis factor-α*

WAIS *Wechsler Adult Intelligence Scale*

WC *Waist circumference*

WHR *Waist to hip ratio*

WMS *Wechsler Memory Scale*

Chapter 1: Introduction

1.1 Diabetes Mellitus

Diabetes mellitus, commonly referred to as diabetes, is one of the most important public health challenges faced in the 21st century (Zimmet et al., 2014). Globally, the number of people suffering from the disease has almost doubled in the last 20 years, with an estimated 451 million adults diagnosed and also suffering undiagnosed from the condition worldwide (Cho et al., 2018). This equates to 1 in 11 adults having a diagnosis; however, it is understood that 1 in 2 adults with diabetes (around 224 million) are undiagnosed (Cho et al., 2018). In 2017, 9.9% of global all-cause mortality was attributable to diabetes (Cho et al., 2018). The global economic burden of diabetes is an estimated 850 billion USD and it is predicted that, by 2045, this figure will rise to 958 billion USD, when an estimated 693 million people will be living with the disease (Cho et al., 2018). Diabetes prevalence in England is reported to be 6.7% of all adults aged above 17 in the period 2016- 2017 (QOF, 2017), while in Scotland, the most recent figures from the Scottish Diabetes Survey (2016) indicate a prevalence of 5.4% and that diabetes accounts for 3.7% of all deaths (all age ranges) in the period 2015- 2016.

Diabetes, characterised by high blood glucose levels, describes a number of metabolic disorders, of which type 2 diabetes is the most common (World Health Organization, 1999). In Scotland, 88.3% of people with diabetes are diagnosed as having type 2 diabetes (Scottish Diabetes Survey, 2016). Type 2 diabetes usually develops in adulthood, although incidence in childhood and adolescence is increasing (Pulgaron and Delamater, 2014), and occurs as a result of the hormone insulin, produced by beta cells of the pancreas, not being effectively utilised by fat, muscle and liver cells to absorb and store dietary glucose. Other less common forms of diabetes include type 1, often diagnosed in childhood where the

pancreas fails to produce adequate insulin (through an immune mediated response) and gestational diabetes occurring during pregnancy (American Diabetes Association, 2014). Genetic predisposition plays a role in all forms of diabetes, including type 2; however, this type is often associated with obesity and adopting a sedentary lifestyle (Chen et al., 2012).

Patients can present with symptoms such as polyuria, polydipsia, fatigue, weight loss, increased appetite, blurred vision, loss of feeling in the fingers and toes and recurring infections. Patients can be asymptomatic for years, or symptoms might only be minimal or non-specific, which can make diagnosis difficult. Criteria for diagnosis include presenting with symptoms along with abnormal blood test results. These include having a fasting plasma glucose concentration greater than 7mmol/L (126mg/dL) (World Health Organization, 2006) or having a glycated haemoglobin (HbA1c) level of above 6.5% (World Health Organization, 2011). HbA1c is an approximate measure of average blood glucose in the previous 2-3 months.

Once diagnosed, treatment aimed at relieving symptoms and preventing or delaying complications, can take the form of a prescribed diet (low in simple carbohydrates), oral medications that stimulate insulin production or reduce insulin sensitivity, or injectable medications such as insulin. A combination of treatments may be prescribed depending on the severity of symptoms. Complications of diabetes include episodes of hyperglycaemia, small vessel disease, heart disease, stroke, neuropathy, nephropathy, retinopathy, cognitive impairment, and dementia (UK Prospective Diabetes Study Group, 1998). Dementia and cognitive decline as a complication of diabetes will be the focus of this thesis and the following sections provide background information on these topics.

1.2 Intelligence and cognition

Individual differences exist when testing human intelligence (also termed cognitive ability, cognitive function or IQ), and are measured using psychometric tests (Deary et al., 2010a). These tests measure different cognitive skills that contribute to a person's overall intelligence and are almost universally positively correlated. These relatively separate skills, termed cognitive domains, are difficult to measure specifically and, although one specific test may in principal measure ability in one domain, e.g. memory, a different domain may also be required to succeed at the test e.g. processing speed, attention etc. For this reason, it is almost always found that many cognitive test results when administered to a number of individuals are positively correlated (Deary et al., 2010a, Carroll, 1993). General intelligence, or general cognitive ability, often referred to as '*g*' describes this observed overlap in cognitive domains (Deary et al., 2010a), and is described formally as the "general mental capability that involves the ability to reason, plan, solve problems, think abstractly, comprehend complex ideas and learn quickly and learn from experience" (Gottfredson, 1997a). First described by Spearman (1904), general intelligence, often a derived factor or component from a number of different cognitive test results using factor/principal component analysis, describes a latent/summary variable which accounts for around 40% of the total variance in test scores. For example, it tends to appear as relatively high loadings of all tests on the first un-rotated principal component on a principal component analysis. This factor '*g*' is usually normally distributed, with males having a slightly wider distribution of scores (Johnson et al., 2008) and is shown to be relatively stable in rank order between individuals throughout life (Deary et al., 2000, Deary, 2014). General intelligence is also shown to be predictive of life outcomes such as school achievement (Deary et al., 2007), occupational achievement (Gottfredson, 1997b), and later life health status and age at death (Calvin et al., 2010, Deary et al., 2010b).

Neural correlates of '*g*' are difficult to localise (Deary et al., 2010a); however through functional and structural Magnetic Resonance Imaging (fMRI) imaging studies it is recognised that the lateral prefrontal cortex and parietal regions are key brain regions associated with general intelligence (Gray et al., 2003) and that the white matter neural connections between these regions play a major role in '*g*' (Gläscher et al., 2010). It is now also well established that genetic heritability of '*g*' increases with age from about 30% in childhood to 80% in later life (Deary et al., 2010a, Plomin and Deary, 2015).

Although '*g*' is important, there are other sources of variance in cognitive tests, at the domain and test-specific levels (Deary, 2013). Therefore, a hierarchal approach is often used when modelling the concept of intelligence or cognition using large data sets that employ cognitive test batteries (Carroll, 1993). Carroll (1993) describes a three stratum model: at the bottom the test specific outcome stratum, at the intermediate level the cognitive domain stratum, and a top stratum represented by '*g*' as a combination of the cognitive domains. Others have described that alternative hierarchal models with differing numbers of strata, e.g. Johnson and Bouchard Jr (2005) describe a four strata model; however, a common feature of all theories is that the general intelligence factor is always on top. General intelligence can also be described as fluid or crystallised, where the former describes the cognitive functions that are susceptible to age-related change, and the latter are the functions whose means are thought to remain more stable with age (Cattell, 1963). Fluid ability is thus a reflection of current cognitive ability or intelligence, while crystallised ability is thought to be an estimation of premorbid level of ability, or peak level of intelligence (Franzen et al., 1997).

1.3 Age related cognitive decline

The process by which we age is complex, involving a progressive impairment of function which increases risk of disease and mortality (Kirkwood, 2005). Aging affects both the body as a whole, as well as the brain, and a number of cellular and molecular processes have been suggested to play a role. These include an altered cellular response to DNA damage, telomere loss impairing cell division, mitochondrial mutations resulting in decreased tissue bioenergenesis, reduced protein turnover resulting in an accumulation of damaged or redundant protein waste products, or a combination of all of these processes (Kirkwood, 2005).

Age related cognitive decline is used here to describe the 'non-pathological' (that is, not dementia or so-called mild cognitive impairment, which are clinical categories of cognitive decline), mean decline in cognitive ability from young to older adulthood (Salthouse, 2009). It affects the fluid cognitive abilities (e.g. memory, executive function, reasoning and processing speed), critical for independent living, to a greater extent than the crystallised abilities (Deary et al., 2009), and so can have great impact on the quality of life of older people (Lawton, 1997, Sloane et al., 2005).

1.4 Cognitive Impairment and Dementia

Differentiating between non-pathological and pathological cognitive decline can be challenging (Deary et al., 2009). Individual differences exist when describing the point, on the cognitive decline continuum, which may be used to distinguish between clinically relevant impairment and normal cognitive ageing. This cut point is also very much dependent on prior intelligence and cognitive reserve and so when exploring non-pathological cognitive decline in a cohort, it should be acknowledged that not all individuals

classed as non- pathological are phenotypically the same (Deary et al., 2009); in other words, some people may be undiagnosed pathological or high functioning pathological and still be classed as non-pathological.

Mild Cognitive Impairment

Mild Cognitive Impairment (MCI) is a pathological cognitive impairment and describes the clinically relevant cognitive condition that can lead to an increased risk of progressive neurological disease. The clinical diagnostic criteria for MCI have evolved over the last 10 years and are now widely accepted to include, self or carer reported cognitive impairment, objective cognitive impairment measured by neuropsychological testing, preserved independence in functional abilities, and no dementia diagnosed (Petersen, 2016). Often confused with the term pre-clinical dementia, where physiological features of disease are picked up in the absence of cognitive symptoms, MCI is a distinct syndrome that may occur before pre-clinical dementia or dementia (Petersen, 2016). The trajectory of pathological cognitive disease begins many years before the diagnosis of MCI or dementia (Sperling et al., 2011), and it is therefore important to explore all types of cognitive impairment or decline, not just when deemed clinically relevant.

Dementia

The World Health Organization reports dementia to be the 7th leading cause of death globally, and is the 3rd leading cause of death in high income countries in 2016 (World Health Organization, 2018). The global prevalence of dementia is currently estimated to be around 30 million and is expected to double by 2030 (Prince et al., 2013). In 2016, the

prevalence of dementia in Scotland and England was calculated to be 0.8% according to ISD Scotland and Public Health England. The economic burden of the disease is predicted to grow as the population ages. Currently estimated to cost the National Health Service more than 25 billion pounds per year, this figure is expected to rise to around 40 billion pounds per year in 2030 (Lewis et al., 2014). Dementia is an umbrella term for a number of cognitive diseases that all have in common a marked degree of cognitive impairment due to physical changes in the brain that are sufficient to impact on daily functioning. The Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-V) criteria for dementia include a marked degree of cognitive decline that affects daily living, as reported by a clinician, carer or patient; and are not as a result of delirium or other mental disorder. Formal diagnosis is made upon referral to a neurologist, who makes a diagnosis of dementia, with reference to a subtype, based on the evidence provided from neuropsychological assessment and MRI imaging. Despite no treatment currently being available to slow, prevent or reverse dementia, pharmacological therapies are available that aim to reduce the symptoms of disease. These drugs do not slow overall disease progression, but do improve the quality of life for a limited period of time. The main medications are acetylcholinesterase inhibitors (Donepezil, Rivastigmine and Galantamine) which inhibit the breakdown of the neurotransmitter acetyl choline and Memantine which regulates the effects of the neurotransmitter glutamate.

The most common subtype of dementia is Alzheimer's disease, which has a community prevalence of around 31%. Other subtypes include vascular dementia (prevalence of around 22%), dementia with Lewy bodies (prevalence of around 11%) and fronto-temporal dementia (prevalence of around 8%). Mixed dementia is also a commonly used term, often describing dementia with Alzheimer's-like and vascular-like pathology (Stevens et al., 2002).

1.5 Neural mechanisms of cognitive ageing and dementia

The main risk factor for neurodegeneration and cognitive decline is the aging of the brain (Bishop et al., 2010). Through research on animal models, pathways and mechanisms involved in the general ageing process have been explored and have also been related to specific areas of the brain. The following sections will discuss the most recent theories for brain ageing and cognitive decline. As yet, it is still unclear how the role of these pathways contribute to neurological disorders such as dementia (Bishop et al., 2010).

The neurovascular unit is a term which refers to the neurons, glia and supporting vasculature that is involved in the homeostasis and functioning of the cerebral micro environment. In dementia, the neurovascular unit is impaired, and this can occur as a result of disruption to a host of processes that lead to a reduction in neurotransmission and neuronal network activation (McGaugh, 2000). In dementia, cerebral changes are observed which are specific to the dementia subtype. Cerebral changes including atrophy and the presence of protein clumps are seen in the neurodegenerative dementias such as Alzheimer's, Lewy body and fronto-temporal dementia where misfolded protein aggregates such as hyper-phosphorylated tau and amyloid beta accumulate and lead to neuronal cell death (Pievani et al., 2011). Neuronal atrophy has been shown to follow functional networks, as opposed to regions close in proximity to each other, suggesting that atrophy in dementia follows pre-existing neuronal networks (Raj et al., 2012).

Cerebral changes observed in vascular dementia also lead to neuronal atrophy but are thought to occur due to cerebral ischaemia. This is understood to occur as a result from both microvascular and macrovascular disease that leads to poor oxygenation of regions of brain (Jellinger, 2002). These vascular pathologies lead to alterations of the blood-brain

barrier, vascular inflammation, oxidative stress and are all believed to have direct impact on neurons and their supporting cells (Iadecola, 2010).

In mixed forms of dementia, it is thought that the vascular pathologies and toxic protein aggregates act together with additive effect on cognition or that one pathology promotes and exacerbates the other (Iadecola, 2010). Although the exact neuronal mechanism is yet to be fully understood, evidence from animal and imaging studies provides evidence to support the notion that the different pathological pathways all culminate in neural atrophy, which has a direct impact on cognitive decline and impairment.

1.6 Diabetes related dementia and cognitive decline

People with diabetes have a 50% increased risk of developing dementia when compared to the general population (Biessels et al., 2006). For Alzheimer's disease, this relative risk is 1.46 while for vascular dementia this is as much as 2.48 (Cheng et al., 2012). The population attributable risk of Alzheimer's disease for people with diabetes is 2.4%, equating to 826,000 cases of Alzheimer's disease being attributable to diabetes worldwide (Barnes and Yaffe, 2011).

Cognitive impairment, short of dementia, has also been shown to be associated with diabetes (Van den Berg et al., 2009). Moreover, the rate of decline has been found to be worse than that of the general population during normal age related cognitive decline (Yaffe et al., 2012). It has been suggested that an increased risk of dementia in people with diabetes translates in practice to an earlier age of onset of clinically relevant impairment by 2.5 years and the effect of accelerated age-related cognitive decline, short of dementia, exacerbates this by lowering the age of diagnosis, as an additive effect (Biessels et al.,

2014). This is suggestive of two distinct processes occurring with a cumulative effect on the point at which clinically relevant cognitive impairment is diagnosed (Biessels et al., 2014).

Because it is relatively rare for an individual diagnosed with dementia to only have one pure subtype, and that often neurodegenerative processes occur alongside other comorbidities and a background of age related cognitive change (Schneider et al., 2007), it is difficult to elucidate the underlying mechanisms of cognitive decline and dementia in diabetes. Experimental studies using rat models have found that cerebral insulin levels may play a role in Alzheimer-like pathologies (Ho et al., 2004), while clinical studies using autopsy data show that people with diabetes related dementia are more likely to have vascular dementia pathology (Ahtiluoto et al., 2010). It is predicted that diabetes related cognitive decline is likely the result of the cumulative effect of multiple processes including vascular lesions, loss of white matter and general brain atrophy (Biessels et al., 2014).

Diabetes related mechanisms proposed include small vessel disease leading to neuronal ischaemia and white matter lesions and cognitive decline (Pantoni, 2010), microvascular disease which leads to alterations in the blood-brain barrier and cognitive decline (Janelidze et al., 2017) and hyperglycaemia where it is predicted that cerebral blood flow and osmotic effects may play a role in cognitive decline (Sommerfield et al., 2004). It has also been suggested that insulin resistance itself may have a direct effect on cognitive decline. Insulin can cross the blood-brain barrier, where it may compete for binding sites on insulin degrading enzymes present in the brain that also play a role in the clearance of amyloid beta plaques found in Alzheimer's disease (Craft et al., 2013). This state of brain specific insulin resistance, which has been suggested to occur even in the absence of global insulin resistance, has been termed by some as 'type 3 diabetes', indicating that this is a distinct

form of diabetes (de la Monte, 2014). Despite some agreement on this, a general consensus is yet to be reached on the appropriateness of this terminology (Kandimalla et al., 2017).

1.7 Risk factors

1.7.1 Risk factors for cognitive decline in the general population

One issue common to cognitive epidemiology is the notion of reverse causality. This describes the concept that early life intelligence traits can impact on later health outcomes and also cognitive health outcomes. This can have an impact on the interpretation of analyses that look at the associations between risk factors and health outcomes where it is often assumed that as a result of the risk factor, the eventual health outcome is realised (Deary et al., 2009). Gow et al. (2012a), illustrate this when investigating the association between physical activity and cognition in older people; where despite finding an association, it could not be determined whether physical activity predicts cognitive status, or whether cognitive status predicts level of physical activity. Commenting on temporal relationships in observational research in general is problematic, especially in studies that investigate cognitive outcomes, as it may be that a superior cognitive ability in early adulthood directly impacts on healthier lifestyle choices throughout the course of an individual's life, and in turn, may affect later life cognitive health outcomes. In these kinds of studies it is therefore advantageous to investigate, not only cross-sectionally but also longitudinally, where cognitive ability in late life takes into account the previous, childhood or peak cognitive ability. This approach provides support for a temporal relationship between a previous exposure and a later health outcome.

Up to half of cases of Alzheimer's disease are thought to be potentially attributable to modifiable risk factors (such as obesity, physical inactivity, hypertension, depression,

smoking, cognitive inactivity and diabetes), and it is predicted that this figure may be similar for all cause dementia (Barnes and Yaffe, 2011). In terms of cognitive decline, the Lothian Birth Cohort 1936, a general population cohort study of older people in Scotland, found that the main risk factors for declining cognitive ability across a 6 year period included age, male sex, childhood IQ and education level. They also found that general fitness, as measured by a composite of different physical activity measures, was associated with cognitive decline (Ritchie et al., 2016). The Edinburgh Artery Study, identified systemic markers of inflammation to be associated with decline in specific cognitive abilities (Rafnsson et al., 2007b), and also cardiovascular disease including stroke and myocardial infarction to be associated with cognitive decline (Rafnsson et al., 2007a) . Other risk factors for cognitive decline often discussed in the literature include hypertension, hyper lipidaemia, smoking, depression, physical inactivity and obesity (Barnes and Yaffe, 2011, Plassman et al., 2010, Cooper et al., 2015, Beydoun et al., 2008, Anstey et al., 2011, Sofi et al., 2011, Blondell et al., 2014).

1.7.2 Risk factors for cognitive decline in people with diabetes

As people with type 2 diabetes are at increased risk of developing cognitive decline or dementia, a number of key risk factors have been identified in this high risk population. It is now fairly well established that the severity of diabetes in terms of impaired fasting glucose and insulin resistance are associated with increased risk of dementia (Luchsinger, 2008, Cooper et al., 2015). Hypertension and heart disease has also be been identified as a risk factor for cognitive decline and dementia in people with type 2 diabetes (Xu et al., 2004, Cukierman-Yaffe et al., 2009). Depression was found be associated with dementia in people with diabetes by some (Katon et al., 2012); however, others found no association

(Koekkoek et al., 2013). It has been suggested that for depression and cognitive decline in diabetes bidirectional associations may exist (Biessels et al., 2014), for example depression may occur as a result of cognitive symptoms or vice versa.

Elevated levels of systemic inflammatory markers have been identified as potential mediators of cognitive decline and dementia in people with diabetes (Mittal and Katare, 2016). In particular, interleukin 6 (IL-6) and C reactive protein have been found to be associated with type 2 diabetes, whereby increased inflammation leads to insulin resistance (Hotamisligil, 2003). As Alzheimer's disease is associated with insulin resistance, inflammation may be involved in diabetes related cognitive decline.

Obesity has also been suggested to play a role in this inflammatory pathway as obesity is characterised as a chronic state of low level inflammation (Hotamisligil, 2003, Matarese et al., 2016), suggesting that obesity itself may be a key component of diabetes related cognitive impairment. Highlighted as an area of research that is as yet not fully understood, it has been suggested that obesity induced insulin resistance, hypertension, increased systemic inflammation, oxidative stress, and hypercholesterolaemia may all contribute to the association between obesity and cognitive decline in diabetes (Mittal and Katare, 2016). Obesity as a modifiable risk factor for diabetes related cognitive decline warrants further exploration (Biessels et al., 2014).

Similar to obesity, physical activity levels have also been shown to influence levels of systemic inflammation (Edwards and Loprinzi, 2018), which in turn may affect cognitive processes. In the general population, the association between physical activity level and cognitive decline is not clear and some report that any observed protective effect of increased activity may be a result of reverse causation (Sabia et al., 2017), where preclinical dementia in the cohort results in lower physical activity. The effect of physical activity on

cognition in people with diabetes is not well understood. Studies are beginning to emerge that explore this topic which indicate that physical activity may be a protective factor for cognitive decline in this high risk population (Shih et al., 2018). This relatively new area of research provides a potential new avenue for finding alternative modifiable risk factors that may have influence on cognitive decline and dementia in diabetes (Callisaya and Nosaka, 2017).

The risk factors for cognitive impairments in people with diabetes are multifaceted and likely to be inter-related whereby one factor is influenced by another and may be related in varying degrees to either diabetes status or cognitive outcome (Strachan et al., 2011), and it is therefore important to explore possible associations in real world, large scale epidemiological studies that can look at individual as well as combinations of risk factors.

Chapter 2: Aims and Objectives

2.1 Aims

The aim of this thesis was to explore lifestyle-related, modifiable risk factors for cognitive decline and dementia in people with type 2 diabetes, focusing on obesity and physical inactivity and possible mediation of any association between these factors and cognitive outcomes by systemic inflammation. The main analyses aimed to determine whether systemic inflammation and/or obesity were associated with cognitive decline or incident dementia in older people with type 2 diabetes over a follow up period of 10 years and the independence of these associations. Additional analyses aimed to determine the association between physical inactivity and cognitive ability, both measured at the same time point.

To meet these aims, a systematic review of the literature was carried out, presented in chapter 3. Following this, data were used from the Edinburgh Type 2 Diabetes Study, a representative cohort of community-dwelling, older people with type 2 diabetes. Longitudinal risk factor associations for cognitive decline and dementia over 10 years as well as cross-sectional associations as measured at baseline and at year 10 were assessed. The main outcome of interest was general cognitive change between baseline and year 10, which was further explored by the outcome of specific cognitive tests. Other outcomes of interest were incident dementia (recorded over 10 years), prevalent dementia (at year 10) and cognitive ability (measured at baseline and at year 10).

The analysis is presented in the thesis in three main sections in chapter 5. The first section explores the longitudinal association between measures of obesity and cognitive decline, followed by the association between inflammation markers and cognitive decline. The second section explores the association between obesity, inflammation and dementia over time. The final section explores cross-sectional associations between physical inactivity and cognitive decline and dementia.

2.2 Objectives

1. To determine the longitudinal association of specific circulating markers of systemic inflammation with cognitive change and incident dementia over 10 years in older people with type 2 diabetes.

2. To determine the longitudinal association of measures of obesity with cognitive change and incident dementia over 10 years in older people with type 2 diabetes, and to assess the possible role of inflammatory markers in any association .

3. To determine the cross-sectional association between measures of physical inactivity and cognitive change and prevalent dementia in older people with type 2 diabetes.

Chapter 3: A systematic literature review on physical inactivity, sedentary behaviour and obesity as risk factors for cognitive decline in people with type 2 diabetes.

In this chapter, the motivation for investigating the risk factors obesity and physical (in) activity and their association with cognitive dysfunction is explored. This is presented in the form of a systematic literature review of all relevant epidemiological studies carried out to date.

3.1 Background

Several key risk factors have been shown to be associated with cognitive decline and dementia (Middleton and Yaffe, 2009). The association between diabetes and cognitive decline is now fairly well established based on both clinical and epidemiological evidence (Alafuzoff et al., 2009, Feinkohl et al., 2015) as well as experimental research (Bitel et al., 2012). A recent review provided an overview of the main risk factors thought to be associated with diabetes related cognitive impairment, highlighting glycaemic control, cerebral blood flow and inflammation as key contributing factors (Riederer et al., 2017). Another recent narrative review explored the association between modifiable risk factors and diabetes related cognitive decline, in which obesity and low levels of exercise were highlighted as key risk factors for cognitive decline in people with type 2 diabetes (Callisaya and Nosaka, 2017).

To date, a comprehensive systematic literature review exploring the evidence for an association of obesity and physical (in) activity with cognitive decline and cognitive ability in

people with diabetes is lacking. Ideally, such a review would systematically evaluate the published and unpublished evidence linking measures of obesity and/or physical (in) activity with change in cognition, poorer cognitive ability at older age and the development of dementia over time and potentially inform strategies for introducing exercise and diet related health interventions aimed at improving cognitive health. This chapter describes the systematic reviews I undertook as part of my doctoral work, although because of time and resource constraints, I was not able to consider unpublished data or to include independent data extraction by a second reviewer.

3.2 Aim

The aim was to determine whether there is an association of physical activity, sedentary behaviour or obesity with poorer cognitive ability, accelerated age related cognitive decline or the development of dementia in older people, aged 65 or more, with type 2 diabetes.

3.3 Methods

3.3.1 Eligibility criteria

The following inclusion and exclusion criteria were developed in order to best address the review's objectives.

Types of studies

All observational cross-sectional and longitudinal cohort studies investigating physical activity, sedentary time and body weight or size as risk factors associated with cognitive

status, cognitive decline, MCI or dementia in both males and females, aged 65 and over, living in the community with type 2 diabetes were included. Cross-sectional studies were included to capture studies investigating associations of the risk factors of interest with dementia prevalence or cognitive status in a diabetes cohort. Longitudinal studies were included to capture studies investigating associations of the risk factors of interest with dementia incidence or cognitive change in a diabetes cohort. All other observational studies such as case control were excluded. Randomised controlled trials (RCTs) were only included if the trial contained relevant cross-sectional/baseline data on (in) activity levels and cognitive status or the intervention was exercise based and carried out over a period of 1 year or more, with relevant measurement of cognitive status. All other RCTs were excluded.

Types of participants

All adults diagnosed with type 2 diabetes aged 65 and over at baseline and/or follow-up (i.e. when cognitive status was measured) were included. For longitudinal studies, this cut-off was applied because this is when age related cognitive change would likely start to appear. For cross-sectional studies, this cut-off was also applied, as the main interest of this review was to investigate cognitive health in later life. Predictor variables could be measured at any age, as I wanted to capture studies looking at premorbid lifestyle factors and how this affects cognitive outcomes later in life. Community based studies as well as those based in a residential care setting were included.

Studies that did not report a formal cognitive assessment or an assessment for clinical diagnosis of dementia or MCI in line with the Diagnostic and Statistical Manual (DSM) IV or V were excluded. Studies were also excluded if the study population was recruited on the

basis of possible mental health comorbidities (e.g. depression), as these may affect cognitive status or change. If a study was solely recruited on the basis of a specific physical health concern (e.g. heart disease) but included people with diabetes (e.g. as a sub group), the study was included, as were studies investigating other health comorbidities within a main diabetic cohort. If a study contained a mix of participants where only some met the inclusion criteria, it was included only if the publication had sufficient information on the study sub-population meeting the inclusion criteria. No restrictions were placed on ethnicity, region or other demographics relating to the study population.

Report/publication characteristics

All studies published up to and including 2018 were included. The search was limited to human studies. No restrictions were placed on publication status or language and when required, a translation was sought.

3.3.2 Search strategy

An electronic search was carried out on the 11th of January 2018, which was designed to capture all literature that met the eligibility criteria up until this date. The final search terms applied to the Ovid Medline database are shown in Figure 1. Similar searches were carried out on the same day in the databases PsychInfo, Embase, SportDiscuss. Manual searches of reference lists were carried out as were online searches of the journals: American Journal of Epidemiology, PLOS One, The Journal of Diabetes Research, Diabetes Care, Diabetologica, and International Journal of Epidemiology. This was done in order to capture articles that may have been incorrectly indexed or indexed with alternative key words or

spellings. This search was done using the following independent search terms: dementia, cognition, memory and intelligence. These searches of the literature included both journal articles and conference proceedings.

1	exp exercise/ or exp physical endurance/ or physical exertion/ or exp physical fitness/ or physical activity.mp.
2	exp Sedentary Lifestyle/ or posture/ or sedentary.mp.
3	sitting.mp.
4	inactivity.mp.
5	2 or 3 or 4
6	body fat distribution/ or adipose/ or body mass index/ or body weight/ or overweight/ or obesity/ or waist circumference/ or skin fold thickness/ or waist-hip ratio/
7	exp cognition/ or intelligence/ or exp executive function/ or exp memory/ or exp problem solving/ or exp Cognitive Ageing/ or exp cognitive dysfunction/ or exp dementia/ or cognitive decline.mp.
8	1 or 5 or 6
9	7 and 8
10	diabetes mellitus/ or exp diabetes mellitus, type 2/
11	9 and 10
12	limit 11 to (humans and "all adult (19 plus years)")

Figure 1. Search terms for systematic review. Terms applied to Ovid Medline, 11/01/2018. exp; explode term, mp.; multipurpose field.

3.3.3 Selection of studies

All abstracts from electronic searches were downloaded and checked for duplicates. Titles and abstracts were screened for eligibility and only the studies matching the pre-defined selection criteria were shortlisted. Articles meeting the selection criteria were then downloaded and assessed for eligibility by myself. Ideally a second independent researcher would have been consulted to verify if inclusion criteria was met, as per Cochrane guidelines (Higgins, 2011), however for the purposes of my thesis, this was not practical. Studies using the same data sets were linked to prevent duplication of data.

3.3.4 Data extraction and management

Data were extracted from the final studies that matched the eligibility criteria using a data extraction form developed for this review.

All literature searches and publications retrieved were stored using Endnote and saved on secure and frequently backed up servers. The data extraction form was electronic and created on Microsoft Excel.

3.3.5 Risk of bias tool

As no tool exactly meeting the needs of this review could be identified, a modified risk of bias tool, adapted from the Cochrane Tool to Assess Risk of Bias in Cohort Studies (The Cochrane Collaboration, 2012), was used to assess quality of each study that met the eligibility criteria. This quantified how reliable the results reported by the authors were. Two versions of the tool were developed for cross-sectional and longitudinal studies. The cross-sectional version of the modified tool is shown in Figure 2. Additional questions were incorporated for the longitudinal version of the tool which included; “Can we be confident that the outcome of interest was not present at the start of study?”, and “Was the follow-up of cohorts adequate?”, which were scored in a similar way. Maximum scores differ per version where the cross-sectional version is out of 16 and the longitudinal version out of 20. In both versions high scores indicate a low risk of bias and low scores indicate a high risk of bias.

	Checklist item	Score			
		Yes (2)	Likely Yes (1)	Likely No (0)	No (-1)
1	Was the population representative of the local diabetic population?				
2	Can we be confident in the assessment of exposure?				
3	Did the statistical analysis adjust for confounding variables?				
4	Can we be confident in the assessment of diabetes in the cohort?				
5	Was the study blinded?				
6a	How well was cognition measured? I.e. Was a cognitive test battery used?				
6b	Was a general cognitive variable calculated?				
7	Was effect size adequately reported?				

Figure 2. The modified risk of bias tool adapted from The Cochrane Collaboration (2012), used in this review during data extraction.

3.4. Results

3.4.1 Studies identified

The systematic review search returned a total of 617 results which were exported to Endnote. A duplication check was run, which identified 78 duplicates leaving 539 articles which were screened by title and abstract. The systematic selection process is detailed in Figure 3. The title and abstract screening phase identified a further 10 duplicates, 78 review articles, 4 animal studies and 356 not relevant articles. This resulted in 91 articles being identified for full text screening. After examination of the article in full, 8 articles were rejected due to the outcome measure not being relevant, 44 were rejected due to the

predictor not being relevant, 2 were rejected as they were protocols for future studies that had not yet come to completion and 18 were rejected as they were either case control studies or trials where the authors failed to report any baseline analysis on the cohort. This resulted in a total of 23 publications that met the selection criteria. Four papers reported analysis on physical activity, 11 papers reported analysis on obesity and a further 4 reported analysis of both physical activity and obesity.

Of the articles identified, a total of 13 studies provide data on the association between obesity and cognitive ability in people with diabetes, 4 studies provide data on the association between obesity and cognitive decline in people with diabetes, 8 studies provide data on the association between physical activity and cognitive ability in people with diabetes and 1 study provided data on the association between physical activity and cognitive decline in people with diabetes.

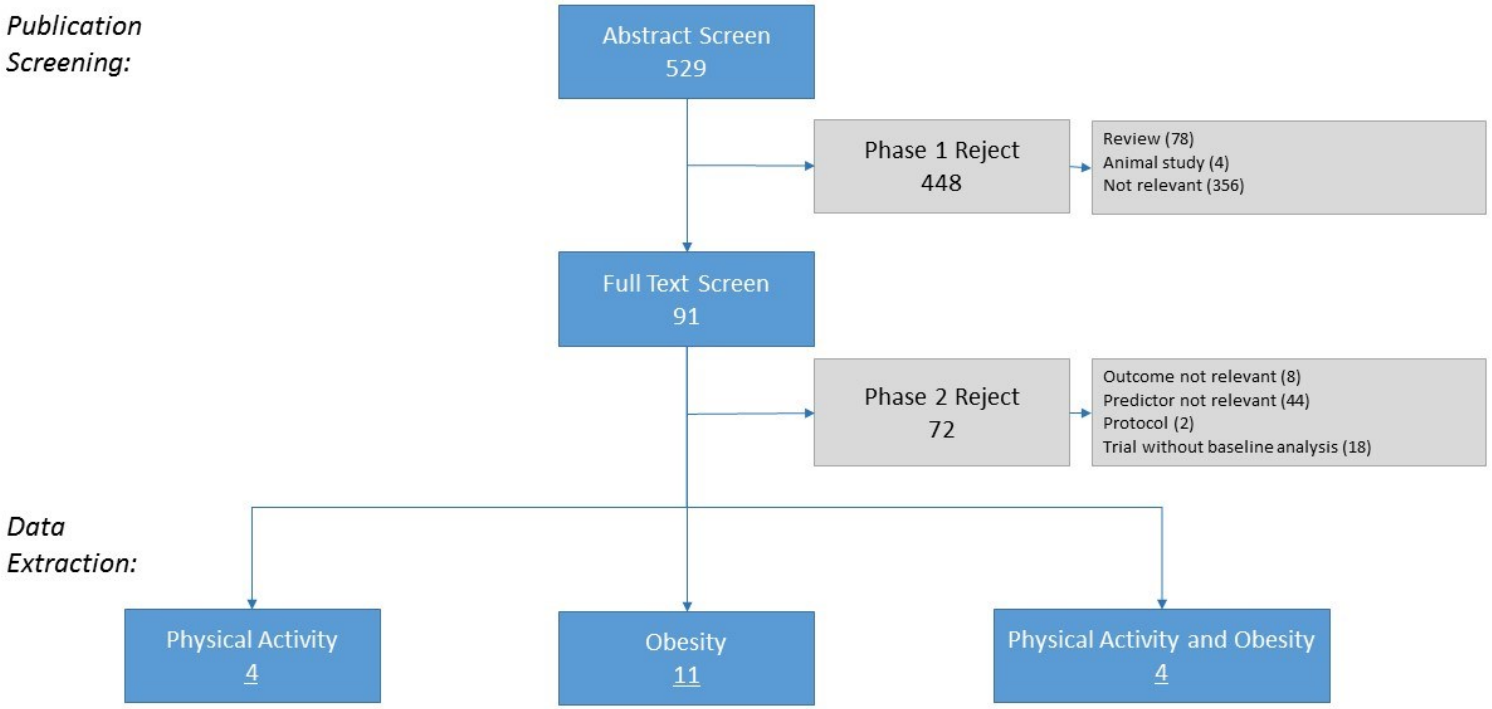

Figure 3. The systematic selection process used to identify publications included in this review after the removal of all duplicates.

3.4.2 Characteristics, risk of bias and findings of studies

Specific characteristics and outcomes of each study are summarised in Tables 1 to 4. Risk of bias is summarised in Table 5. Table 1 summaries the characteristics and results of cross-sectional studies identified by this search strategy exploring the association between obesity and cognitive ability. Table 2 summarises the characteristics and results of longitudinal studies exploring the association between obesity and cognitive decline. Table 3 shows the characteristics and results of cross-sectional studies identified to be exploring the association between physical activity and cognitive ability and Table 4 shows the characteristics and result of the one longitudinal study identified that explored the association between physical activity and cognitive decline. No studies were found that investigated the association between sedentary behaviour and cognitive ability or decline.

Table 1. Studies exploring the cross-sectional association between obesity and cognitive ability

Author	Year	N	Population	Study design	Diabetes criteria	Adjustments	Obesity measure	Cognitive tests	Result§	p-value
Abbatecola et al.	2010	253	Italian hospital outpatients	Cross sectional analysis of a prospective cohort	Glucose tolerance test, 2 weeks self-monitoring of fasting BG	Age, sex, education (years)	BMI	MMSE	not shown	NS
								Composite score: executive function and attention	not shown	NS
							WHR	MMSE	b=-0.240	0.043
								Composite score: executive function and attention	b=-0.238	0.041
							WC	MMSE	b=-0.264	0.041
								Composite score: executive function and attention	b=-0.326	0.013
							Body Fat	MMSE	not shown	NS
								Composite score: executive function and attention	b=-0.272	0.033
West et al.	2016	897	Israeli hospital outpatients, Israel Diabetes and Cognitive Decline Study (IDCD)	Cross sectional	Any of: (1) HbA1c >7.25%, (2) Glucose >200 mg/dl on two examinations more than 3 months apart, (3) purchase of diabetic medication twice within 3 months, (4) diagnosis of	Age, education, BMI, HbA1c, creatinine, LDL, HDL, cholesterol, triglycerides, DBP, SBP, duration of diabetes, anti-diabetic medication, CRP, IL-6, APOE4.	BMI	Factor: all test scores	not shown	NS
								Factor: Similarities/ Letter fluency/ Category fluency	not shown	NS
								Factor: Diamond cancellation/Digits forward/ Digits backward	not shown	NS
								Factor: TMTA/TMTB/ Digit Symbol Substitution/ Constructional praxis	not shown	NS

Author	Year	N	Population	Study design	Diabetes criteria	Adjustments	Obesity measure	Cognitive tests	Result§	p-value
					T2DM (ICD-9 code) by a healthcare professional , supported by HbA1c>6.5% or glucose>125 mg/dl within 6 months			Factor: Immediate and delayed recall/ Recognition	not shown	NS
							WC	Factor: all test scores	r =-0.185 (females); NS (males)	0.003
								Factor: Similarities/ Letter fluency/ Category fluency	r= -0.256 (females), NS (males)	<0.0001
								Factor: Diamond cancellation/Digits forward/ Digits backward	not shown	NS
								Factor: TMTA/TMTB/ Digit Symbol Substitution/ Constructional praxis	r = -0.138 (females); NS (males)	0.026
								Factor: Immediate and delayed recall/ Recognition	not shown	NS
Kim et al.	2008	60	Korean hospital outpatients	Cross sectional	Attending outpatient diabetes clinic at hospital	None	BMI	Elderly verbal learning test	not shown	NS
								Simplified Rey figure test	not shown	NS
								Korean-Boston naming test (short)	not shown	NS
								Digit span forward	not shown	NS
								Digit span backward	not shown	NS
								Choice Reaction Time	not shown	NS

Author	Year	N	Population	Study design	Diabetes criteria	Adjustments	Obesity measure	Cognitive tests	Result§	p-value
								Cognitive Reaction Time	r = 0.23	NS
						None	WC	Elderly verbal learning test	r = -0.23	NS
								Simplified Rey figure test	not shown	NS
								Korean-Boston naming test (short)	not shown	NS
								Digit span forward	r = -0.32	0.01
								Digit span backward	not shown	NS
								Choice Reaction Time	r = 0.29	0.03
								Cognitive Reaction Time	r = 0.27	0.04
						Age, sex, education, HbA1c, HBP medication, HDL, triglycerides	WC	Digit span forward	R^2= 0.11	0.02
								Choice Reaction Time	R^2= 0.08	0.04
								Cognitive Reaction Time	R^2= 0.07	<0.05
Kroes et al.	2012	64	Dutch GP recruited trial participants, Good Intentions Trial	Cross sectional analysis of BL data in an RCT	Medical diagnosis (5 years or more)	sex	BMI (obese (>30 kg/m²) vs non obese (<30 kg/m²)	Utrecht Proactive Coping Competences	F (1,61) =9.17 (ηp^2 = 0.13)	0.004
								Self-efficacy test	not shown	NS
								Brief Self-control Scale	F= 4.65	NS
Greenwood et al.	2003	22	Canadian trial participants	Cross sectional analysis of BL data in an RCT	Presumed medical diagnosis	Age, Triglycerides, Cholesterol, HDL, LDL, BP, Urea, Creatinine,	BMI	Logical Memory	not shown	NS
								TMTB	not shown	NS (presumed)
								Rey Auditory Verbal Learning Test	R^2=0.14	0.029

Author	Year	N	Population	Study design	Diabetes criteria	Adjustments	Obesity measure	Cognitive tests	Result§	p-value
						Fasting Glucose, HbA1c.				
Pearce et al.	2012	44	Australian trial participants, Commonwealth Scientific Industrial Research Organisation (CSIRO)	Cross sectional analysis of BL data in an RCT	HbA1c <9%	Premorbid IQ, education, age, sex, depression, duration of diabetes	BMI	Digit span forward	not shown	NS
								Digit span backward	not shown	NS
								Inspection time	not shown	NS
								Digit Symbol Substitution Test	not shown	NS
								TMTA	not shown	NS
								TMTB	not shown	NS
Valiente-Barroso et al.	2015	59	Spanish hospital out-patients	Cross sectional	Medical diagnosis	Age, sex, education, diabetes type, duration of diabetes, PA, Heart disease, HBP, hypercholesterolemia, depression.	BMI	Stoop Word reading	B= -0.197	<0.05
								Stroop Colour reading	B= -0.217	<0.05
								Stroop Word-colour reading	not shown	NS
								Stroop Interference	not shown	NS
								Digits forward	not shown	NS
								Digits backwards	not shown	NS
								LNS	not shown	NS
								TMTA	not shown	NS
								MMSE	not shown	NS
Lehtisalo et al.	2016	364	Finnish trial participants with diabetes or prediabetes, Diabetes Prevention Study (DPS)	Cross sectional	Glucose tolerance test 5.6- 7.0mmol/l (NB. inclusion criteria does not exclude non-diabetics as originally a prevention study for	Age, education, sex, APOE, smoking, SBP, intervention allocation.	BMI	CERAD	b= -0.23 (95% CI -0.41, -0.04)	0.011
								TMTA	not shown	NS
							WC	CERAD	b= -0.09 (95% CI -0.16, -0.02)	0.012
								TMTA	not shown	NS

Author	Year	N	Population	Study design	Diabetes criteria	Adjustments	Obesity measure	Cognitive tests	Result§	p-value
					prediabetes however cognition study take place after 13 years when 46% are now classed as diabetic)					
Gorska-Ciebiada et al.	2014	276	Polish Hospital outpatients	Cross sectional	Medical diagnosis (1 year or more)	Age, sex, education, marital status, smoking, duration of diabetes, BMI, HbA1c, lipids, diabetes medication, micro/ macrovascular complications, HBP, BP medication, comorbidities (number of), hypoglycaemia	BMI	MoCA	not shown	NS
Rizzo et al.	2010	121	Italian hospital outpatients	Cross sectional	Medical diagnosis (1 year or more)	Age, sex, Medication, PA, MAGE (glucose), SBP, DBP, HbA1c, PPG, BG	BMI	MMSE	B= -0.160	0.004
								Composite score	B= -0.038	NS
							WHR	MMSE	B= -0.083	NS
								Composite score	B= -0.102	NS

Author	Year	N	Population	Study design	Diabetes criteria	Adjustments	Obesity measure	Cognitive tests	Result§	p-value
Espeland et al.	2017	3802	American trial participants (BMI =/> 25 kg/m^2)	Cross sectional analysis of BL data in an RCT, Action for Health in Diabetes (Look AHEAD)	Presumed medical diagnosis	Follow-up time, cognitive testing	BMI	Prevalent MCI/dementia	not shown	NS
Niu et al.	2013	66	Chinese Hospital out patients with MCI	Cross sectional analysis in case control	Medical diagnosis	None reported	BMI	MoCA	not shown	NS
Trento et al.	2015	249	Italian trial participants	Cross sectional analysis of BL and FU data in an RCT	Attending outpatient diabetes clinic	Sex, education, disease duration, medication change, smoking.	BMI	MMSE	not shown	NS

§ All associations are in the direction of higher BMI/WC/WHR/body fat associated with poorer cognition. B; standardised beta (regression analysis), b; unstandardised beta (regression analysis), r; coefficient of correlation (regression analysis), R^2; squared correlation coefficient, F; F value (ANOVA), OR; Odds Ratio (regression analysis), T2DM; Type 2 Diabetes, BMI; Body Mass Index, WHR; Wait to Hip Ratio, WC; Waist Circumference, PA; Physical activity, MMSE; Mini Mental State Exam, MoCA; Montreal Cognitive Assessment, CERAD; Consortium to Establish Registry of Alzheimer's Disease Assessment, TMT; Trail Making Task, LNS; Letter Number Sequencing, MCI; Mild Cognitive Impairment, HbA1c; Glycated haemoglobin, BG; Blood Glucose, BP; Blood Pressure, HBP; Hypertension, SBP; Systolic Blood Pressure, DBP; Diastolic Blood Pressure, LDL; Low Density Lipoprotein, HDL; High Density Lipoprotein, CRP; C Reactive Protein, IL-6; Interleukin 6, APOE 4; Apolipoprotein E 4, MAGE; mean amplitude of glycaemic excursions, PPG; Postprandial glycaemia, RCT; Randomised Controlled Trial, BL; Baseline, FU; Follow-Up, ICD-9; International Classification for Disease 9, NS; Non-significant. It should be noted that p-values are reproduced according to how they were reported in original publications.

Table 2. Studies exploring the longitudinal association between obesity and cognitive decline

Author	Year	N at baseline	Population	Study design	Follow-up (years)	Diabetes criteria	Adjustments	Obesity measure	Cognitive tests	Result§	p-value
Abbatecola et al.	2010	253	Italian hospital outpatients	Prospective cohort with longitudinal data on T2DM	2	Glucose tolerance test, 2 weeks self-monitoring of fasting BG	Age, sex, education years, PA, depression	BMI	MMSE	OR= 0.90 (CI 0.75–1.10)	NS
									Composite score: executive function and attention	b= -0.021 (SE 0.022)	NS
								WHR	MMSE	OR=1.11 (CI 1.01–1.12)	0.04
									Composite score: executive function and attention	b= -2.264 (SE 0.955)	0.042
								WC	MMSE	OR= 1.33 (CI 1.21–2.89)	0.04
									Composite score: executive function and attention	b= -0.020 (SE 0.010	0.02
								Body Fat	MMSE	OR= 1.92 (CI 1.2–3.71)	0.04
									Composite score: executive function and attention	b= -1.085 (SE 0.295)	0.002

Author	Year	N at baseline	Population	Study design	Follow-up (years)	Diabetes criteria	Adjustments	Obesity measure	Cognitive tests	Result§	p-value
Hu et al.	2012	44660	American hospital outpatients	Prospective cohort	10	Presumed medical diagnosis	Age, sex, smoking, income, SBP, diabetes type, duration of diabetes, HbA1c, LDL, triglycerides, eGFR, HBP medication, diabetic medication, cholesterol medication.	BMI	Incident dementia diagnosis	HR = 0.94 (0.91-0.96)	<0.001
Herghelegiu et al.	2016	360	Romanian geriatric/ gerontology inpatients	Prospective cohort	1.5	Medical diagnosis	Age, sex, education, duration of diabetes, HBP, dyslipidaemia, smoking, alcohol, microvascular diabetic complications	BMI	CDT	b= -0.53 (-1.03- -0.04)	<0.05
									MMSE	not shown	NS
Trento et al.	2015	249	Italian hospital outpatients	Prospective cohort	8	Attending outpatient diabetes clinic	Sex, education, disease duration, medication change, smoking, HbA1c.	BMI	MMSE	not shown	NS

§ All associations are in the direction of higher BMI/WC/WHR/body fat associated with poorer cognition. B; standardised beta (regression analysis), b; unstandardised beta (regression analysis), r; coefficient of correlation (regression analysis), F; F value (ANOVA), OR; Odds Ratio (regression analysis), HR; Hazard Ratio, T2DM; Type 2 Diabetes, BMI; Body Mass Index, WHR; Wait to Hip Ratio, WC; Waist Circumference, PA; Physical activity, MMSE; Mini Mental State Exam, CDT; Clock Drawing Test, HbA1c; Glycated haemoglobin, BP; Blood Pressure, HBP; Hypertension, SBP; Systolic Blood Pressure , LDL; Low Density Lipoprotein, HDL; eGRF; Estimated Glomerular Filtration Rate, NS; Non-significant. It should be noted that p-values are reproduced according to how they were reported in original publications.

Table 3. Studies exploring the cross-sectional association between physical activity and cognitive ability

Author	Year	N	Population	Study design	Diabetes criteria	Adjustments	Physical activity measure	Cognitive tests	Result§	p-value
Devore et al.	2009	1550	American female nurses	Cross sectional	Self-report (validated by medical records check of a sample)	Age, education, use of antidepressants, alcohol, smoking, duration of diabetes, diabetic medication, BMI, BP, cholesterol, MI, coronary bypass , TIA, carotid surgery, heart failure, osteoarthritis, emphysema, chronic bronchitis, fatigue, balance problems, body pain, limited walking ability.	LTPA questionnaire	TICS (Telephone interview for Cognitive Status)	Mean difference of tertiles 0.37 standard units, 95%CI (0.02, 0.72)	0.03
								Global (East Boston Memory Test; immediate and delayed, category fluency, TICS 10 word list immediate and delayed recalls, digit span backwards)	Mean difference of tertiles 0.07 standard units, 95%CI (-0.01, 0.15)	NS
								Verbal memory (East Boston Memory Test immediate and delayed recalls, TICS 10 word list immediate and delayed recalls)	Mean difference of tertiles 0.06 standard units, 95%CI (-0.03, 0.15)	NS
Ferreira et al.	2014	50	Brazilian National Health Service users	Cross sectional analysis of diabetic group in case control study	Medical records and fasting BG (>200 mg/dL)	Not reported	TUG	MMSE	not shown	0.037
Valiente-Barroso et al.	2015	59	Spanish hospital out-patients	Cross-sectional	Medical diagnosis	Age, sex, education, diabetes type, duration of diabetes, BMI, heart disease, HBP,	Exercise Questionnaire	Word reading	B= 0.346	<0.01
								Colour reading	B= 0.311	<0.01
								Word-colour reading	B= 0.305	<0.01

Author	Year	N	Population	Study design	Diabetes criteria	Adjustments	Physical activity measure	Cognitive tests	Result§	p-value
						hypercholesterolemia, depression.		Interference	NS	NS
								Digits forward	B= 0.367	<0.001
								Inverse backwards	B= 0.394	<0.001
								LNS	B= 0.330	<0.001
								TMTA	B= 0.274	<0.01
								MMSE	B= 0.400	<0.01
Lehtisalo et al.	2016	364	Finnish trial participants with diabetes or prediabetes, Diabetes Prevention Study (DPS)	Cross sectional cognition sub-study of RCT	Glucose tolerance test 5.6-7.0mmol/l (NB. inclusion criteria does not exclude non- diabetics as originally a prevention study for people with prediabetes however cognition study take place after 13 years when 46% are now classed as diabetic)	Age, education, sex, APOE4, smoking, SBP, intervention allocation.	KIHD questionnaire on LTPA (mean hrs/week)	CERAD	b= 0.26 (-0.05- 0.57)	0.04
								TMTA	not shown	NS

Author	Year	N	Population	Study design	Diabetes criteria	Adjustments	Physical activity measure	Cognitive tests	Result§	p-value
Gorska-Ciebiada et al.	2014	276	Polish Hospital outpatients	Cross sectional	Medical diagnosis (1 year or more)	Age, sex, education, marital status, smoking, duration of diabetes, BMI, HbA1c, lipids, diabetes medication, micro/ macrovascular complications, HBP, HBP medication, comorbidities (number of), hypoglycaemia.	Lack of physical activity question	MoCA	not shown	NS
Rizzo et al.	2010	121	Italian hospital outpatients	Cross sectional	Medical diagnosis (1 year or more)	Age, sex, Medication, PA, MAGE (glucose), SBP, DBP, HbA1c, PPG, BG	LTPA questionnaire	MMSE	not shown	NS
								Composite score	not shown	NS
King et al.	2010	463	American hospital outpatients	Cross sectional analysis of RCT	Medical diagnosis (1 year or more)	Sex, ethnicity, age, health literacy, self-efficacy for exercise, health care support level	CHAMPS	Positive Transfer of Past Experience from the Diabetes Problem-Solving Scale of Hill Briggs	not shown	NS
Rucker	2014	40	American peripheral neuropathy outpatients	Cross-sectional (Main analysis for thesis)	Medical diagnosis	Not reported	LLFDI Frequency	Keep Track	not shown	NS
								N-back	not shown	NS
								TMTA	not shown	NS
								Local Global	not shown	NS
								Stroop	not shown	NS
								Hayling	not shown	NS
								Rey Osterrieth Copy	not shown	NS
								Rey Osterrieth Recall	r= 0.32	0.04

Author	Year	N	Population	Study design	Diabetes criteria	Adjustments	Physical activity measure	Cognitive tests	Result§	p-value
								Wechler Immediate	not shown	NS
								Wechler Delayed	not shown	NS

§ All associations are in the direction of lower physical activity associated with poorer cognition. B; standardised beta (regression analysis), b; unstandardised beta (regression analysis), r; coefficient of correlation (regression analysis), F; F value (ANOVA), OR; Odds Ratio (regression analysis), BMI; Body Mass Index, LTPA; Leisure Time Physical activity, CHAMPS; Community Healthy Activities Model Program for Seniors questionnaire, MMSE; Mini Mental State Exam, TICS; Telephone Interview for Cognitive Status, MoCA; Montreal Cognitive Assessment, CERAD; Consortium to Establish Registry of Alzheimer's Disease Assessment, TMT; Trail Making Task, LNS; Letter Number Sequencing, HbA1c; Glycated haemoglobin, BG; Blood Glucose, BP; Blood Pressure, HBP; Hypertension, SBP; Systolic Blood Pressure, DBP; Diastolic Blood Pressure, APOE 4; Apolipoprotein E 4, MAGE; mean amplitude of glycaemic excursions, PPG; Postprandial glycaemia, MI; Myocardial Infarction, TIA; Transient Ischaemic Attack, RCT; Randomised Controlled Trial, TUG; Timed Up and Go Test, LLFDI; Late Life Function and Disability Index, KIHD; Kuopio Ischemic Heart Disease questionnaire, NS; Non-significant. It should be noted that p-values are reproduced according to how they were reported in original publications.

Table 4. Studies exploring the longitudinal association between physical activity and cognitive decline

Author	Year	N at baseline	Population	Study design	Follow-up (years)	Diabetes criteria	Adjustments in model	Physical activity measure	Cognitive tests	Result§	p-value
Devore et al.	2009	1550	American female nurses	Prospective cohort	2	Self-report (validated by medical records check of a sample)	Age, education, antidepressants, alcohol, smoking, duration of diabetes, diabetic medication, BMI, BP, cholesterol, MI, coronary bypass, TIA, carotid surgery, heart failure, osteoarthritis, emphysema, chronic bronchitis, fatigue, balance problems, body pain, limited walking ability.	LTPA	TICS (Telephone interview for Cognitive Status)	Mean difference of tertiles 0.21 standard units, 95%CI (-0.15, 0.57)	NS
								LTPA	Global (East Boston Memory Test; immediate and delayed, category fluency, TICS 10 word list immediate and delayed recalls, digit span backwards)	Mean difference of tertiles 0.05 standard units, 95%CI (-0.03, 0.12)	NS
								LTPA	Verbal memory (East Boston Memory Test immediate and delayed recalls, TICS 10 word list immediate and delayed recalls)	Mean difference of tertiles 0.07 standard units, 95%CI (-0.03, 0.16)	NS

§ All associations are in the direction of lower physical activity associated with poorer cognition. B; standardised beta (regression analysis), r; coefficient of correlation (regression analysis), F; F value (ANOVA), OR, Odds Ratio (regression analysis), BMI; Body Mass Index, LTPA; Leisure Time Physical activity questionnaire, BP; Blood Pressure, MI; Myocardial Infarction, TIA; Transient Ischaemic Attack, TICS; Telephone Interview for Cognitive Status, NS; Non-significant. It should be noted that p-values are reproduced according to how they were reported in original publications.

Table 5. (a) Risk of bias in reporting in the cross -sectional studies

Study	**Year**	**1**	**2**	**3**	**4**	**5**	**6a**	**6b**	**7**	**TOTAL**
Abbatecola et al.	2010	1	2	1	2	1	1	1	1	10
Espeland et al.	2017	-1	2	0	2	1	1	0	1	6
Greenwood et al.	2003	0	2	2	2	1	1	0	1	9
Kim et al.	2008	2	2	2	2	0	2	1	0	11
Kroes et al.	2012	2	2	2	2	0	1	0	1	10
Niu et al.	2013	-1	2	-1	2	0	0	0	0	2
Pearce et al.	2012	1	2	1	2	0	1	0	1	8
Trento et al.	2015	1	2	1	2	0	0	0	1	7
West et al.	2016	2	2	2	2	0	2	1	0	11
Devore et al.	2009	1	2	1	1	0	2	1	1	9
Ferreira et al.	2014	2	2	-1	2	0	0	0	0	5
King et al.	2010	1	2	1	1	0	0	0	0	5
Rucker	2014	0	2	-1	1	0	2	0	0	4
Gorska-Ciebiada et al.	2014	2	1	2	2	0	0	0	0	7
Lehtisalo et al.	2016	1	2	1	2	0	2	1	1	10
Rizzo et al.	2010	2	1	1	2	0	1	1	0	8
Valiente-Barroso et al.	2015	2	1	1	1	0	2	0	0	7

1 Was the population representative of the local diabetic population?
2 Can we be confident in the assessment of exposure?
3 Did the statistical analysis adjust for confounding variables?
4 Can we be confident in the assessment of diabetes in the cohort?
5 Was the study blinded?
6a How well was cognition measured? I.e. Was a cognitive test battery used?
6b Was a general cognitive variable calculated?
7 Was effect size adequately reported?
Values are scaled; 2, yes; 1, probably yes; 0, probably no; -1, definitely no. Total score is out of 16.

Table 5. (b) Risk of bias in reporting in the longitudinal studies

Study	Year	1	2	3	4	5	6	7a	7b	8	9	TOTAL
Abbatecola et al.	2010	1	2	1	1	2	1	1	1	2	1	13
Herghelegiu et al.	2016	-1	2	2	1	2	0	0	0	2	2	10
Hu et al.	2012	2	2	1	1	1	0	2	1	2	1	13
Trento et al.	2015	1	2	1	1	2	0	0	0	0	1	8
Devore et al.	2009	1	2	1	1	1	0	2	1	2	1	12

1 Was the population representative of the local diabetic population?
2 Can we be confident in the assessment of exposure?
3 Can we be confident that the outcome of interest was not present at the start of study?
4 Did the statistical analysis adjust for confounding variables?
5 Can we be confident in the assessment of diabetes?
6 Was the study blinded?
7a How well was cognition measured? I.e. Was a cognitive test battery used?
7b Was a general cognitive variable calculated?
8 Was effect size adequately reported?
9 Was the follow-up of cohorts adequate?
Values are scaled; 2, yes; 1, probably yes; 0, probably no; -1, definitely no. Total score is out of 20.

Characteristics of studies

The studies included were mostly observational cohort studies, recruiting from hospital clinics from all over the world. A number were studies that reported baseline cross-sectional data from a randomised controlled trial. Most studies report cross-sectional analyses, however a number also report analysis on longitudinal data. Of these studies the majority were analyses using prospective cohorts. There was a wide range of sample sizes, ranging from 22 (Greenwood et al., 2003) to 44660 (Hu et al., 2012). Predictor variables varied with BMI being the most common measure of obesity and physical activity measured by some form of questionnaire based assessment. Outcome variables also varied with a large proportion of studies measuring cognitive ability using the MMSE. The majority of studies made effort to make adjustments to their models for age and sex, and some adjusted further to include vascular and diabetes covariates. Some studies did not make any adjustments to their models.

Risk of Bias

Most studies were selected from the local diabetic population, with a number of studies using trial participants or making no mention of how or if a random sample was used. All studies used validated obesity measures and most used validated physical activity measures, with the exception of a few who made no mention or created their own measure of physical activity (Gorska-Ciebiada et al., 2014, Valiente-Barroso et al., 2015). The majority of longitudinal studies had specific exclusion criteria that ensured cognitive impairment or dementia was not present at baseline, however one study actively recruited people with MCI (Niu et al., 2013) and some failed to mention what steps had been taken. Most studies made basic adjustments in their statistical models while some did not adjust

or made no mention (Ferreira et al., 2014, Niu et al., 2013, Rucker, 2014). Many of the studies fully adjusted for many covariates in their statistical models. All studies made appropriate efforts to ensure that the population had diabetes. Few of the studies mentioned blinding and a relatively small number of studies used a comprehensive cognitive test battery to assess cognitive status, some opting to use a dementia screening tool. This in turn limited the number of studies that used a general cognition variable (for example derived though principal component analysis (PCA)) to determine overall cognitive ability. Longitudinal studies had a range of follow-up time with some studies having as much as 10 years and some at little as 18 months.

3.4.2.1 Findings: Obesity and cognitive ability

Of 13 studies that explored the association between obesity and cognitive ability, all 13 measured obesity using BMI, 4 also measured waist circumference (WC), 2 measured waist hip ratio (WHR) and 1 measured body fat. A variety of cognitive tests were used to assess cognitive ability in different cognitive domains and also to measure general cognitive function.

BMI and cognitive ability

Five studies showed an association between increased BMI and poorer cognitive ability as measured by at least one of a number of cognitive tests and 8 studies showed no association. Between these studies there was little difference in risk of bias scoring (range 2 to 11 out of maximum score of 16), though some studies had limited sample size (e.g. (Greenwood et al., 2003, Pearce et al., 2012)). Greenwood et al. (2003) showed an

association between increased BMI and poorer cognitive ability when using the Rey Auditory Verbal Learning test ($p=0.03$), in 22 men and women from a Canadian trial of the effect of diet on cognitive performance. A similar result was seen by Valiente-Barroso et al. (2015) who showed an association between increased BMI and poorer cognitive ability as measured by both the Stroop Word and Colour reading tasks (both $p<0.05$), in 59 male and female Spanish outpatients. Lehtisalo et al. (2016) showed an association between increased BMI and poorer cognitive ability, as measured by the Consortium to Establish Registry of Alzheimer's (CERAD) test battery ($p=0.01$), in 364 men and women enrolled in the Finnish Diabetes Prevention Study. Rizzo et al. (2010) also showed an association between increased BMI and poorer cognitive ability, as measured by the MMSE ($p<0.01$), in 121 Italian male and female outpatients. Lastly, Kroese et al. (2013) showed an association between increased BMI and poorer cognitive status ($p=0.004$), as measured by a subtest of the Utrecht Proactive Coping Competence Scale, in 64 men and women enrolled in the Dutch Good Intentions trial. Kroese et al. (2013) reported that they used this test as a way to measure cognitive status, however this test is not a conventional way to measure cognition. After deliberation, the article was included in the results because proactive coping, defined as anticipating and understanding a future negative event, may be considered a quantifiable cognitive task (Tielemans et al., 2014), as cognitive processes such as problem solving and executive functioning are likely to be involved in this. Furthermore, this study, despite having a small sample size, scored well in the risk of bias assessment.

Despite these significant associations between BMI and cognitive ability, 8 studies found no statistically significant BMI-cognitive ability association and 3 found mixed results depending on the cognitive test battery used. The majority of these studies finding non-significant and/or inconsistent results scored equally highly on the risk of bias assessment.

Waist circumference (WC) and cognitive ability

All 4 studies which used WC as a measure of obesity showed an association between increased WC and poorer cognitive ability as measured by at least one of a number of cognitive tests. Between these studies there was little difference in risk of bias scoring (range 10 to 11 out of a maximum of 16), though one study had small sample size (Kim et al., 2008) compared to that of the others. West et al. (2016) showed an association between increased WC and lower cognitive ability ($p=0.003$) in women but not in men, as measured by a factor score derived from a number of cognitive tests capturing multiple cognitive domains, in 897 participants in the Israel Diabetes and Cognitive Decline Study. Abbatecola et al. (2010), showed an association between increased WC and poorer cognitive ability ($p=0.013$) when using a composite score of multiple cognitive tests as well as when using the MMSE dementia screen ($p=0.041$), in 253 male and female Italian outpatients. Similarly, Lehtisalo et al. (2016) showed an association between increased WC and poorer cognitive ability ($p=0.012$), in 364 men and women enrolled in the Finnish Diabetes Prevention Study, as measured by the CERAD test battery and Kim et al. (2008) showed an association between increased WC and poorer cognitive ability when using the Digit span forward, Choice Reaction Time and Cognitive Reaction time tests (all $p<0.05$), in both unadjusted and fully adjusted models of Korean male and female outpatients. It should be noted that 3 out of the 4 studies exploring the associations between WC and cognition also found non-significant associations when employing different cognitive tests to measure cognitive ability, namely TMTA and Digits span tests were shown to be non-significantly associated with the predictor WC (Lehtisalo et al., 2016, West et al., 2016, Kim

et al., 2008). All of the studies exploring the association between WC and cognitive ability scored highly on the risk of bias assessment.

WHR and cognitive ability

One study showed an association between increased WHR and poorer cognitive ability as measured by at least one of a number of cognitive tests and 1 study showed no association. Both studies scored similarly in the risk of bias assessment (8 and 10 out of a maximum of 16), with one (Abbatecola et al., 2010) having a slightly larger sample size. In the latter study, Abbatecola et al. (2010) showed an association between WHR and cognitive ability in both a general cognitive ability composite score and the MMSE (both p=0.04), in 253 male and female Italian outpatients. In contrast to this, Rizzo et al. (2010) in a similar study did not find a statistically significant association between WHR and either their general cognitive ability composite score or MMSE, in 121 Italian male and female outpatients.

Body fat and cognitive ability

Only 1 study showed an association between increased body fat and poorer cognitive ability, as measured by at least one of the cognitive tests and this study scored relatively highly in the risk of bias assessment (10 out of 16). No other studies were identified that explored this association. Abbatecola et al. (2010), found an association between increased body fat and poorer cognitive ability as measured by their general cognitive ability composite score (p=0.033), in 253 male and female Italian outpatients. However they did not find an association between body fat and cognitive ability as measured by the MMSE.

3.4.2.2 Findings: Obesity and cognitive decline

Of 4 studies that explored the association between obesity measures and cognitive decline, all four measured obesity using BMI, and 1 study used BMI alongside WHR, WC and body fat to measure obesity.

Two studies showed an association between increased BMI and cognitive decline as measured by at least one of a number of cognitive tests and 2 studies showed no association. Between these studies there was some difference in risk of bias scores (range 8 to 13 out of a maximum of 20) and all studies had reasonable sample sizes. Herghelegiu et al. (2016) showed an association between increased BMI and a decline in ability in completing the clock drawing test ($p<0.05$) in 360 Romanian male and female geriatric/ gerontology inpatients over an 18 month follow-up period. Hu et al. (2012) measured cognitive decline by recording dementia diagnoses and found a positive association between BMI and incident dementia diagnosis ($p<0.001$), in a cohort of 44660 American male and female outpatients, over a 10 year follow-up period. In contrast to these results, Abbatecola et al. (2010) and Trento et al. (2015), both found there to be no statistically significant association between BMI and cognitive decline in different studies (n=253 and n=249, respectively) on male and female Italian outpatients. In assessing cognitive decline, both authors used MMSE as an indication of cognitive ability and, in addition, Abbatecola et al. (2010) also used a composite score of the results of cognitive tests measuring executive functioning and attention. This non-significant association between BMI and decline in MMSE score was also found by Herghelegiu et al. (2016). Of these studies, Abbatecola et al. (2010) and Hu et al. (2012) both scored highly in the risk of bias assessment, in contrast to the studies by Herghelegiu et al. (2016) and Trento et al. (2015) who both scored lower on the assessment. It should be noted that the paper by Abbatecola et al. (2010), contained

an error in the reporting of their results, and after contacting the authors and journal I was provided with comment on the issue and correct data were provided, which is reported in the results table in this thesis chapter.

Only 1 study was identified that explored the association between WHR, WC and body fat and cognitive decline in 253 Italian men and women (Abbatecola et al., 2010). This study scored relatively high on the risk of bias assessment (13 out of 20) and showed an association between increased WHR and cognitive decline in both the MMSE and composite score (both p=0.04), an association between increased WC and cognitive decline in both the MMSE and composite score (p=0.04 and p=0.02, respectively) and also an association between increased body fat and cognitive decline in both the MMSE and composite score (p=0.04 and p=0.002, respectively). No other studies were identified that measured obesity using WHR, WC or body fat in people with type 2 diabetes.

3.4.2.3 Findings: Physical activity and cognitive ability

Six studies showed an association between lower physical activity and poorer cognitive ability as measured by at least one of a number of cognitive tests and 3 studies showed no association. Between these studies there was a range of scores in the risk of bias assessment outcome (3 to 10 out of a maximum of 16), and some studies had very small sample sizes. Devore et al. (2009) scoring relatively highly on the risk of bias assessment, showed an association between lower leisure time physical activity level and poorer cognitive ability as measured by the Telephone Interview for Cognitive Status (TICS), a screening tool for dementia (p=0.03), in 1550 American female nurses. Valiente-Barroso et al. (2015) also showed an association between lower score on their exercise questionnaire and lower MMSE score (p<0.01), along with the rest of their test battery (all p<0.01) in a

Spanish cohort of male and female outpatients. Rucker (2014), showed an association between physical activity as measured by the Late Life Function and Disability Index (LLFDI) and the Rey Osterrieth Recall test (p=0.04), in a different group of 40 American outpatients. All of these studies scored considerably lower on the risk of bias assessment, compared to Devore et al. (2009).

Despite these statistically significant associations, 5 of these authors had mixed results where some analyses were significant while others were not depending on the predictor or outcome variables used, and a further 3 found no associations between physical activity and cognitive ability in any of their analyses. These studies also had wide range of scores on the risk of bias assessment, suggesting that not all findings are equally reliable.

3.4.2.4 Findings: Physical activity and cognitive decline

Only one study, by Devore et al. (2009), was identified that looked at the effect of physical activity on cognitive decline in people with type 2 diabetes. This study scored 12 out of 20 in the risk of bias assessment and had a large sample size, although only of women. No statistically significant association was found between leisure time physical activity level (LTPA) and cognitive decline in a cohort of 1550 American female nurses with type 2 diabetes. The authors used three different cognitive test batteries to assess cognitive ability, namely the Telephone Interview for Cognitive Status (TICS), a verbal memory battery that included the East Boston Memory Test immediate and delayed recalls and the immediate and delayed recall word lists of the TICS, and a global cognitive functioning score that included the immediate and delayed recalls and category fluency of the East Boston Memory Test and the immediate and delayed word lists and digit span backwards from the

TICS. There was no statistically significant association between LTPA and any of the 3 test batteries, TICS, verbal memory and global scores, over a period of 2 year follow-up.

It should be noted that no studies were identified that investigated the effect of sedentary behaviour or sitting on cognitive decline.

3.5. Discussion

In general, findings from studies exploring the association between obesity and cognitive ability and/or decline in people with type 2 diabetes were inconsistent. Although some studies did find a statistically significant association between increased BMI and poorer cognition cross-sectionally in people with type 2 diabetes, a majority of studies failed to show any association, or had inconsistent results depending on which cognitive test was used to assess cognition. Similarly inconsistent results were found for studies investigating BMI and cognitive decline over time. Only a limited number of studies were identified that explored the association between other obesity measures such as WC, WHR and body fat and cognitive ability and/or decline in people with type 2 diabetes. Generally, these studies were more consistent in suggesting an association between these measures and cognitive ability, although there was still a reasonable degree of variability in findings between studies. For example, the two studies which explored the association between WHR and cognitive ability had opposing results, despite relatively similarly methodology and study populations. Only one study explored the association between obesity measures other than BMI and cognitive decline longitudinally. This study found that an increased WHR, WC and body fat were associated with cognitive decline.

Overall, given that there are so few studies, with a range of different obesity and cognitive measures used, it is difficult to assess the likelihood of a true association between obesity

and cognitive deficits and further work is needed before any firm conclusions on any such association can be drawn.

The outcomes of studies exploring the association between physical activity level and cognitive ability and/or decline in people with type 2 diabetes were also mixed. Some associations were found by authors exploring associations of physical activity level with cognitive ability however most authors found mixed results when using different cognitive measures. No association was found between physical activity level and cognitive decline longitudinally, however as only one study explored this association, more work is needed to confirm this finding. It should also be noted that no studies were identified that investigated the effect of sedentary behaviour or sitting on cognitive ability or cognitive decline over time.

3.5.1 Notable features of the studies

A notable feature of all studies is that the cognitive test batteries used were all very different and also that many studies only measured cognition with one test. When only relying on one cognitive test to reflect an individual's general cognitive ability, this test needs to have been shown to correlate highly with general cognition, often by indicating that it has a high factor loading onto a latent cognitive variable (Spearman, 1904). Such tests include trail making tasks, digit symbol coding and letter number sequencing which a number of authors included in this review have used. However, others failed to use tests commonly known to contribute to general cognition and a number of studies failed to justify their selection of cognitive test (Herghelegiu et al., 2016, King et al., 2010, Rizzo et al., 2010, Trento et al., 2015).

Another notable feature was that the number and type of adjustments made in each cognitive model were different for each study. The majority adjusted for age and sex amongst others, however some made no mention of adjustments (Ferreira et al., 2014, Kim et al., 2008, Niu et al., 2013, Rucker, 2014). This impacts the ability to compare results across different studies with confidence.

In general, the vast majority of studies exploring associations between obesity and cognitive ability or decline used only BMI as their measure of obesity and other measures such as WHR and WC were neglected. This observation is of particular importance as the one study that was of relatively high quality, and also explored the association of multiple obesity variables found that it was WHR, WC and body fat that were significantly associated with cognitive decline, as opposed to BMI, where no association was found (Abbatecola et al., 2010). These results should be further explored as they indicate that all these different measures of obesity may not be measuring the same phenotype.

One study also used a population of patients with MCI with diabetes, and explored the association between BMI and cognitive ability in this group (Niu et al., 2013). This study showed a non-significant result, which should be interpreted with caution as the cognitive ability range in this group is very limited, if they all have MCI or pre-dementia, and so it is not surprising that no significant associations were found.

Caution should also be exercised when interpreting the result from the study exploring the association of BMI and WC on cognitive ability in people with diabetes and prediabetes (Lehtisalo et al., 2016). This study initially recruited people with prediabetes, while data collection took place 13 years after initial recruitment with 46% of the population at this stage formally diagnosed with diabetes. Although no subgroup analysis was carried out on the people with confirmed diabetes, the study was included in the final results table. The

reason for inclusion was that as this population did have blood glucose impairments, albeit mild (5.6-7.0mmol/l), it could be argued that any associations found in this population would likely be exacerbated in a fully diabetic population.

Caution should also be taken when interpreting the results presented by studies with very small numbers of study participants. One study included in this review only had 22 participants (Greenwood et al., 2003), which is problematic when considering the role of chance. This was a cross-sectional analysis of the baseline characteristics of participants who were involved in an RCT which gave information on the association between physical activity and cognitive ability. In order to find variation in a sample, where the effect size is likely to be small, the number of participants needs to be large enough to be able to identify if any differences are statistically significant and likely not due to random variation or chance alone (Hackshaw, 2008). The study by Greenwood et al. (2003), was included in this review despite its small sample size after some consideration. The review set out to identify all studies that investigated activity or obesity related risk factors on cognition and for completeness this study was identified though the search strategy, as small sample size was not part of the exclusion criteria. Furthermore, by including this study, it was highlighted that there were not many publications on this specific risk factor and outcome in people with diabetes and showed that of those identified an even more limited number were of a robust sample size to be useful, placing the results of others in some form of context. Nonetheless, the results presented by these authors should be interpreted with care.

3.5.2 Strengths and limitations of this review

The search strategy used in this review was developed to capture all studies that investigated the role of obesity and physical activity measures on cognitive outcomes. Despite efforts made to include a variety of search terms and the use of MeSH terms when possible, studies may have been missed due to multiple or incorrect spellings or other phrasings of terminology used by authors. It should also be noted that not all possible cognitive outcomes, specifically the names of individual cognitive tests, were entered as search terms. The latter may have improved the sensitivity of the search but was not done due to the vast numbers of possible cognitive tests in existence, which made developing this sort of comprehensive search impractical. Another limitation of the search strategy may have been the use of "dementia" as an umbrella term instead of the different dementia sub-types such as Alzheimer's disease, vascular dementia and others, as authors may have used these more specific terms. A variety of databases were searched along with hand searching of selected journals, in the hope of finding additional articles to those retrieved by the principal Medline database search. Although the majority of relevant studies will be identified though Medline and other search methods, articles that are unpublished or only internally published, are incorrectly indexed, or where the abstract is not translated to English would be missed by this search strategy.

The main conclusion of this review is that there appears to be a general lack of studies that explore obesity and physical activity as risk factors for cognitive decline in people with diabetes, demonstrating that this topic is under-researched and that further work is needed before any robust conclusions can be drawn. Similarly, the observation that no results were found on the association between sedentary behaviour and cognitive ability or change in cognitive ability in people with type 2 diabetes was surprising. This indicates that either the

search strategy (despite employing search terms such as “sitting” and “sedentary”) may not have been sufficient to capture all possible studies on this topic or that there is a lack of research in this area.

When comparing the results of the individual studies identified by this review, the main observation is that the lack in comparable methodology makes carrying out a meta-analysis impossible. The studies all measured their outcome of cognitive ability or change in cognitive ability in different ways. A relatively large number used the MMSE test as one outcome, but as this is only a dementia screen and not a comprehensive test of cognitive ability, meta-analysis on this selected outcome would not necessarily be helpful in addressing the aims of this review. Two studies used dementia diagnosis as a cognitive outcome. Caution must be taken when interpreting these results grouped with results of other cognitive outcomes because cognitive decline occurs as part of the natural aging process, while dementia is a clinical disease state and the two definitions of cognitive impairment need not capture the same outcome. In this review, if the study design was longitudinal, dementia as an outcome was grouped with other studies of cognitive decline, and if the study design was cross-sectional, dementia as an outcome was grouped with other studies of cognitive status.

Physical activity was also measured in many different ways by the studies identified, and so a need for comparable physical activity measures to be adopted by authors is also highlighted by this review. For the purposes of this review, the data extraction was carried out by one researcher, which can lead to biases in reporting and selection of results. Having a second independent researcher carry out parallel data extraction would have helped to address this problem and would have improved the overall quality of this review.

3.5.3 Future research

The field of diabetes-related cognitive decline in terms of the modifiable risk factors obesity and physical activity, is under-researched. In general, more high-quality, longitudinal studies are needed to address whether associations exist or not. More specifically, future research needs to focus on the effect of different obesity variables, such as WHR and WC as well as BMI, on cognitive outcomes. In order to explore the mixed nature of the results presented in this review, future research also needs to explore both global cognitive outcomes as well as domain specific analysis, to determine whether risk factors affect overall cognition or whether certain abilities are affected more so than others. Additionally, future research should also be carried out on sedentary behaviour in addition to physical activity, as this area seems to have been identified as a new field of research as yet unexplored.

Lastly, it should be noted that as in all observational studies, the results of the studies shown here only provide information on possible biological associations, and, while longitudinal studies provide some indication of temporal associations, these cannot be used to infer causal relationships. Clinical trials, carried out over a reasonable period of time, are therefore needed to ultimately address the possibility of a causal, directional association.

3.6 Conclusions

This systematic literature review presents current epidemiological evidence on the association of obesity and physical activity with cognitive ability and cognitive decline in older people with type 2 diabetes. I found limited evidence for an association of obesity with both cognitive ability and cognitive decline and for an association of physical activity

with the same outcomes in people with type 2 diabetes. Due to inconsistencies in methodology, reporting and findings, it is not possible to draw any definite conclusions on the validity or strength of these associations. In particular, methods of measuring cognition varied widely between studies and it is possible that different cognitive domains, as measured by the variety of different individual cognitive tests used, are associated with either obesity or physical activity to different extents. Good quality, large scale epidemiological studies that test cognitive ability and change in cognitive ability over time by means of a comprehensive cognitive test battery that can be used to create a general cognitive ability variable alongside individual domain analysis are therefore needed in order to determine associations with confidence.

Chapter 4: Methods

This chapter describes the design and methodology of the Edinburgh Type 2 Diabetes Study (ET2DS). This includes details of the data collection relevant to this thesis, especially the 10 year follow-up phase which I undertook myself. The statistical methodology used to analyse the data is also described.

4.1 The Edinburgh Type 2 Diabetes study

The ET2DS is a population-based prospective cohort study set up in 2006/2007 of 1066 men and women aged between 60 and 75 years at baseline with type 2 diabetes, living in the Lothian region in Scotland. The primary objective of the ET2DS was to explore associations between potentially modifiable risk factors and cognitive decline in people with type 2 diabetes (Price et al., 2008). The majority of other large prospective cohort studies of cognitive ageing recruit from the general population. The ET2DS provides a rare and valuable opportunity to investigate risk factors for cognitive decline, exclusively in people with diabetes, thereby allowing for in-depth analysis on specific potential underlying causes of cognitive decline in this high risk population. The ET2DS has had 4 main phases of data collection to date: a baseline clinic (2006/2007), a liver sub-study clinic (2007/2008), a year 4 clinic (2010/2011), and a cardiovascular events record linkage update (2015/2016). For the purposes of this thesis, I undertook a further follow-up phase, including year 10 clinic (2016/2017) and the focus of this chapter and my subsequent analysis is on this latest data collection phase. The study protocol by Price et al. (2008), provides a detailed description of the early phases of the ET2DS and this is used below along with other publications to describe the aspects of those study phases relevant to this thesis.

4.2 The ET2DS population

Participants for the ET2DS were recruited at random from the Lothian Diabetes Register (LDR), a database established in 2001 containing information on around 20,000 people diagnosed with diabetes according to WHO criteria living in the Lothian region, UK. 5454 participants, selected at random by sex and 5 year age bands from the LDR, were contacted by post, of whom 1252 replied. 1077 participants attended the baseline clinic in 2006/ 2007. Non- native speakers of English and individuals with poor visual acuity (those unable to read large print text or distance vision <6/36) were excluded from the study as these requirements would impact performance during the paper based or verbal-language centric cognitive testing. Diabetic status was assessed at baseline by assessing medical records to exclude participants who were incorrectly recorded as having type 2 diabetes on the LDR. Only individuals treated with oral and/or injection anti-diabetic medications, or individuals managing their diabetes through diet and with an HbA1c >6.5% were included in the study at baseline. Individuals not on a medication (diet controlled) and with an HbA1c <6.5% had their diabetic status reviewed by a consultant diabetologist to confirm their diagnosis. Individuals with pancreatic disease and those on insulin within one year of diagnosis or those on insulin before the age of 35 were also reviewed. Those where clinical information on diabetic history or status could not be obtained, were excluded. Individuals unwilling or unable to provide informed consent were also excluded. This resulted in a total baseline population of 1066 participants. This baseline population allows for 90% power at the two sided 5% significance level to detect correlation of ≥ 0.1 of two continuous variables. At baseline, participants underwent detailed physiological and cognitive testing and completed a questionnaire on past medical history. These data were used, along with linkage to hospital discharge records, to derive the baseline variables subsequently incorporated into the analyses for this thesis. The cognitive test battery and much of the

physiological data collected was the same as collected at the 10-year follow-up clinic (see below). Other details of all the baseline testing done and variables derived have been described previously (Price et al., 2008).

4.3 Ethical approvals

At baseline, the study had full ethical approval from the Lothian Medical Research Ethics Committee and complied with the Declaration of Helsinki. I submitted a new application for the year 10 follow up phase of the study to the Research Ethics Committee and to NHS Lothian R&D, sponsored by The Academic and Clinical Central Office for Research and Development (ACCORD), which was granted. This application was written and submitted through the Integrated Research Application System (IRAS) (See Appendix C). Documentation approved by the REC and NHS Lothian R&D included the application form, protocol, participant information sheet, informed consent form, letters of invitation to the participants, GP letters and amended versions of the various clinical questionnaires and other clinical documentation. Written informed consent was obtained from all subjects on attendance at each clinical phase of the study.

4.4 Participant follow-up at year 10

One year prior to commencing with the year 10 follow up clinics I contacted participants via a newsletter, thanking them for their prior contribution to the ET2DS, informing them of recent developments and disseminating key results of the study (Appendix D). The newsletter also informed them of the intention of holding another phase of clinical data collection and provided contact details of the study, should they wish to opt out or have

questions. The newsletter was followed by a formal invitation to attend the research clinic with a specified appointment date and time. The invitation contained a tear off reply slip (and a stamped self-addressed envelope) to provide opportunity for the participants to indicate their willingness to attend the 10-year follow-up clinic. Upon receiving reply from the participant, I or another member of the study team phoned the participant to confirm their appointment, reschedule an alternative appointment, or record the reason for not taking part in this phase of the study. Participants failing to respond to the written invitation were contacted by telephone to confirm address and future participation. Through telephone contact it was evident that both clinic visit and home visits were appropriate in this phase of the study, due to the age and comorbidities experienced by the cohort. Telephone contact was also key in addressing specific participant concerns that otherwise would have resulted in reduced attendance rates of this phase of the study. Examples of this included medical, mobility, confidentiality, and cognitive concerns that were addressed though organising transport to and from the clinic, organising a home visit or explaining and clarifying the clinical procedures. Considerable effort was made by myself and/or other members of the ET2DS team to contact each participant personally and an updated list of non-contactable participants was kept throughout the data collection year.

4.5 Clinical data collection

Data collection took place at the Wellcome Trust Clinical Research Facility (CRF) at the Western General Hospital, Edinburgh at each clinical phase of the study. In order for the data collection to commence for the year 10 phase, I applied for, and was granted an NHS Lothian Honorary Research Contract and wrote detailed Standard Operating Procedures (SOP) for each aspect of the clinic. I also compiled a CRF site file, detailing ethical approvals,

SOPs, contact details of study personnel and study protocol. Reserved parking spaces were available to participants as was a taxi service, and I ensured participants were reimbursed for travel expenses. Appointments were scheduled at times convenient to participants at 08:45 and 12:45 and were rescheduled should the appointment have been missed for any reason. Participants were instructed to bring an early morning urine sample with them. I and one other ET2DS team member undertook all the physical and cognitive examinations. A maximum of 6 appointments were made per day and the order of clinical examinations varied depending on the time of arrival, as the clinic appointments were staggered. This enabled one participant per time slot (AM or PM) being given self-administered questionnaires to complete while the other two were seen by the researchers in roughly equal share. This enabled a ratio of 3 participants to 2 researchers, and a maximum use of research clinic time. The clinic was wheelchair accessible, nursing and medical staff were available to assist if necessary, and refreshments were offered to all participants upon arrival. The following sections describe the data collected, procedures for which were the same as used at baseline unless specifically stated.

4.5.1 Demographics

The participant questionnaire completed at baseline (See Appendix E) included questions on date of birth, sex and ethnicity and postcode information from 2006 was used to calculate the Scottish Index of Multiple Deprivation (SIMD) score to assess level of deprivation (grouped by quintile). The SIMD is a composite index which combines 38 indicators across seven domains, covering income; employment; health; education, skills and training; housing; geographic access to services; and crime levels provided by The Scottish Government (2006). Lothian quintiles of SIMD are also often used to describe

levels of deprivation in Lothian, which result in a more detailed representation of socio economic status in Lothian. The use of Scottish SIMD may therefore result in a skew in the data and imply that the ET2DS population have a very low level of deprivation. Despite this, Scottish quintiles, as opposed to Lothian quintiles are used in this thesis to describe the ET2DS population as this measure is more commonly used and can also be used to place this population in context of Scotland as a whole. At year 10 follow-up participants completed a similar questionnaire as at baseline in which they were asked to provide updated information on address, marital and employment status.

4.5.2 Medical history and diabetes

As at baseline, the 10-year participant questionnaire contained questions on medical history, prescriptions, alcohol intake, and smoking status and history was given to participants. This questionnaire included specific questions on diabetes status, duration, and medication, and also questions from the WHO Chest Pain and Edinburgh Claudication Questionnaire.

4.5.3 Physiological examination

Consistent with the physiological examination at baseline, systolic and diastolic blood pressure was taken from the right arm manually using a sphygmomanometer and stethoscope. A Doppler scan was used to obtain Ankle Brachial Pressure Index ABPI readings from the left and right brachial, posterior tibial and posterior pedis arteries in supine position. Height (to the nearest 1 mm) hip, waist (to the nearest 0.5 cm) and weight (to the nearest 0.1 kg) measurements were taken. Near vision was assessed using a

standard near vision eye chart. In addition, at baseline the percentage of body fat was assessed using an OMRON BF306 Body Fat Monitor (to the nearest 0.1%), by taking an average of three measures.

4.5.4 Blood and urine samples

At baseline, fasting blood samples were processed at the research clinic, for immediate measurement of vascular risk factors, including those used in this thesis such as low-density lipoprotein (LDL), high-density lipoprotein (HDL), serum triglycerides, inflammatory markers (c-reactive protein, CRP; interleukin-6, IL-6; tumor necrosis factor-alpha, TNF-α, fibrinogen) and HbA1c and plasma was stored at 40°C. Assays for plasma CRP, IL-6, and TNF-α were performed in the University Department of Medicine, Glasgow Royal Infirmary. CRP was assayed using a high-sensitivity immunonephelometric assay. TNF-α and IL-6 antigen levels were determined using high-sensitivity ELISA kits. At year 10 follow-up, blood and urine samples were taken and stored for later analysis (plasma frozen and stored at -80^{o}C, urine samples collected and stored at -20^{o}C.

4.5.5 Physical activity questionnaire

For the first time in the ET2DS, the long version of the International Physical Activity Questionnaire (IPAQ) (Craig et al., 2003) was given to participants at the 10-year clinic. This took the form of an interview. The IPAQ was used to collect detailed information on level of activity within the different domains of daily activity. These domains included indoor and outdoor household activities, occupational activity, self-powered transport, and leisure-time physical activity as well as sedentary time. The data were collected and scored in the

form of minutes of activity per week and was used to generate a physical activity score by weighing scores using predefined Metabolic Equivalent Units (METs). This resulted in a physical activity unit of MET minutes per week (MET^{-1} $minutes^{-1}$ $week^{-1}$), which gives an estimate of frequency and intensity of activity per week. Sedentary time data were gathered by asking the participant to recall in detail a 'typical' day, and sedentary time, in minutes, was recoded. An additional question per physical activity domain was asked to gather information on change in the past 10 years, scored as; (1) lower, (2) no change, or (3) increased. A mean of this score was taken to reflect overall change in physical activity. A similar change score was recorded for sedentary time. According to the scoring guidelines, scores above 3000 MET minutes per week are considered high, scores below 600 MET minutes per week are considered low. For healthy adults aged 40- 64 years, a typical score of 4780 has been reported and for adults aged ≥65 years, a typical score of 5692 has been reported in a Swiss general population cohort (Wanner et al., 2016). A recent validation study of the long version of the IPAQ in older people with diabetes, who had a BMI of ≥30 kg/m^2, indicated that a typical score was 1845 (Minetto et al., 2018).

4.5.6 Cognitive examination

As at baseline, a neuropsychological test battery consisting of 7 tests for cognitive ability, one test which screened for dementia, one test which assessed predicted peak cognitive ability, one test which measured reaction time, and one test that assessed depression and anxiety were administered to all participants. The 7 tests of the main test battery was developed in order to capture the principal cognitive domains thought to be susceptible to decline in people with diabetes, that were commonly used in the literature. The cognitive examination lasted approximately one hour and was administered in the same order

(consistent with the order of the following sub-sections, describing the individual tests). Testing was only carried out after close reading ability was confirmed to be sufficient to read small text, and blood glucose level was above 4 mmol/L. If blood glucose was below this, participants were given the opportunity to consume some food and were then later re-assessed for fitness to be tested. Participants were instructed to bring and wear reading glasses and/or hearing aids if required. Those unable or unwilling to partake in the cognitive examination were excluded if this was apparent at baseline only.

Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983) measured self-reported symptoms of depression and anxiety on separate scales. The maximum score for each was 21 and minimum was zero, with higher scores indicating increased number of symptoms. The scores were used as continuous measures; however, scores above 8 can indicate suspected clinical depression and anxiety. If participants scored above 10, their GP was notified of their score.

Mill Hill Vocabulary Scale (MHVS)

The multiple choice section of the combined junior and senior versions of the Mill Hill Vocabulary Scale (Raven et al., 1998) was used to provide an estimate of premorbid crystallised-type intelligence. This test involved identifying the correct synonym of a given word from a choice of 6 options. The groups of words were arranged in ascending order of difficulty and one score was given for each correct answer. The maximum score was 43 and minimum score was zero, with higher scores indicating increased ability. It should be noted

that despite evidence that scores reflect peak premorbid cognitive ability, this test score can only be assumed reflect an estimate of the true level of ability. A more common test for crystallised-type intelligence is the National Adult Reading Test, which correlates highly with the MHVS (r=0.69) (O'Carroll and Gilleard, 1986). The MHVS was used as opposed to the NART as it takes less time to complete and ease of administration as it can be carried out independently, without the need for a tester being present.

Mini Mental State Exam (MMSE)

The Mini Mental State Exam (Folstein et al., 1975), often used as a screening tool for dementia by clinicians, provided an estimate of global cognitive functioning with respect to likelihood of cognitive impairment. The test evaluates cognition though a host of different exercises to assess domains such as memory, attention, praxis, and orientation. The maximum score is 30 and minimum is zero, where a score of <24 would provide a clinician grounds for referral for fuller cognitive assessment. This test is often used in research for its relative brevity and ease of administration as a measure of overall cognitive ability; however, this test is only intended for use as a brief screening tool and does not provide a full cognitive assessment. For this reason, this test was only administered as a screening tool for cognitive impairment and a comprehensive test battery was used to provide a more robust indication of cognitive ability. Participants with a score <24 had their GP notified of this result.

Logical Memory (LM)

Logical memory, a subtest of the Wechsler Memory Scale 3rd Edition UK version (WMS-III), developed by Wechsler in 1987. This test provided a measure of verbal declarative memory, where participants were asked to recall a short story of 25 units of detail. The test required immediate recall and then again after approximately 30 minutes. As immediate and delayed scores are highly correlated (Tulsky et al., 2003), the scores were summed to provide a measure of overall global verbal memory. The maximum and minimum scores of summed recall were 50 and zero, respectively.

Faces

The Faces test is also a subtest of the WMS-III. This test provided a measure of non-verbal declarative memory, where participants were firstly exposed to set of 24 photographs of different faces, and then asked to identify familiar faces from a second set of 48 faces, of which the original 24 were included at random. Recall was assessed immediately after initial exposure and again after around 30 minutes. Each recall has a maximum score of 48, and minimum score of zero. The test scores were summed to provide a measure of overall non-verbal memory (maximum score 96).

Trail Making Task B (TMTB)

The Trail Making Task B, developed in 1944 as part of the Army Individual Test for General Ability (Tombaugh, 2004), was used to measure the cognitive processes of mental flexibility, processing speed, attention, and executive functioning. The task involved presenting the participants with a sheet of A4 paper with encircled numbers, 1- 13, and

letters, A-L, provided randomly on the page. The task is then to draw a continuous line connecting the circles in alternating order (e.g. 1- A- 2- B- 3- C...) in as short a time as possible; the numbers and letter are set on the page so that the connecting lines do not cross. This test involved 26 connections and used time in seconds as a unit of measurement. A low score is indicative of a superior ability to perform at the task. Participants were given a short practice test to allow them to fully comprehend the instructions given before formal testing, and if a participant made a mistake in the test, this was pointed out immediately and the participant was instructed to continue from the point at which the mistake occurred. The time added to the total time to complete the task is indicative of a poorer performance.

Matrix Reasoning (MR)

The Matrix Reasoning subtest of the Wechsler Adult Intelligence Scale 3rd Edition (WAIS-III), developed by Wechsler in 1997, was used to measure non-verbal reasoning ability. The participants were presented with a series of geometric pictures, with 5 options below each main image to select from. Participants were instructed to choose the one that best completes the sequence, without time pressure. Each correct answer contributes one mark to the overall score, and the test was stopped after 4 consecutive wrong answers were given or 4 wrong answers out of 5 consecutive answers were given. The test had a maximum of score of 26 and minimum score of zero.

Digit Symbol Test (DST)

The Digit Symbol Test, also a subtest of the WAIS-III, was used to provide a measure of processing speed. The participant is presented with an A4 sheet of paper with a grid of symbols and blank boxes. At the top of the page is a key with the symbols and corresponding digits 1-9. After a short practice section, the participants were instructed to fill in as many boxes as possible within 120 seconds. The total test score is based on the number of correct symbols achieved in the time limit. The maximum score is 133 and minimum is zero.

Letter Number Sequencing (LNS)

The Letter number sequencing task is also a subtest from the WAIS-III. This test assessed working memory by requiring participants to listen to sequences of letters and numbers in a random order, and then asking participants to recall the digits sorted firstly by number and then by letter in numerical and alphabetical order. This required the participants to firstly listen, then mentally manipulate the original order and then recall the new order. This began with only one letter and one number, and after every third trial, a new digit (number or letter) was added. This continued up until a maximum of 8 digits and so allowed for a maximum score of 21 and a minimum of zero. In the case of three consecutive wrong order manipulations in a given difficulty block, the test was stopped.

Borkowski Verbal Fluency Task (BVFT)

The Verbal Fluency task developed by Borkowski et al. (1967), provided a measure of executive function and semantic memory. Participants were asked to name as many words

as possible, excluding proper nouns, with a seemingly random letter given to them. This was repeated 3 times and the letters used were always C, F and L. Participants were give a practice opportunity with a different letter (S) and, once confident in the instructions of task, formal testing was initiated. Each time the participant was given 60 seconds to think of words, so was given a maximum time of 180 seconds to complete the task. The task was scored by summing the number of non-repeated, correct words recalled. There was no set maximum for the test, however the minimum was zero.

Deary-Liewald reaction time task

Reaction time was measured using the Deary-Liewald reaction time task (Deary et al., 2011b), which measures processing speed. This task involved the use of a computer where the screen was set up to depict a number of blank boxes on a blue background. The task required participants to press keys corresponding to where an 'X' symbol appeared on the screen, in as short a time as possible. The first part of the task involved only one box and the second part of the task involved 4 boxes. Scores reflect the response times, i.e. the speed of cognitive processing, and the speed of physical movement. Participants are given a short practice opportunity before each part of the task. A mean latency for each part was calculated, and is used to score the two parts of the task.

4.6 Record linkage and Events

4.6.1 Vascular events

At baseline, year 4 and at year 8 (2014/2015), hospital discharge data and death codes were obtained from Information and Services Division of NHS Lothian. At year 10, hospital

discharge and deaths data were updated by consulting TRAK and the National Records of Scotland. Information on diagnoses, prescriptions, admissions and events were obtained in order to build evidence, along with information gathered at the clinics, for cerebrovascular and cardiovascular events. Prevalent cerebrovascular and cardiovascular event variables (stroke, TIA, myocardial infarct or angina) were used as binary variables defined as having either has a stroke or TIA prior to the baseline clinic or either having had a heart attack or angina diagnosis prior to the baseline clinic. These events were all determined by use of a set of criteria developed by members of the study team. For cerebrovascular disease, the criteria were met if 2 out of the 3 following statements applied: (i) self- report, (ii) hospital discharge code, (iii) review of clinical notes. For cardiovascular disease, the criteria were met if 2 out of the 3 following statements applied: (i) self-report, (ii) WHO Chest Pain Questionnaire indication, (iii) ECG indication. Alternative criteria for cardiovascular disease were if a hospital discharge code was found in combination with a self-report.

4.6.2 Incident dementia events

At baseline the majority of participants of the ET2DS were assumed to not have dementia as a written response to the invitation, a scheduling of an appointment and a subsequent clinical attendance was required by the participant, although each participant was not formally assessed. Evidence for prevalent or incident dementia was collected periodically throughout the 10 years of follow-up, with the majority collected at year 10. These included hospital records (TRAK), hospital discharge codes, death certificate codes, GP reporting, prescription for dementia medication, self or carer reporting and MMSE score. The gold standard for dementia diagnosis is through a clinical neuropsychological assessment which in accordance to the DSM V often includes a CT or MRI scan. This diagnostic procedure was

used as primary evidence for the classification of dementia events in the ET2DS, and the basis of the following criteria for probable cases of dementia in the cohort. Primary sources of information include hospital records (TRAK and discharge data), death certificates, and prescription data. These sources all are presumed to provide information on dementia after a formal diagnosis has been made according to DSM V criteria. Other information on dementia diagnosis through self, carer or GP report are considered secondary sources of information as the primary source of diagnosis was consulted to generate this 'second hand' information. Similarly the MMSE dementia screen, often used by GPs prior to formal assessment provides indication of cognitive impairment but alone does not provide information on dementia status. The following criteria were developed by me and clinical experts in the field of diabetes and cognitive aging to classify participants as probable sufferers of dementia and probable not a sufferer of dementia. It should be noted that these criteria are not equivalent to a clinical diagnosis of dementia and thus is termed 'probable' dementia.

'Probable dementia' is at least *one* of **A** and at least *one* of **B**

Or

Two or more of **A**

A: Primary medical record of diagnosis

TRAK diagnosis or hospital discharge code or death code or prescription of dementia medication

B: Secondary source of a medical diagnosis

Self/ carer report or GP report or MMSE<24/ missing at year 10

On the basis of these criteria, participants were classed as having probable dementia at year 10 or no dementia at year 10. A number of participants did not meet the formal criteria but had one source of primary medical evidence (criteria part A) for dementia. These cases had their clinical notes reviewed by a committee and a consensus was reached that, in light of the evidence, they are to be included in the probable dementia category. It should be noted that some participants had a formal MCI diagnosis on TRAK, however these were not included in the final probable dementia group. Date of diagnosis was not available for all reports of dementia, and as disease onset precedes diagnosis no distinction was made at baseline between incident and prevalent events, as such differentiation would be arbitrary and misleading. It should be noted that 'missing at year 10' was incorporated into part B of the criteria, as it would allow participants who did not attend due to dementia to be classed accordingly.

4.6.3 Diabetic Retinopathy

At baseline, participants had digital retinal photography carried out at a separate clinic following initial appointment. A detailed description of procedures is describes by Ding et al. (2010), but in brief, seven field non stereoscopic colour photographs were taken of both eyes and independently graded by two ophthalmologists according to the Early Treatment Diabetic Retinopathy Study Group (1991) scoring system. Scores above 10 were classed as retinopathy and others as no retinopathy present. At year 10 follow-up, routinely collected image data, which was pre- graded by a clinician was collected from SCI Diabetes. Grades R1 and above were classed as retinopathy and others as no retinopathy. For participants known to still be alive at year 10, image data obtained in, or if missing, closest to 2016/17

was used for classification purposes. Diabetic retinopathy was used as a binary variable in all analysis as a proxy for micro vascular disease.

4.7 Data management and cleaning

All participant data were recorded and kept in hard copy in secure, locked filing cabinets in a secured, restricted access room at The University of Edinburgh. At each phase of data collection, all questionnaire, clinical, laboratory and cognitive data were entered manually into a master database using Microsoft Access 2003/2010 software. Data were entered in batches by members of the research team after the clinics finished. This database was backed up on a dedicated university server that required both electronic authorisation and password access. At baseline, double data entry was carried out for all participants which identified an error rate around 0.02%, when omitting easily identifiable typographical errors (e.g. hospital names/abbreviations). At year 4 a random 10% sample group of participants was selected for double data entry. Similarly at year 10, a random 10% sample was selected for double data entry. Data were entered into a separate Microsoft Access database, and this was checked against the original entry. At year 4 this identified an error rate of 0.017% and at year 10 this identified a similar error rate of 0.018%. Any discrepancies were resolved by firstly consulting the original paper file, and then if still unresolved, secondly by committee consensus. Alongside this, all data were checked for outliers and impossible values. For continuous data, outliers were defined as cases ± 2 standard deviations of the mean of that variable. Impossible values, identical to original paper copy were recoded as missing and errors recoded. All other outlier values were retained in the database. These checks were carried out by me and other members of the

current research team at year 10, and by other research team members following the previous phases of data collection.

4.8 Missing HbA1c data

Baseline variables included in this thesis were checked for missing data and it was found that despite previous checks, the variable HbA1c contained relatively high missing data. HbA1c contained 38 cases of missing data (3.56%) at baseline. After checking paper files for laboratory blood results, a number of cases were identified that did have a baseline HbA1c value. If missing data persisted, often due to a blood tube failing, or not able to obtain blood on the day of the clinic, routinely collected data were consulted. The value closest to the day of the participant's baseline clinic date was taken, provided it was within 6 months of the baseline clinic. This approach allowed the overall missing HbA1c data to be reduced to 9 (0.84%) and, as HbA1c level is representative of a 3 month mean value of blood glucose, it is expected to remain relatively stable with in the 6 months either side of the clinic date (Ohde et al., 2018).

4.9 Data analysis

All longitudinal analyses were carried out on predictor variables collected at baseline and outcome variables collected at year 10 follow-up. Cross-sectional analyses were carried out on predictor and outcome variables collected at year 10 follow-up.

4.9.1 Clinical and physiological variables

The obesity variable BMI was calculated from height (cm) and weight (kg) using the standard formula: weight (kg) / [height (m)] ^{2}, and WHR was calculated by dividing waist circumference by hip circumference (cm). Hypertension was used as a binary variable derived from systolic and diastolic blood pressures (mmHg), and was defined as having a systolic blood pressure > 140 mmHg or a diastolic blood pressure of > 90 mmHg. This derived variable used in this thesis captures the most common type of hypertension; isolated systolic hypertension (>140/<90 mmHg), and the less common; systolic–diastolic hypertension (>140/>90 mmHg) and diastolic hypertension (<140/>90 mmHg) (Tsimploulis et al., 2017). For the purposes of this thesis the variable hypertension does not include participants on anti-hypertensive medication, and should be understood to reflect cases of uncontrolled hypertension only. Care should be taken when interpreting findings, as individuals on an anti-hypertensive medication may still be suffering or have suffered from clinically relevant hypertension in the past and this may still present as a risk factor for various vascular outcomes. Unadjusted measures are used in this thesis as it was reasoned that, untreated hypertension at baseline was likely to be a more accurate and clinically important risk factor for the study outcomes, than those who may have had hypertension in the past or who are medically controlled and thus have a considerably lower risk of vascular disease. At baseline only self-reported prescription data was available, which is notoriously unreliable. At year 10 full prescription data was obtained from SCI- Diabetes, however for the purposes of this thesis it was not possible to trace back every anti-hypertensive medication for each participant and so the variable reported in this thesis should be interpreted only as untreated hypertension.

4.9.2 Preparation of cognitive variables prior to analyses

Derived scores

Cognitive data from baseline and year 10 follow-up were used in this thesis. Cognitive tests with immediate and delayed components (Logical Memory test and the Faces test) were summed, at each time point, prior to analysis as temporal scores were highly correlated (for baseline Logical Memory; 0.87 and Faces; 0.55, both $p<0.001$). The terms in this thesis 'Logical Memory' or 'Faces' describe the summed scores, unless otherwise stated.

General cognitive function variable

Latent variables, suggested early on by Spearman (1904), are theoretical constructs that are inferred on the basis of a number of observations, and are not directly quantifiable though one measurement or test alone. These underlying constructs are often used in psychological testing, where one test may not capture the full ability of an individual. This can be the case when aiming to capture a cognitive domain, such as executive functioning or when aiming to capture an individual's general cognitive ability, often termed general intelligence. Factor analysis (FA) is a common data reduction method used in psychological analyses to derive a latent variables. Principal component analysis (PCA), is another data reduction method commonly used when generating a summary, though not strictly latent, variable. The two methods vary as latent variables derived using FA only take into account the shared variance between the data, whereas summary variables derived using PCA use all the variance in the data to generate variables (Gaskin and Happell, 2014). This is important as while FA is often preferred by researchers, as it takes into account testing error and so is deemed more accurate, it generates novel variables that are not purely a summary of the original tests. PCA merely summarises the cognitive test data and so in the

context of this thesis, was the preferred data reduction technique. Associations found using this summary variable can be explored further by the results of the individual cognitive tests, which in the context of multiple testing, is beneficial. A PCA was run using imputed (described in the following section) age adjusted cognitive data from the 7 cognitive tests at baseline (LM, Faces, TMTB, MR, DST, BVFT and LNS) and Eigenvalues of <1 were extracted. The approach was based on that of Gow et al. (2008), where all cognitive data at all time points were stacked into seven columns and a single PCA was carried out. Regression scores of the first component were then saved according to time point and were termed general cognitive function or '*g*'. This approach allowed baseline '*g*' values to be centred on zero with a standard deviation of 1 and allowed follow-up '*g*' values to be relative to baseline scores. This means that a person's '*g*' score can be directly compared to their baseline '*g*' score. If the PCA was carried out separately on baseline scores and then again on follow-up scores, both variables would be have means of zero and could not be used in a cognitive change analysis. It should be noted that, although the assumption of independent samples is violated, this does not bias the factor loadings. It does however over-estimate the variation in the factors. The PCA scree plot indicates that 1 component adequately describes the data, accounting for 48.06% of the variation in the data. The loadings of the cognitive tests on this un-rotated component are described in Table 6.

Table 6. The loading scores of the cognitive tests on the un-rotated component 'g'.

Cognitive test	First Un-rotated Principal Component Loading score
Logical Memory	0.603
Trail Making Task B	-0.827
Faces	0.489
Matrix Reasoning	0.691
Digit Symbol Task	0.790
Borkowski Verbal Fluency Task	0.644
Letter Number Sequencing task	0.749

The log transformed variable for Trail Making Task B was used for analysis. Imputed data were used to generate components and loading scores.

Imputations

Cognitive data at baseline or at follow-up was not always complete for each participant (common reasons being disability, fatigue, time constrains etc.) and so prior to generating the general cognitive function component, the cognitive data sets were imputed separately at baseline and at follow-up. This is because this component can only be produced for cases with complete cognitive data. This technique, commonly used in cognitive aging epidemiology (Van Beijsterveldt et al., 2002) termed multiple imputation, allows for missing values to be predicted by means of generating a number of likely values based on other variables on a case by case basis. A mean of these imputed values is then taken as a substitute for the missing value. This is a superior method of imputation to other more simple methods of imputation such as imputing the sample mean (Sterne et al., 2009). This technique generates a specific value for a missing variable based on the age, sex and other cognitive test results of the participant. Care should be taken when interpreting results using imputed data as it may be the case that a test score higher than the true ability of the participant is generated, especially if the reason for not completing the task is due to poor cognition. To overcome this, extra care was taken when preparing the data set for

imputation by checking if missing values were not in fact true zero scores. Every participant had notes taken regarding their ability and willingness to carry out cognitive testing and on a cases by case basis these were consulted to determine if scored were missing or true zero scores. Furthermore, imputations were only carried out on data where there was less than 3 out of 7 cognitive tests missing and remaining missing data were kept as missing. Imputation was deemed necessary, despite its limitations, as the power of analyses of the variable '*g*' was increased considerably. All data described and analysed in this thesis, except for the latent general cognitive function variable '*g*', is on non-imputed raw data.

4.9.3 Statistical analysis

Descriptive Statistics

Histograms and Q-Q plots were visually inspected to check if data were normally distributed for all data used in this thesis (see Appendix A and B). Any variables found to have skewed distributions were natural log-transformed prior to analysis and median values were reported, with respective interquartile ranges. Log transformations are used to convert skewed data to fit a more normal distribution in order to meet the assumption of normality when carrying out specific parametric analyses. It should be noted that other transformations were carried out (e.g. square root), however, the log transformation was used as it allowed the data to fit a normal bell–shaped distribution upon visual inspection. It should also be noted that predictor variables in regression analysis need not be normally distributed, and so if the data were not fully normalised this would have little effect on the outcome of the various analyses. Mean values and standard deviations were reported for normally distributed continuous data. Categorical data were described in terms of frequencies.

Statistical significance

The statistical cut point $p<0.05$ was used to reject the null-hypothesis, which reflects a <5% probability of incorrectly rejecting the null-hypothesis (a type 1 error). This error rate increases with the number of comparisons made, and so often post hoc corrections (e.g. Bonferroni corrections) are applied to analyses of multiple comparisons. However, this approach leads to an increased level of type 2 errors, where the null-hypothesis is incorrectly accepted. For the purposes of this thesis, a specific hypothesis is tested using the outcome summary variable '*g*', as derived though PCA, and then further explored by the same model using the individual cognitive test scores as outcome variables to find if one or multiple tests drive the association with '*g*'. The main analysis is on '*g*' and is only illustrated further by the other cognitive tests, and so for this reason, it was not appropriate to correct further for multiple comparisons. In light of this, caution should be taken when interpreting results close to the $p<0.05$ cut point, and results equal to or above this point should be assumed as not significant.

Cognitive outcomes

The main outcomes described in this thesis are general cognitive ability, change in general cognitive function and incidence of dementia at follow-up. These outcomes are described in relation to key risk factors measured at baseline.

Cognitive ability was measured at baseline and at follow-up by individual cognitive test performance and by general cognitive function score. The scores obtained at follow-up

represent the outcome of cross-sectional analysis between risk factors and cognitive ability at year 10.

Change in cognition was measured by adjusting cognitive ability scores at follow-up, by scores obtained at baseline. This approach, known as the Adjustment Method, models change over time and is commonly used in the literature of cognitive aging (Gow et al., 2008). Another approach to obtaining a change in cognition variable, is by calculation a difference variable. This approach is affected by regression to the mean (Reynolds et al., 2002), whereby random errors in measurements distort the true mean of the sample (Barnett et al., 2004). When measurements are repeated at follow-up, cases with extreme baseline scores tend to have scores closer to the mean at follow-up, resulting in the observation that people with high scores perform relatively less well and people with low scores perform relatively better than before (Gow et al., 2012b). Both methods typically yield identical results (Willett and Sayer, 1994), and so because of the downfalls of the difference method, the adjustment method was adopted in this thesis to describe and analyse change in cognitive ability. It should be noted that this was carried out for both the individual cognitive tests and for the general cognitive ability score.

Incident dementia, described previously (see section 4.5.7), was determined at follow-up by fulfilling predefined criteria. This is a categorical outcome variable where risk factors measured at baseline or at follow-up are modelled against the binary outcome variable of probable dementia vs the remaining study population.

Principal Analysis

Univariate analysis

Differences between year 10 follow-up attenders vs non attending population in terms of risk factors, demographics and cognitive scores was described by means of chi-squared tests and t-tests in order to show how representative the follow-up population was of the original cohort. In order to justify the use of the summary variable, Pearson's correlations coefficients were used to describe cognitive scores and predictor variables thought to be inter-correlated. All analyses were two-tailed.

Multivariable analysis

Linear regression analyses (multivariable) were employed to determine the longitudinal associations between baseline risk factors and cognitive outcomes and the cross-sectional associations between year 10 risk factors and cognitive ability. For analyses on categorical outcome data on dementia status, multivariable binary logistic regression was used. For both types of model, a hierarchal approach, whereby blocks of related risk factors were sequentially added to the models was used to describe how the association of each predictor risk factor and cognitive outcome was modified by the addition of other covariates to the model. This approach was utilised in addition to the adjustment method to determine the association of a risk factor on cognitive change over time. All analyses were carried out in SPSS version 21 (IBM Corporation, New York).

Chapter 5: Results

This chapter describes the baseline and 10 year follow-up characteristics of the ET2DS population. Also presented are the analyses of key risk factor inter-correlations and associations of obesity and systemic inflammation markers with other variables. This is followed by the main analysis on the associations of obesity with cognitive change, considering adjustment for other variables and for inflammation.

The distribution of variables used in this thesis are shown in Appendix A and B. Most variables met the assumption for normality and those skewed were natural log transformed. The variables transformed are reported in the tables with the prefix 'ln', and in the text reported without reference to the transformation, unless specified.

5.1 CHARACTERISTICS OF BASELINE STUDY POPULATION AND 10-YEAR FOLLOW-UP

5.1.1 Baseline characteristics

Baseline characteristics of the ET2DS population (n=1066) are presented in Table 7. The population had an average age of 67.9 years, 51.3 % were male and the majority of participants were retired (n=864; 81%). The highest percentage of participants belonged to the 5th quintile of the Scottish Index of Multiple Deprivation (SIMD), indicating that 32.7% of the study population was considered to be least deprived when compared to that of the rest of Scotland while only 11.9% belonged to the most deprived quintile. This was reflected by the observation that further education was achieved by 44.8% (n=478) of the study population and 54.4% (n=581) secondary level education.

The median duration of diabetes was 6 years (range 0 to 43 years). The majority of participants were on an oral diabetes medication alone (without insulin) (63.9%), 17.4% were on insulin and/or an oral medication and the rest controlled their diabetes through diet alone (18.7%). The population had a median HbA1c of 7.20 %, which ranged from 5.0 to 14.9%.

The population had a mean systolic blood pressure of 1.33±16.44 mmHg and a mean diastolic blood pressure of 69.06±9.01. When adopting the definition of hypertension as having a systolic blood pressure of >140mmHg or a diastolic blood pressure of >90mmHg, 367 (34.4%) were classed as hypertensive. 172 (16.1%) of participants had high levels of cholesterol as defined as having more than 5 mmol/l of total cholesterol. Diabetic retinopathy was prevalent in 32.5% of the study population, the majority of whom had only mild retinopathy (86%). The prevalence of macrovascular disease, defined as having had one or more macrovascular event (MI, angina, stroke or TIA), was 35.1% (n=374), of which angina and MI were most common (28.0% and 14.1%, respectively).

Most of the study population were non-smokers (n=912; 85.6%), consisting of those who had never smoked (n=498; 46.7%) or those having quit smoking (n=414; 38.8%) and on average 9 units of alcohol were consumed per week.

The mean BMI was 31.42±5.69 kg/m^2, with a minimum of 18.39 kg/m^2 and maximum of 55.44 kg/m^2, with 55.3% of participants being classed as obese (BMI >30 kg/m^2). The other obesity variables reflect this as WC was on average 107.00±12.82 cm, WHR was on average 0.96±0.76 and body fat was 38.09±7.55 %.

Mean clinical anxiety and depression levels as measured by the Hospital Anxiety and Depression Scale were 5.72 and 3.85, respectively. One hundred and eighty nine participants (17.7%) had mild anxiety, 103 (9.7%) had moderate anxiety and 29 (2.7%) had

severe anxiety, when screened using this tool. Ninety eight participants (9.2%) had mild depression, 24 (2.3%) had moderate depression and 4 (0.4%) had severe depression, when screened using this tool. Clinical cases of anxiety or depression, as indicated by a score of 11 or more (Snaith, 2003), were 132 (12.4%) and 28 (2.6%), respectively.

Table 7. Baseline characteristics of the ET2DS and the percentage of missing data

Characteristic	Population Mean ± SD or n (%)	Minimum	Maximum	N	Missing data %
Demographic:					
Age (years)	67.91 ± 4.20	60.14	76.1	1066	0
Sex males (n %)	547 (51.3)	-	-	1066	0
SIMD rank:				1066	0
1st quintile	127 (11.9)	-	-	-	-
2nd quintile	208 (19.5)	-	-	-	-
3rd quintile	188 (17.6)	-	-	-	-
4th quintile	194 (18.2)	-	-	-	-
5th quintile	349 (32.7)	-	-	-	-
Educational attainment:				1066	0
University/ college	171 (16.0)	-	-	-	-
Professional/ technical	307 (28.8)	-	-	-	-
Secondary school	581 (54.4)	-	-	-	-
Primary School	7 (0.7)	-	-	-	-
Employment status:				1066	0
Full-time	75 (7.0)	-	-	-	-
Part-time	77 (7.2)	-	-	-	-
Unemployed	9 (0.8)	-	-	-	-
Retired	864 (81.1)	-	-	-	-
Homemaker	19 (1.8)	-	-	-	-
Other	22 (2.1)	-	-	-	-
Vascular related:					
Systolic blood pressure (mmHg)	133.30 ± 16.44	90	210	1064	0.19
Diastolic blood pressure (mmHg)	69.06 ± 9.01	20	110	1064	0.19
Hypertension (n)	367 (34.4)	-	-	1064	0.19
Total cholesterol (mmol/l)	4.31 ± 0.90	2.3	9.40	1057	0.84
High density lipoprotein (mmol/l)	1.29 ± 0.36	0.39	3.34	1057	0.84

Serum triglycerides (mmol/l)	1.70 ± 0.65	0.64	5.89	1058	0.75
Retinopathy (n)	339 (32.5)	-	-	1044	2.06
Any macro vascular disease (n)[a]	374 (35.1)	-	-	1066	0
- MI (n)[a]	150 (14.1)	-	-	1066	0
- Angina (n)[a]	298 (28.0)	-	-	1066	0
- Stroke (n)[a]	62 (5.8)	-	-	1066	0
- TIA (n)[a]	31 (2.9)	-	-	1066	0
Smoking status				1066	0
- Current	154 (14.4)	-	-	-	-
- Former	414 (38.8)	-	-	-	-
- Never	498 (46.7)	-	-	-	-
Total cigarettes per day	2.34 ± 6.94	0	60	1061	0.47
Alcohol units per week	9.01 (14.48)	0	112	1066	0
Diabetes related:					
Diabetes duration (median years (IQR))	6 (2-10)	0	43	1053	1.21
HbA1c (%) (median (IQR))	7.20 (6.6-7.8)	5	14.9	1056	0.94
Plasma Glucose (mmol/l)	7.56 ± 2.10	2.1	22.2	1049	1.59
Medication status (n)				1066	0
- Insulin ± oral	186 (17.4)	-	-	-	-
- Oral	681 (63.9)	-	-	-	-
- Diet controlled	199 (18.7)	-	-	-	-
Obesity related:					
Body mass index (kg/m2)	31.42 ± 5.69	18.39	55.44	1065	0.09
Underweight BMI (<18.5 kg/m^2)	1 (0.1)	-	-	-	-
Normal BMI (18.5- 24.9 kg/m^2)	108 (10.1)	-	-	-	-
Overweight BMI (25-29 kg/m^2)	366 (34.3)	-	-	-	-
Obese BMI (>30 kg/m^2)	590 (55.3)	-	-	-	-
Waist circumference (cm)	107.00 ± 12.82	73	159.00	1061	0.47
Waist to hip ratio	0.96 ± 0.76	0.74	1.21	1061	0.47
Body fat (%)	38.09 ± 7.55	15.5	50.00	1052	1.31
Inflammatory related:					
Fibrinogen (median ng/ml)	3.60 (0.97)	0.7	7.14	1063	0.28
CRP (median mg/ml)	1.86 (3.50)	0.1	47.10	1042	2.25
IL-6 (median pg/ml)	2.86 (2.54)	0.49	34.18	1064	0.19
TNFα (median pg/ml)	1.07 (0.93)	0.1	28	1063	0.28

Psychological:					
MMSE <24	47(4.4)	-	-	1063	0.28
HADS A	5.72 ± 3.91	0	20	1065	0.09
HADS D	3.85 ± 2.89	0	16	1065	0.09

Total n=1066. Values are means ± SD, median (interquartile range) or n (%). SIMD, Scottish Index of Multiple Deprivation; HbA1c, haemoglobin A1c; CRP, c-reactive protein; IL-6, interleukin-6; TNFα, tumour necrosis factor α; MI, Myocardial Infarct; TIA, transient ischaemic attack; BMI, Body Mass Index, MMSE, Mini Mental State Exam; HADS A, Hospital Anxiety and Depression Scale-Anxiety subscale; Hospital HADS D, Hospital Anxiety and Depression Scale- Depression subscale. [a] These data are not cumulative.

5.1.2 Missing data

The majority of the variables, collected at baseline, had zero or few missing data (Table 7). Binary disease variables were sourced from NHS discharge data. These variables are all complete as only those with a diagnosis were recorded, and so it is possible some missing data are present in these variables if they have suffered the condition without it being recorded. Variables with the highest percentage missing include, CRP (n=24; 2.25%) and retinopathy (n=28; 2.06%). Retinopathy was determined by photographs taken by the study team at a separate appointment and so this may account for the relatively high percent of missing data.

It should be noted that HbA1c also had a high percentage of missing data (n=28; 2.63%), however, after looking at NHS routine haematology data, levels from blood samples taken within a period of 6 months on either side of the original clinic appointment date were used in analysis reducing the missing data by 10 cases to 0.94%.

5.1.3 Representativeness

The representativeness of the recruited sample compared to the true population of older people with type 2 diabetes living in Lothian was determined at baseline by the ET2DS

research team by comparing the socio-demographic and clinical characteristics of the study population to that of the total population included on Lothian Diabetes Register (Marioni et al., 2010). On average, the ET2DS population was found to have similar, age, duration of diabetes, HbA1c, medication type, and SIMD quintile to the non- responders (n=4386), while some differences were observed in sex (n=547, 51.3% male versus n=1839, 41.9% male; $p<0.001$), systolic blood pressure (137.2 mmHg ± 18.2 versus 133.3 mmHg ± 16.4; $p<0.01$) and total cholesterol (4.2 mmol/l ± 0.96 versus 4.3 mmol/l ± 0.90; $p<0.001$) (Marioni et al., 2010).

5.1.4 Ten year follow-up attendance and attrition

A total of 581 participants attended for cognitive re-testing at the year 10 follow-up clinic. A flow chart of attendance over the 10 years of the ET2DS study is shown in Figure 3. Table 8 describes the reasons given by either the participant or participant's representative for non-attendance and the levels of attrition since baseline. The attrition rate over the full 10 years of the study was 45.5% (n=485). The most common reason for non-attendance was death of participant (n=310) accounting for 63.9% of the total non-attending population (n=485), and 29.1% of the total study population (n=1066). The second highest reason given for non-attendance was health concerns that resulted in the participant not being fit to attend an appointment (n=80) accounting for 16.5% of the total non-attending population (n=485) and 7.5% of the total study population (n=1066). Of the total study population, we were not able to obtain a reason for non-attendance for 24 participants accounting for 2.3% of participants.

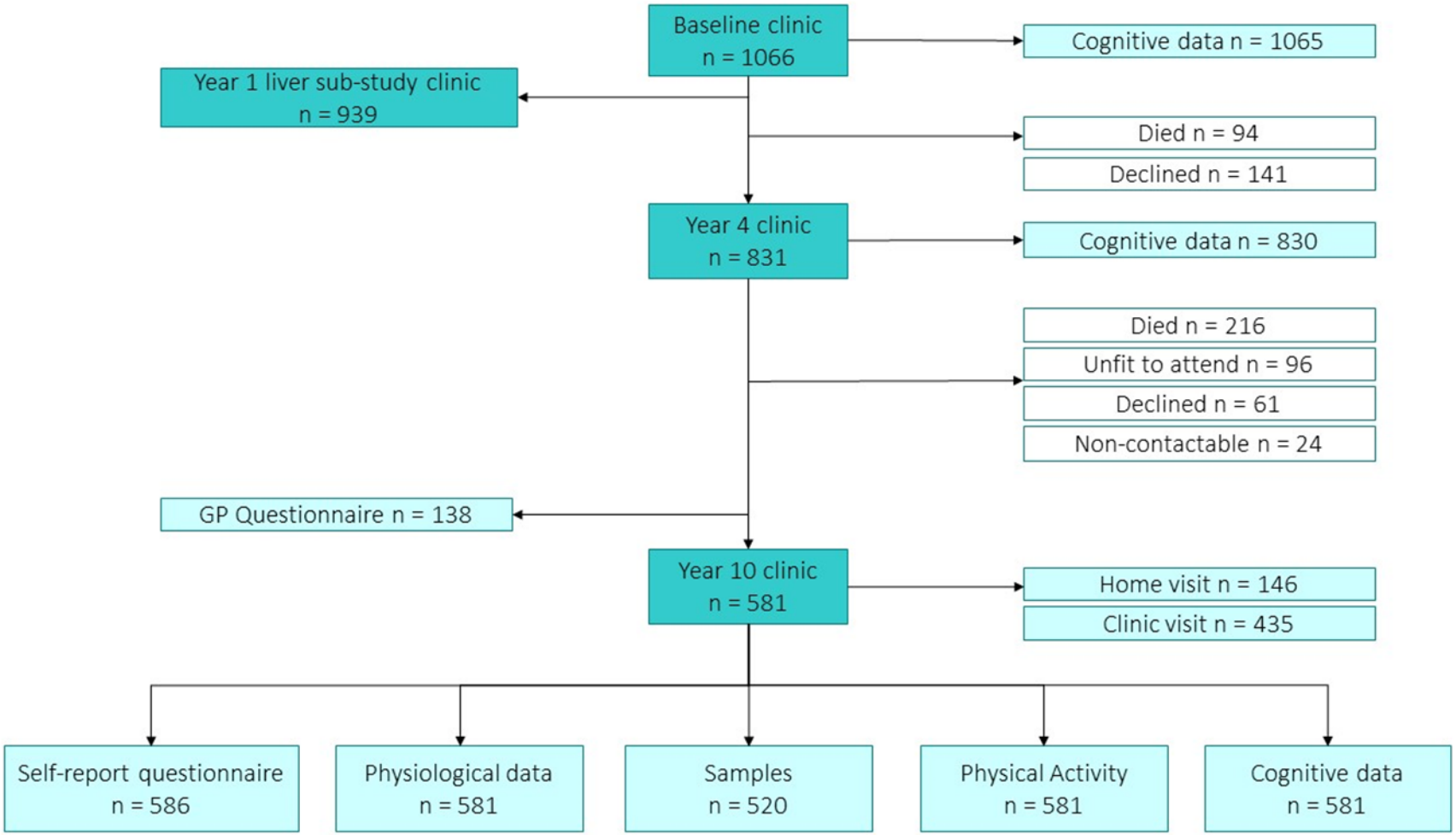

Figure 4. Attenders of the year 10 follow up of the ET2DS

Table 8. Reasons for non-attendance at year 10 follow-up

Principle reason for non-attendance (self/ participant's representative/ medical report)	Attrition at year 10 follow-up (n)	% of non-attenders (n=485)
Health concerns	80	16.49
Full-time carer	10	2.06
Relocation	8	1.65
Withdrawn	53	10.93
Non-contactable	24	4.95
Deceased	310	63.92

Total baseline n = 1066. Total invited back at year 10 follow-up n = 845. Total attenders at year 10 follow-up = 581. Total non-attenders at year 10 follow-up = 485.

5.1.5 Baseline characteristics of 10-year follow-up population versus non-attenders

Table 9 compares the baseline characteristics of the 10-year follow-up population (n=581) with those who did not attend for cognitive re-testing (n=485). The attending population was significantly different in age ($p<0.001$), deprivation status ($p=0.005$) and education ($p=0.041$) with participants who attended tending to be younger, less deprived and having achieved a higher level of education at baseline.

The attending population had a lower systolic blood pressure ($p=0.008$), a higher prevalence of hypertension ($p=0.004$) and a lower prevalence of stroke ($p=0.010$). There was also a statistically significant difference in smoking status ($p=0.009$), with less of the attenders being current smokers, and on average smoking less cigarettes ($p<0.001$). Conversely, the attending population consumed more units of alcohol than the non-attending population at baseline ($p=0.038$).

The status of diabetes was less severe in the attending population, with differences seen in duration of diabetes (p=0.004), and type of medication (p=0.005) - more of the attenders managed their diabetes with diet alone.

Obesity variables BMI (p=0.023), WC (p=0.014), and body fat (p=0.045) were lower in the attending population at baseline, except for waist to hip ratio, where no difference between the groups was observed. Markers of systemic inflammation were also significantly lower in the attending population (Fibrinogen; p<0.001, CRP; p<0.001, IL-6; p<0.001, TNF alpha; p=0.029).

The attending population also scored less on levels of anxiety or depression (both, p<0.001), and fewer people had a score of <24 on their MMSE test (p=0.022), 24 being the clinical cut-off used for referral when employed as a dementia screen.

Table 9. Baseline characteristics of attenders and non-attenders of the ET2DS at Year 10

Characteristic	Attenders		Non-Attenders		T or X^2 (p-value)
	N	Mean ± SD, median (IQR) or n (%)	N	Mean ± SD, median (IQR) or n (%)	
Demographic:					
Age (years)	581	67.31 ± 4.2	485	68.62 ± 4.2	-5.077 (<0.001)
Sex males (n %)	581	296 (50.9)	485	251 (51.8)	0.069 (0.793)
SIMD rank:	581		485		14.725 (0.005)
1st quintile		56 (9.6)		71 (14.6)	
2nd quintile		116 (20.0)		92 (19.0)	
3rd quintile		92 (15.8)		96 (19.8)	
4th quintile		103 (17.7)		91 (18.8)	
5th quintile		214 (36.8)		135 (27.8)	
Educational attainment:	581		485		8.234 (0.041)
University/ college		109 (18.8)		62 (12.8)	
Professional/ technical		169 (29.1)		138 (28.5)	
Secondary school		300 (51.6)		281 (57.9)	
Primary School		3 (0.5)		4 (0.8)	
Employment status:	581		485		21.438 (0.001)
Full-time		47 (8.1)		28 (5.8)	
Part-time		54 (9.3)		23 (4.7)	
Unemployed		7 (1.2)		2 (0.4)	
Retired		443 (76.2)		421 (86.8)	
Homemaker		15 (2.6)		4 (0.8)	
Other		15 (2.6)		7 (1.4)	

Vascular related:					
Systolic blood pressure (mmHg)	580	132.06 ± 14.7	484	134.79 ± 18.2	-2.651 (0.008)
Diastolic blood pressure (mmHg)	580	69.36 ± 8.5	484	68.69 ± 9.6	1.198 (0.231)
Hypertension (n)	580	178 (30.7)	484	189 (39.0)	8.161 (0.004)
Total cholesterol (mmol/l)	578	4.33 ± 0.9	479	4.29 ± 0.9	0.739 (0.462)
High density lipoprotein (mmol/l)	578	1.31 ± 0.4	479	1.27 ± 0.4	1.975 (0.049)
Serum triglycerides (mmol/l)	581	5.13 ± 58.5	485	14.04 ± 110.4	-1.601 (0.110)
Retinopathy (n)	575	173 (30.1)	469	166 (35.4)	3.318 (0.069)
Stroke (n)	581	24 (4.1)	485	38 (7.8)	6.621 (0.010)
TIA (n)	581	20 (3.4)	485	11 (2.3)	1.291 (0.256)
Smoking status (n)	581		485		9.456 (0.009)
- Current		70 (12.0)		84 (17.3)	
- Former		246 (42.3)		168 (34.6)	
- Never		265 (45.6)		233 (48.0)	
Total cigarettes smoked	577	1.66 ± 5.81	484	3.14 ± 8.02	6.874 (<0.001)
Alcohol units	581	9.85 ± 14.5	485	8.00 ± 14.5	2.081 (0.038)
Diabetes related:					
Duration (median years (IQR))	581	8.19 ± 9.8	485	10.33 ± 13.9	-2.857 (0.004)
HbA1c (median (IQR))	578	7.37 ± 1.1	479	7.45 ± 1.2	-1.133 (0.258)
Plasma Glucose (mmol/L)	574	7.48 ± 1.9	475	7.66 ± 2.3	-1.406 (0.160)
Medication status (n)	581		485		10.511 (0.005)
- Insulin ± oral		89 (15.3)		97 (20.0)	
- Oral		365 (62.8)		316 (65.2)	
- Diet controlled		127 (21.9)		72 (14.8)	

Obesity related:					
Body mass index (kg/m2)	581	31.06 ± 5.5	484	31.86 ± 5.9	-2.273 (0.023)
Waist circumference (cm)	580	106.01 ± 12.7	481	107.95 ± 12.9	-2.463 (0.014)
Waist to hip ratio	580	0.96 ± 0.1	481	0.96 ± 0.1	-1.004 (0.315)
Body fat (%)	574	37.67 ± 7.7	478	38.60 ± 7.4	-2.010 (0.045)
Inflammatory related:					
Fibrinogen (median ng/ml)	580	3.57 ± 0.7	483	3.74 ± 0.8	-3.677 (<0.001)
CRP (median mg/ml)	569	3.15 ± 4.5	473	4.77 ± 7.4	-4.161 (<0.001)
IL-6 (median pg/ml)	580	3.45 ± 3.2	484	4.49 ± 3.8	-4.771 (<0.001)
TNFα (median pg/ml)	579	1.26 ± 1.7	484	1.47 ± 1.3	-2.184 (0.029)
Psychological:					
MMSE <24	581	18 (3.1)	485	29 (6.0)	5.247 (0.022)
HADS A	581	5.29 ± 3.7	484	6.24 ± 4.1	-3.922 (<0.001)
HADS D	581	3.47 ± 2.7	484	4.32 ± 3.0	-4.785 (<0.001)

Total attenders n = 581 (max). Total non-attenders n = 485 (max). Analysis is a two-tailed independent t-test or Pearson's chi squared. Values are means ± SD, median (interquartile range) or n (%). SIMD, Scottish Index of Multiple Deprivation; HbA1c, haemoglobin A1c; CRP, c-reactive protein; IL-6, interleukin-6; TNFα, tumour necrosis factor α; TIA, transient ischaemic attack; MMSE, Mini Mental State Exam; HADS A, Hospital Anxiety and Depression Scale-Anxiety subscale; Hospital HADS B, Hospital Anxiety and Depression Scale-Depression subscale.

5.1.6 Baseline cognitive status of total study population and those attending 10-year follow-up

The correlations between the individual cognitive tests are shown in Table 10a and 10b. The cognitive tests at baseline were all highly correlated ($p<0.001$), and this was also observed at follow-up ($p<0.001$). Note that for TMTB, the correlations are all negative as for this test a higher score represents a worse performance.

Table 11 presents the cognitive ability of the total study population at baseline (n=1066). It also compares the baseline cognitive ability of the population who attended the follow-up clinic (n=581) with those who did not attend (n=485).

At baseline, the general cognition, as measured by '*g*', of the total population was arbitrarily centred on 0 with a standard deviation of 1. The population who went on to attend the 10-year follow-up had a higher mean '*g*' score than those who did not attend (0.21±0.95 versus -0.26±1.00; R 0.25). Similarly, when looking at the constituent cognitive tests the attending population consistently had a superior score when compared with those of the non-attending population.

Table 10. (a) Inter-correlations of cognitive test scores at baseline

	MHVS	LM	Faces	MR	DST	lnTMTB	LNS	BVFT
MHVS	-	0.38	0.28	0.45	0.37	-0.37	0.40	0.44
LM		-	0.24	0.28	0.27	-0.28	0.31	0.25
Faces			-	0.24	0.29	-0.26	0.20	0.22
MR				-	0.38	-0.46	0.40	0.36
DST					-	-0.63	0.40	0.40
lnTMTB						-	-0.50	-0.39
LNS							-	0.46
BVFT								-

Cognitive tests are non-imputed. Values for all individual cognitive tests are correlation coefficients from two-tailed Pearson correlations. All p<0.001. MHVS, Mill Hill Vocabulary Scale; LM, Logical Memory; MR, Matrix Reasoning; DST, Digit Symbol Test; lnTMTB, Trail Making Test B (Natural log transformed); LNS, Letter Number Sequencing; BVFT, Borkowski Verbal Fluency Test.

Table 10. (b) Inter-correlations of cognitive test scores at year 10

	MHVS	LM	Faces	MR	DST	lnTMTB	LNS	BVFT
MHVS	-	-0.42	0.33	0.46	0.43	-0.37	0.44	0.45
LM		-	0.35	0.38	0.45	-0.46	0.44	0.29
Faces			-	0.33	0.41	-0.36	0.31	0.33
MR				-	0.49	-0.52	0.52	0.40
DST					-	-0.74	0.52	0.45
lnTMTB						-	-0.57	-0.40
LNS							-	0.46
BVFT								-

Cognitive tests are non-imputed. Values for all individual cognitive tests are correlation coefficients from two-tailed Pearson correlations. All p<0.001. MHVS, Mill Hill Vocabulary Scale; LM, Logical Memory; MR, Matrix Reasoning; DST, Digit Symbol Test; lnTMTB, Trail Making Test B (Natural log transformed); LNS, Letter Number Sequencing; BVFT, Borkowski Verbal Fluency Test.

Table 11. Baseline cognitive test scores for total population and for 10 year follow-up population

Cognitive test	Total Population (maximum n=1066)				Population attending follow-up (maximum n = 581)				Population not attending follow-up (maximum n = 485)			
	N	mean ± SD	Min	Max	N	mean ± SD	Min	Max	N	mean ± SD	Min	Max
g	1061	0.00 ± 1.00	-3.37	3.08	581	0.21 ± 0.95	-2.65	3.08	480	-0.26 ± 1.00	-3.37	2.26
MMSE	1063	28.30 ± 1.89	14	30	580	28.51 ± 1.62	21	30	483	28.06 ± 2.14	14	30
MHVS	1049	30.93 ± 5.23	9	43	574	31.59 ± 5.23	11	43	475	30.13 ± 5.11	9	43
LM	1050	25.24 ± 8.17	0	46	577	25.83 ± 8.06	4	46	473	24.52 ± 8.26	0	45
TMTB	1052	119.00 ± 59.63	38	570	578	109.63 ± 51.09	38	570	474	130.43 ± 66.93	40	498
Faces	1059	65.82 ± 7.88	40	88	580	66.89 ± 7.84	40	88	479	64.52 ± 7.75	42	84
MR	1052	12.81 ± 5.28	3	25	575	13.74 ± 5.32	4	25	477	11.69 ± 5.01	3	25
DST	1057	49.21 ± 14.77	9	99	579	51.78 ± 4.56	9	99	478	46.09 ± 14.43	10	93
BVFT	1060	36.93 ± 12.83	5	79	580	38.28 ± 12.65	8	79	480	35.29 ± 12.87	5	76
LNS	1048	9.67 ± 2.75	0	19	575	10.07 ± 2.70	2	19	473	9.19 ±2.74	0	17

Values are mean ± SD. Data for *g* has been imputed; for remaining cognitive tests are non-imputed. *G* was arbitrarily standardised through principal components analysis, resulting in mean = 0 and SD = 1. Data for TMTB was log transformed prior to analysis. MMSE, Mini-Mental-State Examination; MHVS, Mill Hill Vocabulary Scale; LM, Logical Memory; TMTB, Trail-Making Test-B; MR, Matrix Reasoning; DST, Digit Symbol Test; BVFT, Borkowski Verbal Fluency Test; LNS, Letter Number Sequencing.

5.1.7 Change in cognitive scores from baseline to year 10 in those attending follow-up

Table 12 describes the cognitive test scores of the population attending follow-up at baseline and at year 10. General cognition, '*g*' was 0.34±0.85 at baseline in the attending population which fell to -0.10±0.90 at year 10. This was reflected by the other cognitive tests, where performance in all cognitive tests worsened at follow-up, except for the Faces test where performance improved slightly at follow-up (66.99±7.83 versus 67.86±8.75). Mean performance in the MHVS was poorer at follow-up, despite being used as a measure of crystallised intelligence that was predicted to remain relatively stable over time.

5.1.8 Baseline characteristics of people with incident dementia by year 10

Table 13 compares the baseline characteristics of the people classed as having probable dementia at year 10 (n=106) with those without dementia (n=960).

The probable dementia group was significantly different in age ($p<0.001$). After adjusting for age and sex, the probable dementia group consumed on average significantly less alcohol at baseline ($p=0.013$), than those without dementia. Percentage of body fat was lower at baseline in the group with probable dementia ($p=0.025$) and psychological tests revealed that the probable dementia group had a higher percentage of people scoring less than 24 on their MMSE dementia screen test ($p<0.001$), 24 being the clinical cut-off used for referral, and this group had higher levels of anxiety and depression when compared to the remaining sample ($p=0.001$, $p<0.001$, respectively).

Table 12. Cognitive test scores of attenders at follow-up at baseline and year 10 follow-up

Cognitive test	N	Baseline score of population attending follow-up mean ± SD	Year 10 follow-up score of population attending follow-up mean ±SD
g	526	0.34 ± 0.85	-0.10 ± 0.90
MMSE	580	28.51 ± 1.62	27.62 ± 3.16
MHVS	550	31.45 ± 5.13	30.76 ± 5.59
LM	577	25.83 ± 8.06	23.32 ± 9.21
TMTB†	544	97.00 (76.00-124.00)†	127.00 (98.00-178.00)†
Faces	563	66.99 ± 7.83	67.86 ± 8.75
MR	568	13.77 ± 5.32	10.96 ± 5.32
DST	553	52.37 ± 14.39	43.90 ± 14.28
BVFT	576	38.37 ± 12.62	35.50 ± 13.29
LNS	567	10.09 ± 2.69	7.73 ± 3.31

Maximum n = 581. Values are mean ± SD (unless indicated†). Data for *g* have been imputed; for remaining cognitive tests are non-imputed. *G* was arbitrarily standardised through principal components analysis, resulting in mean = 0 and SD = 1. MMSE, Mini-Mental-State Examination; MHVS, Mill Hill Vocabulary Scale; LM, Logical Memory; TMTB, Trail Making Test B; MR, Matrix Reasoning; DST, Digit Symbol Test; BVFT, Borkowski Verbal Fluency Test; LNS, Letter Number Sequencing. †TMTB values are median (IQR), as not normally distributed, analysis is Natural Log transformed.

Table 13. Baseline demographic characteristics of dementia patients and sample without dementia at year 10

Demographic:	Dementia (total n = 106)	Remaining sample (total n = 960)	B (SE)	OR (95% CI)
Demographic:				
Age (years)	69.40 ± 3.95	67.74 ± 4.20	**0.097*** (0.025)**	1.102 (1.048-1.158)
Sex males (n %)	64 (60.4)	483 (50.3)	**0.409* (0.209)**	1.505 (0.999-2.266)
SIMD rank:			-0.32 (0.074)	0.968 (0.838-1.119)
1st quintile	13 (12.3)	114 (11.9)		
2nd quintile	17 (16.0)	191 (19.9)		
3rd quintile	20 (18.9)	168 (17.5)		
4th quintile	27 (25.5)	167 (17.4)		
5th quintile	29 (27.4)	320 (33.3)		
Educational attainment:			0.141 (0.142)	1.151 (0.872-1.519)
University/ college	18 (17.0)	153 (15.9)		
Professional/ technical	21 (19.8)	286 (29.8)		
Secondary school	65 (61.3)	516 (53.8)		
Primary School	2 (1.9)	5 (0.5)		
Employment status:			-0.085 (0.118)	0.918 (0.728-1.158)
Full-time	8 (7.5)	67 (7.0)		
Part-time	5 (4.7)	72 (7.5)		
Unemployed	0	9 (0.9)		
Retired	92 (86.8)	772 (80.4)		
Homemaker	1 (0.9)	18 (1.9)		
Other	0	22 (2.3)		
Vascular related:				
Systolic blood pressure (mmHg)	133.90 ± 15.73	133.24 ±16.53	0.000 (0.006)	1 (0.988-1.013)

Diastolic blood pressure (mmHg)	68.78 ± 9.88	69.09 ± 8.92	-0.001 (0.012)	0.999 (0.976-1.023)
Hypertension (n)	38 (35.8)	329 (34.3)	0.043 (0.216)	1.044 (0.684-1.1593)
Total cholesterol (mmol/l)	4.26 ± 0.98	4.32 ± 0.89	0.002 (0.120)	1.002 (0.792-1.268)
High density lipoprotein (mmol/l)	1.27 ± 0.33	1.30 ± 0.37	-0.165 (0.303)	0.848 (0.469-1.534)
Serum triglycerides (mmol/l)	1.64 ± 0.75	1.70 ± 0.64	-0.073 (0.169)	0.929 (0.667-1.295)
Retinopathy (n)	43 (40.6)	60 (56.6)	0.423 (0.214)	1.526 (1.003-2.322)
Stroke (n)	7 (6.6)	55 (5.7)	0.001 (0.421)	1.001 (0.438-2.286)
TIA (n)	5 (4.7)	26 (2.7)	0.530 (0.507)	1.699 (0.629-4.593)
Smoking status			0.047 (0.158)	1.049 (0.769-1.430)
- current	10 (9.4)	144 (15.0)		
- Former	59 (55.7)	439 (45.7)		
- Never	37 (34.9)	377 (39.3)		
Total cigarettes per day	1.73 ± 5.97	2.40 ± 7.04	-0.012 (0.018)	0.988 (0.954-1.022)
Alcohol units	6.23 ± 10.63	9.32 ± 14.82	**-0.026* (0.010)**	0.975 (0.955-0.995)
Diabetes related:				
Diabetes duration (median years (IQR)) †	7 (10)	6 (8)	0.121 (0.128)	1.129 (0.878-1.451)
HbA1c (median (IQR)) †	7.2 (1.4)	7.2 (1.2)	0.744 (0.726)	2.103 (0.507-8.729)
Plasma Glucose (mmol/L)	7.35 ± 2.67	7.59 ± 2.67	-0.057 (0.054)	0.945 (0.849-1.051)
Medication status (n)			0.176 (0.171)	1.193 (0.852-1.669)
- Insulin ± oral	22 (20.8)	164 (17.1)		

- Oral	66 (62.3)	615 (64.1)		
- Diet controlled	18 (17.0)	181 (18.9)		
Obesity related:				
Body mass index (kg/m2)	29.97 ± 5.19	31.59 ± 5.72	-0.040 (0.021)	0.961 (0.922-1.002)
Waist circumference (cm)	104.41 ± 12.98	107.17 ± 12.78	-0.016 (0.009)	0.984 (0.968-1.001)
Waist to hip ratio	0.97 ± 0.08	0.96 ± 0.07	0.022 (0.017)	1.023 (0.989-1.057)
Body fat (%)	35.83 ± 7.18	38.34 ± 7.56	**-0.044* (0.019)**	0.957 (0.922-0.994)
Inflammatory related:				
Fibrinogen (median ng/ml)	3.54 (1.00)	3.61 (0.96)	-0.095 (0.144)	0.909 (0.685-1.206)
CRP (median mg/ml) †	1.51 (2.53)	1.92 (3.62)	-0.155 (0.091)	0.856 (0.716-1.024)
IL-6 (median pg/ml) †	2.91 (2.72)	2.87 (2.49)	0.141 (0.152)	1.152 (0.854-1.553)
TNFα (median pg/ml) †	1.09 (1.13)	1.07 (0.92)	0.014 (0.141)	1.014 (0.768-1.337)
Psychological:				
MMSE <24 (n)	16 (15.1)	31 (3.2)	**1.605*** (0.334)**	4.977 (2.589-9.568)
HADS A	6.60 ± 4.57	5.63 ± 3.82	**0.089** (0.026)**	1.093 (1.038-1.151)
HADS D	4.70 ± 3.15	3.76 ± 2.85	**0.121*** (0.034)**	1.129 (1.057-1.206)

Total dementia cases n = 106. Total remaining sample n = 960. Analyses are logistic regression adjusting for age and sex. Values are means ± SD, median (interquartile range) or n (%), B; Unstandardised beta (Standard error), OR; Odds Ratio (95% Confidence interval). SIMD, Scottish Index of Multiple Deprivation; HbA1c, haemoglobin A1c; CRP, c-reactive protein; IL-6, interleukin-6; TNFα, tumour necrosis factor α; TIA, transient ischaemic attack; MMSE, Mini Mental State Exam; HADS A, Hospital Anxiety and Depression Scale-Anxiety subscale; Hospital HADS B, Hospital Anxiety and Depression Scale- Depression subscale. † Log transformed for analyses

5.1.9 Baseline cognitive ability of people with incident dementia at year 10

The baseline cognitive test scores of the people with probable incident dementia by year 10 follow-up are shown in Table 14. All cognitive test scores in the dementia group were lower than those of the remaining sample at baseline. MHVS, providing a measure of crystallised cognitive ability was lower in the probable dementia group, despite this group not having been diagnosed with dementia at baseline and so was predicted to be the same. MMSE, used to screen for dementia, was lower at baseline in the probable incident dementia group than the remaining sample, which indicates that the sample at baseline who went on to develop dementia in the following 10 years, may have already been experiencing a form of pre-dementia.

Table 14. Baseline cognitive test scores in dementia patients and sample without dementia at year 10 follow up

	Y10 Dementia group at BL (max n=106)		Remaining Sample at BL (max n= 960)	
Cognitive test	Total (N)	Mean ± SD	Total (N)	Mean ± SD
g	105	-0.61 ± 1.10	956	0.08 ± 0.96
MMSE	106	27.11 ± 2.77	957	28.43 ± 1.72
MHVS	104	29.34 ± 5.89	945	31.11 ± 5.12
LM	100	22.04 ± 8.57	950	25.58 ± 8.06
Faces	105	63.55 ± 7.74	954	66.07 ± 7.86
MR	105	11.27 ± 5.49	947	12.99 ± 5.23
DST	104	42.74 ± 14.30	953	49.91 ± 14.66
TMTB†	104	132.50 ± 96.00	948	102.00 ± 55.00
LNS	106	8.22 ± 2.77	942	9.84 ± 2.70
BVFT	106	32.97 ± 13.07	954	37.37 ± 12.74

Values are mean ± SD (unless indicated†). Data for *g* has been imputed; for remaining cognitive tests are non-imputed. *G* was arbitrarily standardised through principal components analysis, resulting in mean = 0 and SD = 1. Data for TMTB was log transformed prior to analysis. MMSE, Mini-Mental-State Examination; MHVS, Mill Hill Vocabulary Scale; LM, Logical Memory; TMTB, Trail-Making Test-B; MR, Matrix Reasoning; DST, Digit Symbol Test; BVFT, Borkowski Verbal Fluency Test; LNS, Letter Number Sequencing. †TMTB values are median (IQR), as not normally distributed.

5.2 INTER-CORRELATIONS AND RISK FACTOR ASSOCIATIONS OF OBESITY AND SYSTEMIC INFLAMMATION MARKERS

5.2.1 Inter-correlations of obesity measures and association with other risk factors at baseline

Table 15a shows the correlations between all the obesity measures collected at baseline. All variables were significantly correlated with each other (all $p<0.001$), with correlation coefficients being larger for BMI with WC and BF (0.84 and 0.68), than WHR with WC and BF (0.49 and 0.19). BMI and WHR were significantly correlated at baseline but with a relatively low correlation coefficient of 0.10, indicating a weak effect.

Table 15b shows the correlations between all obesity measures collected at follow-up. Again, all were significantly associated with each other (all $p<0.001$). Correlation coefficients between the variables reflected those seen at baseline, with smaller associations between BMI and WHR (0.18) than that seen with WC (0.81).

Table 16 shows the association of BMI and WHR with the other baseline risk factors. To summarise, higher BMI was significantly associated with more intensive types of diabetic medication status ($p =0.003$) as was a higher WHR ($p<0.001$). Both higher BMI and higher WHR were also associated with male sex (both $p<0.001$), increased risk of angina (both $p<0.001$), lower level of HDL (both $p<0.001$), increased serum triglycerides (both $p<0.001$) and increased severity of depression (both $p<0.001$).

Increased BMI was as also significantly associated with age ($p<0.001$), diastolic BP ($p=0.024$) and number of alcohol units consumed ($p=0.025$), while WHR was not. In contrast, Increased WHR was significantly associated with the duration of diabetes ($p<0.001$), HbA1c ($p<0.001$, plasma glucose ($p=0.004$), diabetic retinopathy ($p=0.006$), anxiety ($p=0.005$), smoking status ($p=0.002$) and number of cigarettes smoked ($p=0.006$), while BMI was not.

This highlights that while BMI and WHR are often used to measure the same clinical outcome (obesity), subtle differences are present when looking at risk factor associations.

Table 15. (a) Inter-correlations of obesity measures at baseline

	BMI	WHR	WC	BF (%)
BMI	-	0.099	0.843	0.682
WHR		-	0.499	0.192
WC			-	0.444
BF (%)				-

Values for all individual obesity measures are correlation coefficients from two-tailed Pearson correlations. All p<0.001. BMI, Body Mass Index; WHR, Waist to Hip Ratio; WC, Waist circumference; BF, Body fat.

Table 15. (b) Inter-correlations of obesity measures at year 10 follow-up

	BMI	WHR	WC
BMI	-	0.179	0.814
WHR		-	0.571
WC			-

Values for all individual obesity measures are correlation coefficients from two-tailed Pearson correlations. All p<0.001. BMI, Body Mass Index; WHR, Waist to Hip Ratio; WC, Waist circumference.

Table 16. Associations between BMI and WHR with baseline risk factors

Characteristic	n	BMI			WHR		
		r	Beta (SE)	P value	r	Beta (SE)	P value
Demographic:							
Age (years)	1066	-0.194		<0.001	-0.049		0.109
Sex males	1066		2.218 (0.342)	<0.001		-0.075 (0.004)	<0.001
Diabetes related:							
Diabetes duration (years)†	1053	0.050		0.109	0.115		<0.001
HbA1c†	1057	0.047		0.132	0.161		<0.001
Plasma Glucose (mmol/l)	1049	0.035		0.275	0.092		0.004
Diabetic medication	1066		0.823 (0.279)	0.003		0.016 (0.003)	<0.001
Vascular related:							
Systolic BP (mmHg)	1064	0.057		0.076	-0.027		0.393
Diastolic BP (mmHg)	1064	0.072		0.024	0.042		0.188
Hypertension	1064		0.602 (0.353)	0.089		-0.001 (0.004)	0.822
Stroke	1066		1.170 (0.726)	0.107		0.020 (0.009)	0.023
TIA	1066		-0.873 (1.000)	0.383		0.003 (0.012)	0.775
MI	1066		0.823 (0.496)	0.098		0.010 (0.006)	0.081
Angina	1066		1.569 (0.377)	<0.001		0.018 (0.005)	<0.001
Diabetic retinopathy	1044		0.162 (0.361)	0.653		0.012 (0.074)	0.006
High density lipoprotein (mmol/l)	1057	-0.185		<0.001	-0.187		<0.001

Serum triglycerides (mmol/l)	1058	0.127		<0.001	0.128		<0.001
Smoking status (current, ex, non-smoker)	1066		0.005 (0.251)	0.983		-0.009 (0.003)	0.002
Total cigarettes per day	1061	-0.039		0.220	0.087		0.006
Alcohol units	1066	-0.071		0.025	-0.025		0.425
Psychological related:							
HADS A	1065	0.032		0.309	0.090		0.005
HADS D	1065	0.183		<0.001	0.183		<0.001

Analyses are two-tailed Pearson correlations, Spearman's correlations (if indicated) or ANCOVA adjusted for age and sex ('Demographic', unadjusted). Values are Spearman's correlation coefficients for duration of diabetes, HbA1c, smoking pack years, alcohol units. Values are Beta coefficients for sex, hypertension, stroke, TIA, MI, Angina, Diabetic Retinopathy, Smoking status. BMI, Body Mass Index; WHR, Waist to Hip Ratio; HbA1c, haemoglobin A1c, TIA, Transient Ischaemic Attack; MI, Myocardial Infarction; HADS A, Hospital Anxiety and Depression Scale-Anxiety subscale; Hospital HADS B, Hospital Anxiety and Depression Scale- Depression subscale. †Spearman's correlation analysis.

5.2.2 Inter-correlations of inflammatory markers and associations with obesity measures

Table 17 shows the correlation between the individual markers for systemic inflammation at baseline. A significant but weak positive correlation between all markers (fibrinogen, CRP, IL-6 and TNF alpha) was observed ($p<0.001$). The association of BMI and WHR with the inflammation markers (fibrinogen, CRP, IL-6 and TNF alpha) are shown in Table 18. Both increased BMI and increased WHR were significantly associated with each of the markers (r 0.071- 0.237; all $p<0.05$).

Table 17. Inter-correlations of inflammatory biomarkers at baseline

	Fibrinogen (ng/mol)	lnCRP (mg/mol)	lnIL-6 (pg/mol)	lnTNFα (pg/mol)
Fibrinogen (ng/mol)	-	0.533	0.338	0.128
lnCRP (mg/mol)		-	0.426	0.119
lnIL-6 (pg/mol)			-	0.314
lnTNFα (pg/mol)				-

Values for all individual inflammatory measures are correlation coefficients from two-tailed Pearson correlations. All $p<0.001$. TNFα, Tumour Necrosis Factor Alpha; IL-6, Interleukin-6; CRP, C- Reactive Protein.

Table 18. Associations between BMI and WHR with potential mediating inflammatory risk factors at baseline

Marker	BMI		WHR	
	r	p-value	r	p-value
Fibrinogen	0.177	<0.001	0.071	0.023
lnCRP	0.231	<0.001	0.118	<0.001
lnIL-6	0.237	<0.001	0.124	<0.001
lnTNFα	0.106	0.001	0.099	0.001

Analyses are two-tailed Pearson correlations controlling for age and sex. Log-transformed variables were used for CRP, IL-6 and TNF-α. BMI, Body Mass Index; WHR, Waist to Hip Ratio; CRP, c-reactive protein; IL-6, interleukin-6; TNFα, tumour necrosis factor α.

5.2.3 The association between systemic inflammatory markers and cognitive ability at baseline

Table 19 (re-analysed and adapted from Marioni et al. (2010)), shows the outcome of the regression models investigating the effect of inflammation on cognitive ability as measured at baseline.

General cognitive ability was negatively associated with IL-6, both when adjusted for age and sex (standardised beta= -0.159; p<0.001), and in the fully adjusted model (standardised beta= -0.126; p<0.001). This result was mirrored by the majority individual cognitive tests where fully adjusted models for lnTMTB (standardised beta= 0.144; p<0.001), Faces (standardised beta= -0.078; p=0.017), MR (standardised beta= -0.105; p=0.002) and DST (standardised beta= -0.111; p<0.001) were associated with lower levels of IL-6 when adjusted for diabetes and vascular risk factors. General cognitive ability was also associated with TNF alpha (standardised beta= -0.085; p=0.007); however, in fully adjusted models this

association was no longer significant. The association between TNF alpha and cognitive tests TMTB and MR was however found to be statistically significant in fully adjusted models (standardised beta= 0.064; p= 0.042, standardised beta= -0.098; p= 0.002, respectively).

Other inflammatory markers were associated with performance in a selection of the cognitive tests. Fibrinogen was associated with performance in TMTB (standardised beta= 0.092; p=0.004) and MR (standardised beta= -0.029, p=0.030) when adjusted for age and sex; however, this association diminished in fully adjusted models. TNF alpha was found to be associated with performance in MR, when adjusted for age and sex but also in fully adjusted models (standardised beta= -0.097, p=0.002).

It should be noted that for the analysis on CRP, cases with CRP level above 10 mg/ml were removed, as these are indicative of acute inflammation likely as a result of a temporary infection. Despite this, statistically significant associations with CRP were found.

In summary, inflammatory markers TNF alpha and IL-6 were shown to be associated with cognitive ability in fully adjusted models, the latter marker being also significantly associated with the general cognitive ability as measured by '*g*'.

Table 19. The association between inflammatory markers and cognitive status as measured by individual cognitive tests and *g* at baseline

Inflammation marker	*g*	LM	ln TMTB	Faces	MR	DST	BVFT	LNS
	Standardised Beta (SE)							
Fibrinogen + age and sex	-0.047 (0.032)	-0.016 (0.033)	**0.092**** **(0.032)**	-0.029 (0.032)	**-0.070 *** **(0.032)**	-0.024 (0.032)	0.012 (0.033)	0.001 (0.032)
+ full adjustment of baseline covariates	-0.006 (0.032)	-0.004 (0.034)	0.055 (0.033)	-0.016 (0.033)	-0.037 (0.032)	0.024 (0.032)	0.035 (0.033)	0.021 (0.033)
lnCRP + age and sex	-0.051 (0.038)	0.030 (0.039)	0.073 (0.038)	-0.020 (0.038)	-0.075 (0.038)	-0.033 (0.038)	-0.030 (0.039)	0.035 (0.038)
+ full adjustment of baseline covariates	-0.010 (0.038)	0.054 (0.041)	0.042 (0.039)	-0.020 (0.040)	-0.032 (0.039)	0.007 (0.039)	-0.006 (0.040)	-0.012 (0.040)
lnIL-6 + age and sex	**-0.159 ***** **(0.031)**	-0.029 (0.032)	**0.176 ***** **(0.031)**	**-0.084 **** **(0.031)**	**-0.127***** **(0.031)**	**-0.149 ***** **(0.031)**	**-0.087 **** **(0.032)**	**-0.075*** **(0.032)**
+ full adjustment of baseline covariates	**-0.126 ***** **(0.031)**	-0.022 (0.034)	**0.144 ***** **(0.032)**	**-0.078 *** **(0.033)**	**-0.105 ***** **(0.033)**	**-0.111 ***** **(0.032)**	-0.063 (0.033)	-0.058 (0.033)
lnTNFα + age and sex	**-0.085 **** **(0.031)**	-0.025 (0.032)	**0.084 **** **(0.032)**	**-0.063 *** **(0.031)**	**-0.114 ***** **(0.031)**	-0.019 (0.031)	-0.044 (0.032)	-0.047 (0.032)
+ full adjustment of baseline covariates	-0.058 (0.031)	-0.022 (0.033)	**0.064 *** **(0.032)**	-0.055 (0.032)	**-0.098 *** **(0.032)**	0.018 (0.031)	-0.020 (0.032)	-0.038 (0.032)

*p<0.05 **p<0.01 ***p<0.001. Baseline covariates: duration of diabetes (years), HbA1c (haemoglobin A1c), diabetic medication, hypertension, Cerebral Event (Stroke or TIA), Heart disease (Angina or MI), HDL (mmol/l), serum triglycerides (mmol/l), smoking (current, ex, or non-smoker), alcohol units, Diabetic retinopathy, anxiety, depression. Data for *g* have been imputed, for remaining cognitive tests are non-imputed. LM, Logical Memory; MR, Matrix Reasoning; DST, Digit Symbol Test; lnTMTB, Trail Making Test B (Natural log transformed); BVFT, Borkowski Verbal Fluency Test; CRP, c-reactive protein; IL-6, interleukin-6; TNFα, tumour necrosis factor α.

5.2.4 Associations between obesity measures and cognitive ability at baseline

The cross-sectional associations between obesity measures and cognitive ability at baseline are shown in Table 20. Higher BMI was significantly associated with poorer general cognition (r= -0.08; p=0.008), when adjusting for age and sex. Higher BMI was also significantly associated poorer scores in a number of the individual cognitive tests; MR (r=-0.08; p=0.014), DST (r=-0.11; p=0.001) and BVFT (r=-0.07; p=0.027), when adjusting for age and sex. Higher WHR was also significantly associated with poorer general cognition (r=-0.16; p<0.001), when adjusting for age and sex. Notably, this effect size was almost double that of BMI. Higher WHR was also significantly associated with poorer scores in the majority of the individual cognitive tests. WHR was associated with Faces (r=-0.09; p=0.006), MR (r=-0.11; p= 0.001), DST (r=-0.14; p<0.001), lnTMTB (r=0.14; p<0.001), LNS (r=-0.09; p=0.007) and BVFT (r=-0.11; p=0.001). The effect sizes for the associations between cognitive ability and WHR were all greater than for those with BMI, with the greatest differences in effect size observed for InTMTB and LNS.

Table 20. Cross-sectional associations between BMI and WHR and cognitive test scores at baseline

Cognitive test	BMI		WHR	
	r	p-value	r	p-value
g	-0.083	0.008	-0.161	<0.001
LM	0.010	0.758	-0.052	0.100
Faces	-0.037	0.245	-0.086	0.006
MR	-0.077	0.014	-0.108	0.001
DST	-0.109	0.001	-0.143	<0.001
lnTMTB	0.057	0.068	0.144	<0.001
LNS	-0.025	0.430	-0.085	0.007
BVFT	-0.070	0.027	-0.107	0.001

Analyses are two-tailed Pearson correlations controlling for age and sex. Data for *g* have been imputed, for remaining cognitive tests are non-imputed. BMI, Body Mass Index; WHR, Waist to Hip Ratio; LM, Logical Memory; lnTMTB, Trail Making Test B (Natural log transformed); MR, Matrix Reasoning; DST, Digit Symbol Test; BVFT, Borkowski Verbal Fluency Test; LNS, Letter Number Sequencing.

5.3 OBESITY, INFLAMMATION AND COGNITIVE CHANGE

5.3.1 The association between BMI and cognitive decline

As BMI is often associated with cardiovascular outcomes in a non-linear or J-shaped manner, the main association of BMI with the cognitive outcome 'g' was investigated for linearity. As the conventional clinical cut off scores, developed for cardiovascular outcomes did not generate equal categories in this data set, namely that only 1 person had a BMI of <18.5 kg/m^2 and 590 had a BMI of >30 kg/m^2 (see Table 7), quintile scores were derived which distributed the data equally among 5 groups. The cut-points of the quintiles along with the distribution of age and sex are described in Table 21. As there was slight variation in age and sex within the quintiles, analyses were adjusted for age and sex. When plotting

the 5 quintile BMI groups against the mean follow-up ‘g’ score per group there appeared to be no strong evidence for a non-linear association. Similarly, scatterplots of BMI as a continuous variable against follow-up ‘g’, indicated that there was also no evidence for a non-linear association (See Figure 5).

Table 21. The cut-points and distribution of age and sex per BMI quintile

BMI quintile	Quintile cut - point		% Male	Mean age (years) (± SD)
	Minimum BMI (kg/m^2)	Maximum BMI (kg/m^2)		
1	18.39	26.70	22.30	68.85 (3.79)
2	26.72	29.17	24.00	68.3 (4.13)
3	29.19	32.00	21.20	68.13 (4.15)
4	32.02	35.49	19.20	67.44 (4.32)
5	35.50	55.44	13.20	66.78 (4.32)

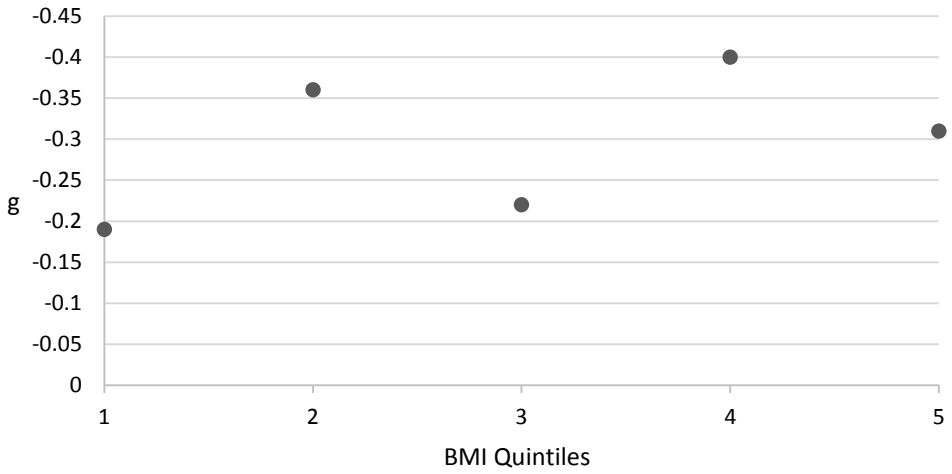

Figure 5. Baseline BMI categorised by quintile plotted against follow-up ‘g’

Outcomes of the regression models investigating the association between BMI and change in cognition are shown in Table 22. After adjusting for age and sex, higher BMI was associated with poorer scores in follow-up '*g*' (standardised beta= -0.093; p=0.033), MR (standardised beta= -0.107; p=0.016) and DST (standardised beta= -0.096; p=0.032). These initial associations did not remain after adjusting for baseline cognitive test score or any other subsequent adjustments for diabetes or vascular risk factors.

A higher BMI was associated with a worse performance in LNS when adjusting for baseline cognitive test score. When adjusting for age, sex and baseline LNS score, an increased BMI was associated with a significantly poorer performance in LNS (standardised beta= -0.087; p=0.027) thereby indicating an association with a change in cognition. This association persisted after further adjusting for diabetes related risk factors (standardised beta= -0.082; p=0.039). However, in the fully adjusted model, which included vascular covariates, this association was no longer significant. All other associations between BMI and cognitive test at follow-up were not significant and remained so after each adjustment.

In summary, despite observed associations between increased BMI and poorer follow-up cognitive ability, an increased BMI was only associated with worsened cognitive decline in the LNS subtest, where performance is related to working memory and processing speed.

Table 22. The association between BMI and cognitive decline as measured by individual cognitive tests and *g* at year 10 follow-up

BMI	*g*	LM	ln TMTB	Faces	MR	DST	BVFT	LNS
	Standardised Beta (SE)							
+ age and sex	**-0.093*** **(0.045)**	-0.033 (0.047)	0.077 (0.047)	-0.004 (0.045)	**-0.107*** **(0.046)**	**-0.096*** **(0.047)**	-0.068 (0.047)	-0.083 (0.047)
+ baseline cognition score	-0.041 (0.029)	-0.040 (0.039)	0.039 (0.038)	0.022 (0.038)	-0.062 (0.036)	-0.027 (0.034)	-0.047 (0.031)	**-0.087*** **(0.041)**
+ baseline diabetes covariates	-0.038 (0.029)	-0.040 (0.039)	0.039 (0.038)	0.030 (0.038)	-0.058 (0.036)	-0.028 (0.034)	-0.046 (0.031)	**-0.082*** **(0.041)**
+ baseline vascular covariates	-0.017 (0.031)	-0.018 (0.041)	0.022 (0.040)	0.044 (0.040)	-0.036 (0.038)	-0.012 (0.035)	-0.036 (0.033)	-0.043 (0.043)

*p<0.05 **p<0.01 ***p<0.001. Baseline diabetes covariates: duration of diabetes (years) (natural log transformed), HbA1c (haemoglobin A1c) (natural log transformed), diabetic medication. Baseline vascular covariates: hypertension, Cerebral Event (Stroke or TIA), Heart disease (Angina or MI), HDL (mmol/l), serum triglycerides (mmol/l), smoking (current, ex, or non-smoker), alcohol units, Diabetic retinopathy, anxiety, depression. Data for *g* have been imputed, for remaining cognitive tests are non-imputed. BMI, Body Mass Index; LM, Logical Memory; MR, Matrix Reasoning; DST, Digit Symbol Test; lnTMTB, Trail Making Test B (Natural log transformed); BVFT, Borkowski Verbal Fluency Test.

5.3.2 The association between WHR and cognitive decline

Outcomes of the regression models investigating the effect of WHR on change in cognition are shown in Table 23. After adjusting for age and sex, increased WHR was associated with poorer follow-up '*g*' (standardised beta= -0.265; p<0.001). This association was mirrored by the majority of the other cognitive tests.

When adjusting for baseline cognitive performance associations persisted for '*g*' (standardised beta= -0.105; p=0.001) and also for the majority of the individual cognitive tests. This indicates that higher WHR is associated with greater cognitive decline, in general cognition and also in several of the cognitive domains, over time. Furthermore, in the fully adjusted models, these significant associations remained for '*g*' (standardised beta= -0.076; p=0.020), DST (standardised beta= -0.162; p<0.001), BVFT (standardised beta= -0.079; p=0.022) and LNS (standardised beta= -0.124; p=0.006). Despite these significant associations between increased WHR and cognitive decline in fully adjusted models, it should be noted that the effect sizes drop considerably, ranging from around 30% to 60% decrease in effect.

These results indicate that an increased WHR at baseline is significantly associated with a greater decline in general cognition, as well as in the performance in DST, BVFT and LNS, where performance was related to processing speed, executive function, and working memory, respectively.

Table 23. The association between WHR and cognitive decline as measured by individual cognitive tests and *g* at year 10 follow-up

WHR	*g*	LM	ln TMTB	Faces	MR	DST	BVFT	LNS
	Standardised Beta (SE)							
+ age and sex	**-0.265*** (0.049)**	**-0.164** (0.051)**	**0.166** (0.052)**	-0.076 (0.050)	**-0.205*** (0.051)**	**-0.270*** (0.051)**	**-0.181*** (0.052)**	**-0.227*** (0.051)**
+ baseline cognition score	**-0.105** (0.033)**	**-0.102* (0.043)**	0.056 (0.042)	-0.032 (0.043)	**-0.105* (0.041)**	**-0.178*** (0.038)**	**-0.097** (0.034)**	**-0.161*** (0.045)**
+ baseline diabetes covariates	**-0.095** (0.033)**	**-0.093* (0.044)**	0.048 (0.043)	-0.011 (0.043)	**-0.094* (0.041)**	**-0.171*** (0.038)**	**-0.092** (0.035)**	**-0.152*** (0.046)**
+ baseline vascular covariates	**-0.076* (0.034)**	-0.074 (0.045)	0.031 (0.044)	-0.003 (0.045)	-0.065 (0.043)	**-0.162*** (0.039)**	**-0.079* (0.036)**	**-0.124** (0.047)**

*p<0.05 **p<0.01 ***p<0.001. Baseline diabetes covariates: duration of diabetes (years) (natural log transformed), HbA1c (haemoglobin A1c) (natural log transformed), diabetic medication. Baseline vascular covariates: hypertension, Cerebral Event (Stroke or TIA), Heart disease (Angina or MI), HDL (mmol/l), serum triglycerides (mmol/l), smoking (current, ex, or non-smoker), alcohol units, Diabetic retinopathy, anxiety, depression. Data for *g* have been imputed, for remaining cognitive tests are non-imputed. WHR, Waist to Hip Ratio; LM, Logical Memory; MR, Matrix Reasoning; DST, Digit Symbol Test; lnTMTB, Trail Making Test B (Natural log transformed); BVFT, Borkowski Verbal Fluency Test; CRP, c-reactive protein; IL-6, interleukin-6; TNFα, tumour necrosis factor α.

5.3.3 The association between systemic inflammatory markers and cognitive decline

Outcomes of the regression models investigating the association between the individual inflammation markers and change in cognition are shown in Table 24. Similar to what was shown at baseline, cognitive ability at follow-up was associated with a number of the inflammatory markers measured at baseline. At follow-up the majority of associations were seen with IL-6, followed by Fibrinogen and CRP. In contrast to the associations observed at baseline, TNF alpha was not significantly associated with follow-up cognitive ability.

In models that made further adjustment for baseline cognitive test performance, higher Fibrinogen (standardised beta= -0.059; p=0.032), CRP (standardised beta= -0.067; p=0.036) and IL-6 (standardised beta= -0.064; p=0.018) were found to be significantly associated with a decline in general cognitive ability. In fully adjusted models these associations observed between higher Fibrinogen, CRP and IL-6 and a decline in general cognitive ability were no longer significant. However, in the test MR, a significant association was observed, when fully adjusted for diabetic and vascular risk factors.

Worsened performance in the DST test was shown to be associated with higher levels of a number of the inflammatory markers. In fully adjusted models, DST performance was associated with Fibrinogen (standardised beta= -0.087; p=0.008), CRP (standardised beta= -0.091; p=0.022) and also TNF alpha (standardised beta= -0.086; p=0.005). This last association with TNF alpha is particularly striking as levels were shown to not be significantly associated with the ability to perform the test at either baseline or follow-up. Despite this, a clear association between this marker and a decline in performance over time is demonstrated in this analysis.

It should be noted that for the analysis on CRP, cases with CRP level above 10 mg/ml were removed, as these are indicative of acute inflammation likely as a result of a temporary infection.

Table 24. The association between inflammatory markers and cognitive decline as measured by individual cognitive tests and *g* at year 10 follow-up

Inflammation marker	*g*	LM	lnTMTB	Faces	MR	DST	BVFT	LNS
	Standardised Beta (SE)							
Fibrinogen + age and sex	**-0.110**** **(0.048)**	-0.023 (0.049)	**0.150***** **(0.049)**	-0.063 (0.049)	**-0.100*** **(0.049)**	**-0.124**** **(0.049)**	-0.066 (0.050)	-0.068 (0.049)
+ baseline cognition score	**-0.059*** **(0.031)**	0.000 (0.041)	**0.090*** **(0.040)**	-0.037 (0.041)	-0.060 (0.038)	**-0.115***** **(0.036)**	-0.051 (0.033)	-0.071 (0.043)
+ full adjustment of baseline covariates	-0.029 (0.032)	0.045 (0.043)	0.057 (0.042)	0.015 (0.043)	-0.017 (0.040)	**-0.087**** **(0.037)**	-0.025 (0.035)	-0.037 (0.045)
lnCRP + age and sex	**-0.113*** **(0.051)**	-0.043 (0.051)	**0.123**** **(0.052)**	-0.048 (0.051)	-0.072 (0.052)	**-0.153**** **(0.051)**	-0.102 (0.053)	-0.075 (0.052)
+ baseline cognition score	**-0.067*** **(0.032)**	-0.026 (0.044)	**0.061*** **(0.041)**	-0.032 (0.043)	-0.025 (0.041)	**-0.125***** **(0.038)**	-0.072 (0.035)	-0.063 (0.045)
+ full adjustment of baseline covariates	-0.036 (0.034)	0.028 (0.046)	0.034 (0.044)	-0.013 (0.045)	0.004 (0.043)	**-0.091*** **(0.040)**	-0.038 (0.037)	-0.033 (0.048)
lnIL-6 + age and sex	**-0.153***** **(0.042)**	**-0.098*** **(0.043)**	**0.165***** **(0.044)**	-0.048 (0.043)	**-0.175***** **(0.043)**	**-0.156***** **(0.044)**	-0.084* (0.044)	**-0.090*** **(0.044)**
+ baseline cognition score	**-0.064*** **(0.028)**	**-0.071*** **(0.036)**	**0.095**** **(0.036)**	-0.013 (0.036)	**-0.127***** **(0.034)**	**-0.091**** **(0.033)**	-0.018 (0.029)	-0.072 (0.038)
+ full adjustment of baseline covariates	-0.030 (0.029)	-0.033 (0.039)	0.065 (0.039)	0.013 (0.039)	**-0.098**** **(0.037)**	-0.056 (0.034)	0.020 (0.032)	-0.035 (0.041)
lnTNFα + age and sex	-0.056 (0.042)	-0.029 (0.042)	0.082 (0.042)	-0.048 (0.042)	-0.051 (0.043)	-0.048 (0.042)	-0.001 (0.043)	-0.039 (0.043)
+ baseline cognition score	-0.023 (0.027)	-0.025 (0.036)	0.056 (0.034)	-0.035 (0.035)	-0.010 (0.034)	**-0.084**** **(0.031)**	-0.014 (0.028)	0.000 (0.037)
+ full adjustment of baseline covariates	-0.018 (0.027)	-0.015 (0.036)	0.056 (0.035)	-0.024 (0.036)	-0.003 (0.034)	**-0.086**** **(0.031)**	0.017 (0.029)	0.018 (0.038)

*p<0.05 **p<0.01 ***p<0.001. Baseline covariates: duration of diabetes (years), HbA1c (haemoglobin A1c), diabetic medication, hypertension, Cerebral Event (Stroke or TIA), Heart disease (Angina or MI), HDL (mmol/l), serum triglycerides (mmol/l), smoking (current, ex, or non-smoker), alcohol units, Diabetic retinopathy, anxiety, depression. Data for *g* have been imputed, for remaining cognitive tests are non-imputed. LM, Logical Memory; MR, Matrix Reasoning; DST, Digit Symbol Test; lnTMTB, Trail Making Test B (Natural log transformed); BVFT, Borkowski Verbal Fluency Test; CRP, c-reactive protein; IL-6, interleukin-6; TNFα, tumour necrosis factor α.

5.3.4 The association between BMI and cognitive decline when adjusting for inflammation

The outcome of the fully adjusted regression model that explores the possible effect of inflammation on the association between BMI and cognitive decline is given in Table 25a.

When adjusting for inflammation after other vascular covariates, there was no statistically significant association between BMI and cognitive decline (as measured by '*g*' and also the other cognitive tests).

Table 25b shows the result of a similar model in which inflammatory markers were entered into the model before the vascular covariates (rather than afterwards, as in Table 25a). The rationale for this was that the effect of adjusting for inflammation after vascular covariates may mask a very weak association between predictor on outcome, as inflammation is known to have an impact on vasculature. When inflammation was added to the model before vascular covariates (Table 25b), a larger effect was observed for the association between BMI and cognitive decline when compared to the models in Table 25a. Despite this, both variations of the regression model showed no significant association between BMI and cognitive decline, when adjusting for inflammation regardless of when inflammation is entered into the model.

Table 25. (a) The association between BMI and cognitive decline as measured by individual cognitive tests and *g*, adjusting for systemic inflammation after vascular covariates

	g	LM	lnTMTB	Faces	MR	DST	BVFT	LNS
BMI	Standardised Beta (SE)							
+ age and sex	**-0.093* (0.045)**	-0.033 (0.047)	0.077 (0.047)	-0.004 (0.045)	**-0.107* (0.046)**	**-0.096* (0.047)**	-0.068 (0.047)	-0.083 (0.047)
+ baseline cognition score	-0.041 (0.029)	-0.040 (0.039)	0.039 (0.038)	0.022 (0.038)	-0.062 (0.036)	-0.027 (0.034)	-0.047 (0.031)	**-0.087* (0.041)**
+ baseline diabetes covariates	-0.038 (0.029)	-0.040 (0.039)	0.039 (0.038)	0.030 (0.038)	-0.058 (0.036)	-0.028 (0.034)	-0.046 (0.031)	**-0.082* (0.041)**
+ baseline vascular covariates	-0.017 (0.031)	-0.018 (0.041)	0.022 (0.040)	0.044 (0.040)	-0.036 (0.038)	-0.012 (0.035)	-0.036 (0.033)	-0.043 (0.043)
+ TNFα, IL-6, CRP, Fibrinogen	-0.008 (0.032)	-0.020 (0.043)	0.004 (0.041)	0.046 (0.042)	-0.020 (0.039)	0.019 (0.037)	-0.036 (0.034)	-0.033 (0.045)

*p<0.05 **p<0.01 ***p<0.001. Baseline diabetes covariates: duration of diabetes (years) (natural log transformed), HbA1c (haemoglobin A1c) (natural log transformed), diabetic medication. Baseline vascular covariates: hypertension, Cerebral Event (Stroke or TIA), Heart disease (Angina or MI), HDL (mmol/l), serum triglycerides (mmol/l), smoking (current, ex, or non-smoker), alcohol units, Diabetic retinopathy, anxiety, depression. Data for *g* have been imputed, for remaining cognitive tests are non-imputed. BMI, Body Mass Index; LM, Logical Memory; MR, Matrix Reasoning; DST, Digit Symbol Test; lnTMTB, Trail Making Test B (Natural log transformed); BVFT, Borkowski Verbal Fluency Test.

Table 25. (b) The association between BMI and cognitive decline as measured by individual cognitive tests and *g*, adjusting for systemic inflammation before vascular covariates

BMI	*g*	LM	lnTMTB	Faces	MR	DST	BVFT	LNS
	Standardised Beta (SE)							
+ age and sex	**-0.093* (0.045)**	-0.033 (0.047)	0.077 (0.047)	-0.004 (0.045)	**-0.107* (0.046)**	**-0.096* (0.047)**	-0.068 (0.047)	-0.083 (0.047)
+ baseline cognition score	-0.041 (0.029)	-0.040 (0.039)	0.039 (0.038)	0.022 (0.038)	-0.062 (0.036)	-0.027 (0.034)	-0.047 (0.031)	**-0.087* (0.041)**
+ baseline diabetes covariates	-0.038 (0.029)	-0.040 (0.039)	0.039 (0.038)	0.030 (0.038)	-0.058 (0.036)	-0.028 (0.034)	-0.046 (0.031)	**-0.082* (0.041)**
+ TNFα, IL-6, CRP, Fibrinogen	-0.023 (0.031)	-0.035 (0.041)	0.011 (0.040)	0.038 (0.040)	-0.036 (0.038)	-0.014 (0.036)	-0.038 (0.033)	-0.065 (0.044)
+ baseline vascular covariates	-0.008 (0.032)	-0.020 (0.043)	0.004 (0.041)	0.046 (0.042)	-0.020 (0.039)	0.019 (0.037)	-0.036 (0.034)	-0.033 (0.045)

*p<0.05 **p<0.01 ***p<0.001. Baseline diabetes covariates: duration of diabetes (years) (natural log transformed), HbA1c (haemoglobin A1c) (natural log transformed), diabetic medication. Baseline vascular covariates: hypertension, Cerebral Event (Stroke or TIA), Heart disease (Angina or MI), HDL (mmol/l), serum triglycerides (mmol/l), smoking (current, ex, or non-smoker), alcohol units, Diabetic retinopathy, anxiety, depression. Data for *g* have been imputed, for remaining cognitive tests are non-imputed. BMI, Body Mass Index; LM, Logical Memory; MR, Matrix Reasoning; DST, Digit Symbol Test; lnTMTB, Trail Making Test B (Natural log transformed); BVFT, Borkowski Verbal Fluency Test.

5.3.5 The association between WHR and cognitive decline in total population and in men and women separately

As WHR was shown to be associated with cognitive decline ('*g*', standardised beta= -0.105; p=0.001), a post hoc analysis to the results shown in Table 23 was carried out. This aimed to address concerns that as body shape and fat distribution are known to vary between the sexes (Karastergiou et al., 2012), the observed significant association may be driven by sex, and that WHR is acting as a proxy to sex. In this analysis, a model adjusting for age and baseline cognitive score was applied to men and women in separate analyses. These models showed a significant association between WHR and cognitive decline in men (standardised beta= -0.109; p=0.004) and also in women (standardised beta= -0.101; p=0.008). This significant result for both sexes was also found for DST (men, standardised beta -0.158, p<0.001; women, standardised beta -0.162, p<0.016), MR (men, standardised beta= -0.118, p=0.12; women, standardised beta= -0.103, p=0.023) and LNS (men, standardised beta= -0.152, p=0.003; women, standardised beta= -0.163, p=0.002). In men, a decline in the BVFT test was also significantly associated with WHR (men, standardised beta= -0.137, p=0.003), as was TMTB (men, standardised beta= 0.120, p=0.011), however these associations were not significant in women. LM and Faces tests were also not significant, for men and for women, although this may also be due to a lack of power to detect an association.

5.3.6 The association between WHR and cognitive decline when adjusting for inflammation

The result of the fully adjusted model showing the association between WHR and cognitive decline when accounting for diabetes and vascular covariates (described in Table 23), and when also accounting for inflammation markers is given in Table 26. As shown previously,

the fully adjusted model, exploring the association between WHR and cognitive decline, showed a statistically significant association for '*g*' (standardised beta= -0.076; p=0.020), DST (standardised beta= -0.162; p<0.001), BVFT (standardised beta= -0.079; p=0.022) and LNS (standardised beta= -0.124; p=0.006). When introducing the inflammation markers into the model, the standardised beta for the association between WHR and '*g*' fell only slightly and remained statistically significant (standardised beta -0.074; p=0.023). Similarly, the association between WHR and the cognitive tests DST, BVFT and LNS also persisted after adjusting for inflammation (DST, standardised beta= -0.158, p=0.038; BVFT, standardised beta= -0.079, p=0.036; LNS, standardised beta -0.121, p= 0.048).

As a final adjustment step, BMI was also included into the model. This made little difference to the model and after this final step, the significance level persisted for '*g*' (standardised beta= -0.074; p=0.026), indicating that WHR is associated with cognitive decline, irrespective all previously mentioned adjustment covariates, and also irrespective of BMI. Again, this association was also found in the cognitive tests DST (standardised beta= -0.166; p=0.039), BVFT (standardised beta= -0.077; p=0.037) and LNS (standardised beta= -0.114; p=0.048).

Table 26. The association between WHR and cognitive decline as measured by individual cognitive tests and *g*, adjusting for systemic inflammation

WHR	*g*	LM	lnTMTB	Faces	MR	DST	BVFT	LNS
	Standardised Beta (SE)							
+ age and sex	**-0.265*** (0.049)**	**-0.164** (0.051)**	**0.166** (0.052)**	-0.076 (0.050)	**-0.205*** (0.051)**	**-0.270*** (0.051)**	**-0.181*** (0.052)**	**-0.227*** (0.051)**
+ baseline cognition score	**-0.105** (0.033)**	**-0.102* (0.043)**	0.056 (0.042)	-0.032 (0.043)	**-0.105* (0.041)**	**-0.178*** (0.038)**	**-0.097** (0.034)**	**-0.161*** (0.045)**
+ baseline diabetes covariates	**-0.095** (0.033)**	**-0.093* (0.044)**	0.048 (0.043)	-0.011 (0.043)	**-0.094* (0.041)**	**-0.171*** (0.038)**	**-0.092** (0.035)**	**-0.152*** (0.046)**
+ baseline vascular covariates	**-0.076* (0.034)**	-0.074 (0.045)	0.031 (0.044)	-0.003 (0.045)	-0.065 (0.043)	**-0.162*** (0.039)**	**-0.079* (0.036)**	**-0.124** (0.047)**
+ TNFα, IL-6, CRP, Fibrinogen	**-0.075* (0.034)**	-0.074 (0.046)	0.030 (0.044)	-0.001 (0.045)	-0.060 (0.042)	**-0.158*** (0.038)**	**-0.079* (0.036)**	**-0.121** (0.048)**
+ BMI	**-0.074* (0.035)**	-0.065 (0.046)	0.033 (0.045)	0.007 (0.045)	-0.057 (0.043)	**-0.166*** (0.039)**	**-0.077* (0.037)**	**-0.114* (0.048)**

*p<0.05 **p<0.01 ***p<0.001. Baseline diabetes covariates: duration of diabetes (years) (natural log transformed), HbA1c (haemoglobin A1c) (natural log transformed), diabetic medication. Baseline vascular covariates: hypertension, Cerebral Event (Stroke or TIA), Heart disease (Angina or MI), HDL (mmol/l), serum triglycerides (mmol/l), smoking (current, ex, or non-smoker), alcohol units, Diabetic retinopathy, anxiety, depression. Data for *g* have been imputed, for remaining cognitive tests are non-imputed. WHR, Waist to Hip Ratio; BMI, Body Mass Index; LM, Logical Memory; MR, Matrix Reasoning; DST, Digit Symbol Test; lnTMTB, Trail Making Test B (Natural log transformed); BVFT, Borkowski Verbal Fluency Test; CRP, c-reactive protein; IL-6, interleukin-6; TNFα, tumour necrosis factor α.

5.3.7 The association between waist circumference (WC) and cognitive decline when adjusting for inflammation

As WHR is derived from WC, another post hoc analysis that aimed to explore if the WHR analyses could be driven purely by visceral fat as measured by WC was carried out. The outcome of the fully adjusted regression model that explores the possible effect of inflammation on the association between WC and cognitive decline is given in Table 27. For the association between WC and decline in '*g*', a significant association was found after adjusting for age, sex and baseline '*g*' (standardised beta= 0.059; p= 0.032). This association did not persist after further adjustments to the model. This was reflected by findings for the cognitive tests DST and LNS (all $p<0.05$). The association between WC and decline in BVFT persisted after adjusting for vascular covariates, however this association diminished when making further adjustments for inflammation.

Table 27. The association between WC and cognitive decline as measured by individual cognitive tests and *g*, adjusting for systemic inflammation

WC	*g*	LM	lnTMTB	Faces	MR	DST	BVFT	LNS
	Standardised Beta (SE)							
+ age and sex	**-0.133** (0.044)**	-0.039 (0.045)	**0.087* (0.045)**	-0.032 (0.044)	**-0.117** (0.044)**	**-0.147*** (0.045)**	**-0.109* (0.045)**	**-0.120** (0.045)**
+ baseline cognition score	**-0.059* (0.028)**	-0.043 (0.038)	0.038 (0.036)	-0.004 (0.037)	-0.067 (0.035)	**-0.074* (0.033)**	**-0.072* (0.030)**	**-0.096* (0.039)**
+ baseline diabetes covariates	-0.053 (0.029)	-0.039 (0.038)	0.035 (0.037)	0.014 (0.037)	-0.058 (0.036)	**-0.074* (0.034)**	**-0.070* (0.030)**	**-0.086* (0.040)**
+ baseline vascular covariates	-0.033 (0.030)	-0.019 (0.040)	0.018 (0.039)	0.026 (0.040)	-0.037 (0.037)	-0.057 (0.035)	**-0.061* (0.032)**	-0.051 (0.042)
+ TNFα, IL-6, CRP, Fibrinogen	-0.025 (0.031)	-0.020 (0.042)	0.004 (0.040)	0.026 (0.041)	-0.020 (0.038)	-0.034 (0.036)	-0.062 (0.033)	-0.042 (0.044)

*p<0.05 **p<0.01 ***p<0.001. Baseline diabetes covariates: duration of diabetes (years) (natural log transformed), HbA1c (haemoglobin A1c) (natural log transformed), diabetic medication. Baseline vascular covariates: hypertension, Cerebral Event (Stroke or TIA), Heart disease (Angina or MI), HDL (mmol/l), serum triglycerides (mmol/l), smoking (current, ex, or non-smoker), alcohol units, Diabetic retinopathy, anxiety, depression. Data for *g* have been imputed, for remaining cognitive tests are non-imputed. WC, Waist Circumference; LM, Logical Memory; MR, Matrix Reasoning; DST, Digit Symbol Test; lnTMTB, Trail Making Test B (Natural log transformed); BVFT, Borkowski Verbal Fluency Test; CRP, c-reactive protein; IL-6, interleukin-6; TNFα, tumour necrosis factor α.

5.3.8 Summary of analysis

To summarise, results indicated an association between measures of increased levels of obesity at baseline with reduced cognitive ability at follow-up and also with increased decline in cognitive ability over 10 years. This result was most pronounced in the association between higher WHR and more cognitive decline. In fully adjusted models this association between WHR and cognitive decline persisted, which was not the case for either BMI or WC.

Results also indicated that the predominant inflammation marker associated with general cognitive ability and decline in cognitive ability was IL-6. However, when inflammation was incorporated into the regression model investigating the association between WHR and general cognitive decline, this latter association was not greatly affected, suggesting that inflammation may not have a major mediating effect.

5.4 OBESITY, INFLAMMATION AND DEMENTIA

5.4.1 The association between inflammation and Dementia

The outcome of the regression models exploring the relationship between baseline inflammatory markers and incident dementia is shown in Table 28. Models were adjusted first for age and sex, then diabetes-related and vascular risk factors, followed by further adjustment of each model for the other inflammatory markers.

For fibrinogen TNF alpha and CRP, there was little evidence of an association between raised levels of these inflammatory markers and incident dementia; ORs for dementia per unit increase in inflammatory marker ranged from 0.78 to 1.02 across age and sex adjusted and multi-adjusted models, and none of the models reached statistical significance at the

0.05 level. It should be noted that for the analysis on CRP, cases with CRP level above 10 mg/ml were removed, as these are indicative of acute inflammation likely as a result of a temporary infection.

For IL-6, the odds of dementia appeared to increase per unit increase in inflammatory marker (age and sex adjusted OR 1.24; 95% CI 0.91, 1.70), although again, this association did not reach statistical significance ($p<0.05$) until after adjustment for the other inflammation markers (Fibrinogen, CRP and TNF alpha); at this point the odds ratio rose to 1.56 per unit increase in IL-6 (95% CI 1.08, 2.27, $p<0.05$).

Table 28. The association between IL-6, TNF α, CRP and Fibrinogen at baseline and dementia at year 10 follow-up

Risk factor	Fibrinogen	lnCRP	lnIL-6	lnTNF α
	OR (95% CI)			
+ age and sex	0.93 (0.69-1.25)	0.82 (0.70-1.01)	1.24 (0.91-1.70)	1.02 (0.76-1.36)
+ baseline diabetes covariates	0.89 (0.66-1.21)	0.82 (0.66-1.02)	1.21 (0.88-1.66)	0.99 (0.74-1.33)
+ baseline vascular covariates	0.86 (0.63-1.19)	0.84 (0.66-1.06)	1.31 (0.93-1.84)	0.99 (0.73-1.35)
+ respective other inflammatory markers†	0.94 (0.65-1.36)	0.78 (0.60-1.01)	**1.56 (1.08-2.27)***	0.93 (0.68-1.28)

Analyses are logistic regressions. *p<0.05 **p<0.01 ***p<0.001. Baseline diabetes covariates: duration of diabetes (years) (Natural log transformed), HbA1c (haemoglobin A1c) (Natural log transformed), diabetic medication. Baseline vascular covariates: hypertension, Cerebral Event (Stroke or TIA), Heart disease (Angina or MI), HDL (mmol/l), serum triglycerides (mmol/l), smoking (current, ex, or non-smoker), alcohol units, Diabetic retinopathy, anxiety, depression. BMI, Body Mass Index. †For Fibrinogen analysis; adjusted for CRP, c-reactive protein; IL-6, interleukin-6; TNFα, tumour necrosis factor α. For CRP analysis; adjusted for Fibrinogen; IL-6, interleukin-6; TNFα, tumour necrosis factor α. For IL-6 analysis; adjusted for Fibrinogen, CRP, c-reactive protein; TNFα, tumour necrosis factor α. For TNFα analysis; adjusted for Fibrinogen, CRP, c-reactive protein; IL-6, interleukin-6.

5.4.2 The association between Obesity and Dementia

The assumption of linearity between obesity measures and dementia was explored by means of plotting the main obesity measure BMI, as categorised by quintiles, against the percentage of individuals categorised as having dementia. This provided evidence for a linear relationship (see Figure 6).

The outcome of the regression models exploring the relationship between obesity measures and incident dementia are shown in Table 29. Models were adjusted first for age and sex, then diabetes-related risk factors, vascular risk factors, followed by further adjustment of each model for the inflammatory markers.

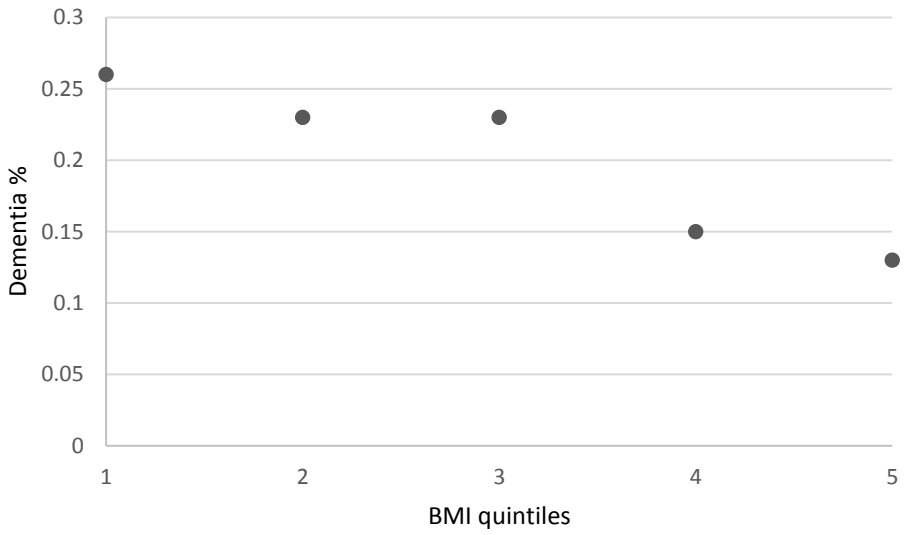

Figure 6. Baseline BMI categorised by quintile plotted against follow-up Dementia

BMI and Dementia

For BMI, the odds of dementia appeared to decrease per unit increase of BMI (age, sex adjusted OR 0.97; 95% CI 0.93, 1.01), which remained unchanged when further adjusting for diabetes covariates. This association did not reach statistical significance ($p<0.05$) until after making further adjustment for vascular covariates; when at this point the OR decreased slightly to 0.95 per unit increase of WC (95% CI 0.90, 0.99, $p=0.29$), and this association persisted and remained unchanged after making further adjustment for inflammation (see Table 29).

WHR and Dementia

For WHR, there was little evidence of an association between WHR and incident dementia; ORs for dementia per unit increase of WHR ranged from 1.01 to 1.02 across age and sex adjusted and multi- adjusted models, and none of the models reached statistical significance at the 0.05 level (see Table 29).

WC and Dementia

For WC, the odds of dementia appeared to decrease per unit increase in WC (age and sex adjusted OR 0.99; 95% CI 0.97, 1.00), which remained unchanged when further adjusting for diabetes covariates. This association did not reach statistical significance ($p<0.05$) until after adjustment for vascular risk factors; when at this point the OR decreased slightly to 0.98 per unit increase of WC (95% CI 0.96, 0.99, $p<0.05$), and this association persisted and remained unchanged after making further adjustment for inflammation (see Table 29).

Percentage body fat and Dementia

For percentage body fat, the odds of dementia appeared to decrease per unit increase of body fat (age and sex adjusted OR 0.97; 95% CI 0.93, 1.00), which changed little when further adjusting for diabetes covariates (age and sex adjusted OR 0.96; 95% CI 0.92, 1.00). This association did not reach statistical significance ($p<0.05$) until after adjustment for vascular risk factors; when at this point the OR deceased to 0.94 per unit increase of body fat (95% CI 0.90, 0.98, $p<0.01$), and this association persisted and remained unchanged after further adjustment for inflammation (see Table 29).

Table 29. The association between BMI, WHR, WC and % Body Fat at baseline and dementia at year 10 follow-up

Risk factor	BMI	WHR†	WC	% Body Fat
	OR (95% CI)			
+ age and sex	0.97 (0.93-1.01)	1.02 (0.99-1.05)	0.99 (0.97-1.00)	0.97 (0.93-1.00)
+ baseline diabetes covariates	0.97 (0.93-1.01)	1.02 (0.99-1.06)	0.99 (0.97-1.00)	0.96 (0.92-1.00)
+ baseline vascular covariates	**0.95 (0.91-0.99)***	1.01 (0.98-1.05)	**0.98 (0.96-0.99)***	**0.94 (0.90-0.98)****
+ TNFα, IL-6, CRP, Fibrinogen	**0.95 (0.90-0.99)***	1.01 (0.98-1.05)	**0.97 (0.96-0.99)***	**0.94 (0.90-0.98)****

Analyses are logistic regressions. *p<0.05 **p<0.01 ***p<0.001. †In analysis WHR is transformed so that 1 unit is 0.01. Baseline diabetes covariates: duration of diabetes (years) (Natural log transformed), HbA1c (haemoglobin A1c) (Natural log transformed), diabetic medication. Baseline vascular covariates: hypertension, Cerebral Event (Stroke or TIA), Heart disease (Angina or MI), HDL (mmol/l), serum triglycerides (mmol/l), smoking (current, ex, or non-smoker), alcohol units, Diabetic retinopathy, anxiety, depression. BMI, Body Mass Index; WHR, Waist to Hip Ratio; WC, Waist Circumference; CRP, c-reactive protein; IL-6, interleukin-6; TNFα, tumour necrosis factor α.

5.4.3 Summary of dementia analyses

To summarise, results provide evidence for an association between some inflammatory markers and risk of dementia. These results also indicate that the predominant inflammation marker associated with general dementia was IL-6. Whereby strong inter-correlations with the other inflammatory markers, some of which not associated with dementia, may suppress the effect of IL-6 on the model.

Evidence is also presented on the association between obesity and dementia, however the direction of these associations, whereby a reduced body mass, size or fat percentage is a risk factor for dementia, indicates that the effect of undiagnosed pre dementia in the cohort may play a role in this outcome.

5.5 PHYSICAL ACTIVITY, SEDENTARY BEHAVIOUR, COGNITIVE CHANGE AND DEMENTIA

5.5.1 Follow-up characteristics of the attending population

Year 10 follow-up characteristics of the ET2DS population (n=581) are presented in Table 30. The population had an average age of 77.3 years and 50.9% were male. The median duration of diabetes was 16 years, mean HbA1c was 58.08 mmol/mol (International Federation of Clinical Chemistry units), which equates to an average of approximately 7.5%. Most participants were on an oral medication (58.7%), 28.2 % were on an oral plus injection based medication, and only 13.1% controlled their diabetes through diet alone. The mean systolic blood pressure was 144.23 and diastolic blood pressure was 68.39, with 52.3% of the population being classed as having a form of hypertension. Mean total cholesterol was 4.15 mmol/l, ranging from 1.7 to 8.8 mmol/l. Cardiovascular events consisted mainly of angina, where 174 people (29.9 %) had been diagnosed with the disease. Eighty three

people (14.3%) had experienced at least one myocardial infarct, 60 people (10.3%) had experienced at least one stroke, and 44 people (7.6%) had been diagnosed as having had a transient ischaemic attack. Microvascular events in the form of having experienced any degree of diabetic retinopathy (grade 1-4) was found in 60.8% of the population (353 cases).

Mean anxiety and depression levels as measured by the Hospital Anxiety and Depression Scale were 4.96 and 4.39, respectively. Sixty five people (11.2%) had mild anxiety, 43 (7.4%) had moderate anxiety and 14 (2.4%) had severe anxiety, when screened using this tool. Seventy people (12.0 %) had mild depression, 23 (4.0%) had moderate depression and 3 (4.5%) had severe depression, when screened using this tool. Clinical cases of anxiety or depression, as indicated by a score of 11 or more (Snaith, 2003), were 57 (9.8%) and 26 (4.5%), respectively.

Median physical activity score, as measured by the International Physical Activity Questionnaire (IPAQ), was 1690 MET^{-1} $minutes^{-1}$ $week^{-1}$, which ranged from 0 to 14024 MET^{-1} $minutes^{-1}$ $week^{-1}$. Sedentary behaviour, was on average 4119 minutes per week, ranging from 420 to 8190. Both physical activity and sedentary behaviours reflecting a wide range in participant activity levels and abilities. The mean BMI was 30.1 ±5.70 kg/m^2, with a minimum of 17.31 kg/m^2 and maximum of 53.22 kg/m^2, with 42.9% of participants being classed as obese (BMI >30 kg/m^2).

The majority of individuals had never smoked (47.2%), a similar proportion were former smokers (44.4%) and only 7.1% were current smokers. The population consumed on average 5.8 units of alcohol per week.

Table 30. Characteristics of the ET2DS at follow-up and the percentage of missing data

Characteristic	Population Mean ± SD or n (%)	Minimum	Maximum	N	Missing data %
Demographic:					
Age (years)	77.31 ± 4.16	70.14	85.74	581	0
Sex males (n %)	296 (50.9)			581	0
Diabetes related:					
Duration of Diabetes (median years(IQR))	16 (8)	10	53	577	0.69
HbA1c (mmol/mol)	58.08 ± 13.48	28	119	551	5.45
Diabetes medication:				581	0
- Diet controlled only	76 (13.1)				
- Oral medication only	341 (58.7)				
- Injection ± Oral	164 (28.2)				
Vascular related:					
Systolic blood pressure (mmHg)	144.23 ± 20.30	90	220	579	0.34
Diastolic blood pressure (mmHg)	68.39 ± 11.53	30	112	579	0.34
Total cholesterol (mmol/l)	4.15 ± 1.02	1.7	8.8	550	5.64
Hypertension (n)	304 (52.3)			581	0
Any macro vascular disease (n)[a]	240 (41.3)			581	0
Angina (n)[a]	174 (29.9)			581	0
Myocardial infarct (n)[a]	83 (14.3)			581	0
Stroke (n)[a]	60 (10.3)			581	0
TIA (n)[a]	44 (7.6)			581	0
Diabetic Retinopathy (n)[a]	353 (60.8)			581	0

Psychological:					
Anxiety	4.96 ± 3.71	0	18	580	0.17
Depression	4.39 ± 3.17	0	18	580	0.17
Lifestyle:					
Physical activity (MET^{-1} $minutes^{-1}$ $week^{-1}$)	1690 (2438)	0	14024	581	0
Sedentary time (min/week)	4119 ± 1336	420	8190	581	0
Body Mass Index (kg/m2)	30.07 ± 5.70	17.31	53.22	571	1.72
Smoking				573	1.38
- Current	41 (7.1)				
- Former	258 (44.4)				
- Never	274 (47.2)				
Alcohol units	5.84 ± 10.9			581	0

Total n=581. Values are means ± SD, median (interquartile range) or n (%). HbA1c, haemoglobin A1c; MI, Myocardial Infarct; TIA, transient ischaemic attack; HADS A, Hospital Anxiety and Depression Scale-Anxiety subscale; Hospital HADS D, Hospital Anxiety and Depression Scale-Depression subscale. [a] These data are not cumulative.

5.5.2 Follow-up characteristics of the clinic visit and home visit attending population

Table 31 describes the characteristics of the year 10 follow-up population who attended a clinic visit (n=435) and who received a home visit (n=146). On average at follow-up, more women received a home visit than men (p=0.003). Those who were seen at home had both lower systolic (p=0.014) and diastolic (p<0.001) blood pressure and were less likely to suffer from untreated hypertension (p=0.018). Home visit participants were more likely to suffer from Angina (p=0.001) or have had a macrovascular event (p=0.001). There were more people with probable dementia seen as a home visit (p <0.001), reflected by a lower 'g' score in the home visit population on average (p<0.001). Levels of anxiety and depression were higher in those seen at home (p= 0.026 and p=0.001, respectively) as were levels of sedentary behaviour (p<0.001) and inactivity (p<0.001), possibly as a result of higher numbers of dementia in this population. Other characteristics such as age and BMI did not differ between the home visit and clinic visit attending populations.

These results reflect an important difference in these two attending populations that may introduce a systematic bias by means of mode effect, whereby different testing circumstances affect cognitive outcomes in individuals. For example it is possible that participants find it stressful having researchers enter their home, exacerbating anxiety and thus having a direct impact on cognitive test results. Alternatively, it may also be that people with dementia experience higher levels of anxiety and depression in general and are also known to be more likely to request a home visit. Similarly, the observation that participants seen at home have lower blood pressure and lower prevalence of hypertension, may be due to not having had to walk prior to the clinic. On the other hand, those seen at home are more likely to have medications prescribed in a daily pill box from their pharmacist or have a carer ensure medication are taken correctly and not forgotten.

In the home visit group both a lower cognition score for '*g*', as measured during the clinic/home visit, and a higher number of people with dementia are recorded, as derived by criteria that take advantage of independent clinical diagnoses, are noted. This indicates that poorer cognitive test scores in the home visit group are likely as a direct result of dementia diagnoses and that specific mode effects introduced as a result of different testing circumstances do not have a strong effect on the findings. Despite this the possible effect of testing environment should be acknowledged when interpreting findings.

Table 31. Follow-up characteristics of the ET2DS at year 10 who received a clinic or home visit

Characteristic	Clinic Visit		Home Visit		T or X2 (p-value)
	N	Population Mean ± SD or n (%)	N	Population Mean ± SD or n (%)	
Demographic:					
Age (years)	435	77.20 ± 4.08	146	77.67 ± 4.37	-1.21 (0.229)
Sex males (n %)	435	237 (54.5)	146	59 (40.4)	8.66 (0.003)
Diabetes related:					
Duration of Diabetes (median years(IQR))	432	16 (7)	145	17 (8)	-1.96 (0.052)
HbA1c (mmol/mol)	417	57.35 ± 12.29	134	60.34 ± 16.50	-1.94 (0.055)
Diabetes medication:	435		146		6.20 (0.045)
- Diet controlled only		54 (12.4)		22 (15.1)	
- Oral medication only		268 (61.6)		73 (50.0)	
- Injection ± Oral		113 (26.0)		51 (34.9)	
Vascular related:					
Systolic blood pressure (mmHg)	435	145.43 ± 19.73	144	140.65 ± 21.62	2.46 (0.014)
Diastolic blood pressure (mmHg)	435	69.71 ± 11.24	144	64.42 ± 11.49	4.86 (<0.001)
Total cholesterol (mmol/l)	414	4.14 ± 1.03	136	4.19 ± 0.99	-0.45 (0.653)
Hypertension (n)	435	240 (55.2)	146	64 (43.8)	5.63 (0.018)
Any macro vascular disease (n)[a]	435	163 (37.5)	146	77 (52.7)	10.51 (0.001)
Angina (n)[a]	435	114 (26.2)	146	60 (41.1)	11.55 (0.001)
Myocardial infarct (n)[a]	435	63 (14.5)	146	20 (13.7)	0.05 (0.815)
Stroke (n)[a]	435	39 (9.0)	146	21 (14.4)	3.47 (0.063)
TIA (n)[a]	435	29 (6.7)	146	15 (10.3)	2.03 (0.154)
Diabetic Retinopathy (n)[a]	435	257 (59.1)	416	85 (58.2)	0.03 (0.855)

Psychological:					
Anxiety	434	4.76 ± 3.62	146	5.55 ± 3.93	-2.23 (0.026)
Depression	434	4.15 ± 3.05	146	5.12 ± 3.39	-3.25 (0.001)
Probable dementia	435	17 (3.9)	146	18 (12.3)	13.69 (<0.001)
'g'	433	-0.08 ± 0.94	142	-0.95 ± 1.17	8.05 (<0.001)
Lifestyle:					
Physical activity (MET^{-1} $minutes^{-1}$ $week^{-1}$)	435	1952 (2564)	146	675 (1502)	6.92 (<0.001)
Sedentary time (min/week)	435	3881 ± 1217	146	4826 ± 1427	-7.16 (<0.001)
Body Mass Index (kg/m2)	430	30.20 ± 5.74	141	29.65 ± 5.59	1.00 (0.317)
Smoking	435		146		0.26 (0.878)
- Current		22 (5.1)		19 (13.0)	
- Former		202 (46.4)		56 (38.4)	
- Never		203 (46.7)		71 (48.6)	
Alcohol units		6.11 ± 10.64	581	5.03 ± 11.65	1.04 (0.298)

Total n=581, total clinic visit n=435, total home visit n=146. Values are means ± SD, median (interquartile range) or n (%). HbA1c, haemoglobin A1c; MI, Myocardial Infarct; TIA, transient ischaemic attack; HADS A, Hospital Anxiety and Depression Scale-Anxiety subscale; Hospital HADS D, Hospital Anxiety and Depression Scale- Depression subscale. [a] These data are not cumulative.

5.5.3 Inter-correlations of (in) activity measures

Table 32 shows the correlations between all the (in) activity measures collected at year 10. All variables were significantly correlated with each other (all p<0.001), with correlation coefficients being strongest for physical activity with sedentary behaviour (-0.58). Increased BMI was significantly correlated with both lower levels of physical activity and increased sedentary behaviour but with a relatively low correlation coefficient of -0.18 and 0.23, respectively. BMI is often used in correlation analyses to aid in validating a new (in) activity measure (Hagströmer et al., 2006). These correlation coefficients are consistent with others (Hagströmer et al., 2006) and indicate that although significant, the effect size is relatively weak.

Table 32. Inter-correlations of activity and obesity measures at follow-up

	BMI	Physical Activity	Sedentary behaviour
BMI	-	-0.180	0.228
Physical Activity		-	-0.584
Sedentary behaviour			-

Values are correlation coefficients from two-tailed Pearson correlations. All p<0.001. BMI, Body Mass Index; PA, Physical Activity (MET^{-1} $minutes^{-1}$ $week^{-1}$) (Log transformed); SB, Sedentary behaviour time (min/week).

5.5.4 Physical activity, sedentary behaviour and decline in general cognition

Table 33 shows the outcome of the cross sectional linear regression models investigating the association of physical activity and sedentary behaviour with cognition.

After adjusting for age and sex, increased physical activity was associated with improved '*g*' (standardised beta= 0.301; p<0.001). This significant association was sustained after making

further adjustments for diabetes and vascular risk factors (standardised beta= 0.290; p<0.001).

A next step in the model adjusted for baseline '*g*' as a measure of prior fluid-type cognitive ability. Despite a noticeable drop in standardised beta, a significant association persisted between increased physical activity level and a reduced decline in cognitive ability (standardised beta= 0.199; p<0.001). The last step in the model, included as a post hoc sensitivity analysis, aimed to find if this association between increased physical activity and reduced decline in cognitive ability level persisted even when taking into account people diagnosed with dementia. This analysis revealed that, when accounting for dementia, the association between physical activity and cognitive decline remained, albeit with a marked reduction in standardised beta (standardised beta= 0.171; p<0.001).

Similarly, after adjusting for age and sex, increased sedentary time was associated with poorer '*g*' (standardised beta= -0.273; p<0.001). This significant association persisted after making further adjustments for diabetes and vascular risk factors (standardised beta= -0.257; p<0.001). When adjusting for baseline cognitive ability, increased sedentary time was shown to be associated with decline in '*g*' (standardised beta= -0.162; p<0.001). This association remained significant even when taking into account those diagnosed with dementia (standardised beta= -0.135; p<0.001), although a noticeable drop in effect size was observed.

Table 33. The cross-sectional association between physical activity and sedentary time score and *g* at year 10 follow-up

Risk factor	Physical Activity (PA)	Sedentary Behaviour (SB)
	Standardised beta (standard error)	
+ age and sex	**0.301 (0.042)*** **	**-0.273 (0.042)*** **
+ year 10 diabetes covariates	**0.298 (0.042)*** **	**-0.269 (0.042)*** **
+ year 10 vascular covariates	**0.290 (0.044)*** **	**-0.257 (0.044)*** **
+ Baseline *g*	**0.199 (0.028)*** **	**-0.162 (0.029)*** **
+ Dementia	**0.171 (0.027)*** **	**-0.135 (0.027)*** **

Analyses are multiple linear regressions. *p<0.05 **p<0.01 ***p<0.001. Physical activity (MET^{-1} $minutes^{-1}$ $week^{-1}$) (Natural log transformed), Sedentary behaviour (min/week), Year 10 diabetes covariates: HbA1c (mmol/l), Diabetes medication status, duration of diabetes (years) (Natural log transformed), Year 10 vascular covariates: Systolic blood pressure (mmHg), hypertension, cerebrovascular disease (transient ischaemic attack or stroke), cardiovascular disease (myocardial infarct or angina), Diabetic retinopathy, Total cholesterol (mmol/l), smoking (current, ex, or non-smoker), alcohol units, anxiety, depression, BMI; Body Mass Index.

5.5.5 Association of physical activity and sedentary behaviour with prevalent dementia at year 10

The outcomes of the analysis exploring the associations of physical activity and sedentary behaviour with prevalent dementia at year 10 are shown in Table 34. When adjusting for age and sex, lower physical activity levels were shown to be significantly associated with risk of dementia (OR 0.53; 95% CI 0.37, 0.76, $p<0.001$) per MET unit decrease in activity level. This association remained when making further adjustments for diabetes and vascular risk factors (OR 0.53; 95% CI 0.36, 0.78, $p<0.001$).

For the association between sedentary behaviour and dementia, age and sex adjusted analyses showed an association between increased sedentary time and risk of dementia (OR 1.83; 95% CI 1.26, 2.65, $p<0.001$) per increase in minutes/week spent sedentary. This association persisted when further adjusting for diabetes and vascular covariates (OR 2.01; 95% CI 1.31, 3.08, $p<0.001$).

5.5.6 Summary of analysis

In summary, these results indicate that there is evidence to suggest an association between physical activity and sedentary behaviour and either a decline in cognitive ability or dementia. However, no comment can be made about the direction of these associations.

Table 34. The cross-sectional association between physical activity and sedentary time score and dementia at year 10 follow-up

Risk factor	Physical Activity (PA)	Sedentary Behaviour (SB)
	OR (95% CI)	
+ age and sex	**0.53 (0.37-0.76)*** **	**1.83 (1.26-2.65)*** **
+ year 10 diabetes covariates	**0.53 (0.37-0.77)*** **	**1.84 (1.26-2.68)*** **
+ year 10 vascular covariates	**0.53 (0.36-0.78)*** **	**2.01 (1.31-3.08)*** **

Analyses are logistic regressions. *p<0.05 **p<0.01 ***p<0.001. Physical activity (MET^{-1} $minutes^{-1}$ $week^{-1}$) (Natural log transformed) Sedentary behaviour (min/week), Year 10 diabetes covariates: HbA1c (mmol/l), Diabetes medication status, duration of diabetes (years) (Natural log transformed), Year 10 vascular covariates: Systolic blood pressure (mmHg), hypertension, cerebrovascular disease (transient ischaemic attack or stroke), cardiovascular disease (myocardial infarct or angina), Diabetic retinopathy, Total cholesterol (mmol/l), smoking (current, ex, or non-smoker), alcohol units, anxiety, depression, BMI; Body Mass Index.

Chapter 6: Discussion

This chapter provides a summary of the main results of this thesis and discusses these in the context of previous studies. The strengths and limitations of the methods are discussed and recommendations for further work are presented.

6.1 Main results

In the ET2DS, a prospective cohort representative of older people living in Scotland, the work presented in this thesis has shown that a selection of potentially modifiable risk factors are associated with cognitive decline over a 10 year follow-up period in older people with type 2 diabetes. By using data collected at baseline and at the year 10 follow-up, multivariable analyses models showed associations of measures of systemic inflammation, obesity and physical activity with cognitive outcomes, including cognitive decline and dementia. Statistical models were developed to adjust for known vascular and diabetes-related risk factors in an attempt to determine independence of the findings and explore potential biological mechanisms underlying the development of cognitive decline.

6.1.1 Inflammation

Inflammation and cognitive decline

Results presented in this thesis provide evidence for an association between increased levels of systemic inflammation as measured at baseline and subsequent cognitive decline over a ten year period. Of four inflammatory markers tested, those significantly associated with a decline in general cognition were IL-6 and fibrinogen, however, in fully adjusted

models for a wide range of potential confounding and/or mediating factors, these associations were no longer statistically significant. Although the inflammatory markers were all shown to be highly correlated, the results indicated that only specific markers may be associated with cognitive decline, and that at least some of the association may be due to confounding effects of vascular and diabetes risk factors. Alternatively, it may also be that power in the fully adjusted model may not be sufficient to detect a significant association.

Inflammation and dementia

Results from a range of models adjusted for age and sex alone, or additionally for vascular and diabetes-related risk factors indicated no strong association between increased levels of any of the inflammatory markers measured at baseline and incident dementia over the 10 years of the study. However, a possible suppression effect of other inflammatory markers was observed in fully-adjusted models which included all inflammatory markers. In these models, a statistically significant association was seen between increased level of IL-6 and incident dementia. This suggests that increased levels of IL-6 may be associated with an increased risk of dementia once generalised systemic inflammatory status is taken into account. IL-6 was strongly correlated with the other inflammatory markers, some of which showed very little positive association with dementia (and possibly even a negative association for CRP), and so it is plausible that the effect of IL-6 level on risk of dementia is only evident when accounting for the other inflammatory markers and removing their suppression effect, sometimes considered negative confounding, on the model (MacKinnon et al., 2000). Similarly, an association between CRP and dementia was also shown which may also be masked by the effects of the other inflammatory markers. However, results

indicated that in the case of CRP, lower levels of this individual inflammatory mediator may be associated with a higher risk of dementia once overall systemic inflammatory status is taken into account.

The work presented in this thesis is supportive of the theory that the inflammatory marker IL-6 may act directly on cognitive decline although is confounded by other lifestyle factors such as obesity and inactivity. Furthermore, IL-6 is able to cross the blood-brain barrier and so may have a direct or indirect intracerebral effect on cognition (Varatharaj and Galea, 2017). Other factors are likely at play and findings presented here are also suggestive of a network effect of a combination of factors each contributing to a different extent on the relationship between inflammation and cognitive decline. This suggests that by reducing inflammation, by means of obesity and activity levels, risk of cognitive impairment may be reduced.

6.1.2 Obesity

Obesity and cognitive decline

Results indicated an association of increased WHR and WC with subsequent cognitive decline over 10 years in people with type 2 diabetes, but no strong association with BMI. However, after adjustment for diabetes risk factors, the association between increased WC and cognitive decline was no longer statistically significant, suggesting that diabetes may be confounding factor in this association. On the other hand, the association between increased WHR and cognitive decline persisted even after further adjustment for inflammation and BMI. As BMI is a measure of total body mass, and WHR is predominantly a measure of visceral fat, these findings suggest that visceral fat, or body shape, is

associated with cognitive decline independent of diabetes, vascular and inflammatory risk factors, and also independent of total body mass.

WHR is known to vary considerably between men and women and is known to have different effects on cardiovascular disease in men and women in models that adjust for total body mass (Li et al., 2006). The unexpectedly different findings for BMI and WHR were therefore explored further by performing the analyses on WHR separately for men and women, in case the result may simply be a reflection of WHR acting as a proxy for sex. The association between WHR and cognitive decline remained significant in fully adjusted models that included inflammation and BMI for both men and women separately, suggesting that WHR may indeed be a risk factor for cognitive decline, and in both men and women

A final analysis on WC as a predictor for cognitive decline was carried out. WC is a component of WHR and so it was important to explore the associations shown in models of WHR further by looking at only WC. The results of this analysis indicated that WHR measures a unique obesity phenotype that is distinct from WC, which measures only visceral fat, and is also distinct from BMI, which measures overall mass.

Overall, results suggest that WHR is a distinct obesity-related phenotype, greater levels of which are associated with cognitive decline, and that this relationship is not confounded by diabetic/ vascular-related risk factors or by systemic inflammation.

Obesity and dementia

In contrast to the association between increased levels of obesity-related markers and ten-year cognitive decline as measured by '*g*', results suggested that decreased BMI, WC and

percentage body fat at baseline were associated with an increased risk of incident dementia. This association was only found to be statistically significant when fully adjusting for vascular risk factors, indicating that there may be a suppression effect or negative confounding effect of vascular disease risk factors on this association. This shows that increased body fat is only protective of dementia, if vascular disease (known to also be associated with dementia) is accounted for. An increased WHR was shown to be associated with risk of incident dementia, however this association was not statistically significant.

As weight loss is a symptom of dementia (Johnson et al., 2006), it is possible that the direction of these associations, where it seems a higher BMI or WC reduce the risk of dementia (contrasting the results shown with '*g*'), are due to pre dementia being present in the cohort at baseline. If cases of pre dementia are affecting the direction of the association, it may be that using an obesity measure taken during mid adulthood, as a predictor variable, would change the direction and strength of this association. For WHR, the association with dementia was in the same direction as the results of the analyses with '*g*', which could be consistent with WHR being a measure of body shape, which although associated, is less affected by weight loss than BMI, especially in men (Wing et al., 1992). This pattern where increased WHR and decreased BMI and WC are associated with dementia are also seen in other general population cohorts, especially when measures of obesity were taken just prior to dementia diagnosis (Gustafson et al., 2009). WHR has also been shown to increase the risk of cardiovascular disease in the general population by 5%, which was more than double the risk by increased WC alone (De Koning et al., 2007). In people with diabetes, WHR has also been shown to be the best indicator of cardiovascular disease outcomes when compared to WC alone and there was no significant association with BMI (Czernichow et al., 2011).

6.1.3 Physical activity

Physical activity and cognitive impairment

Cross-sectional analyses showed that lower levels of physical activity and higher levels of sedentary behaviour were associated with lower levels of cognition and also with decline in general cognition. This association persisted in post hoc sensitivity analyses that corrected for dementia. It should be noted that the associations with (in) activity and cognitive decline, despite using a baseline variable, should be regarded as cross-sectional and the likelihood of reverse causation should be considered when interpreting these results. From these analyses no temporal association can be assumed and it is likely that a decline in cognition promotes a sedentary, inactive lifestyle. The directionality of these associations cannot be inferred from the results presented in this thesis.

Physical activity and dementia

Cross-sectional analyses showed that lower levels of physical activity and higher levels of sedentary behaviour were associated with increased risk of dementia, indicating that a lower level of activity and a higher level of sedentary time may be associated with an increased risk of dementia. It should be noted that because this analysis is cross-sectional, and that dementia was diagnosed over a period of 10 years, preceding the (in) activity measurement, in this analysis dementia should be regarded as cross- sectional prevalence variable at year 10. Dementia likely precedes the observed (in) activity levels and it is possible that more sitting and less activity occur as a direct result of dementia or are

symptoms of pre dementia and so it is likely that these associations are examples of reverse causation. Therefore the directionality of these associations cannot be inferred.

6.1.4 Biological Mechanism

Adipose tissue is an endocrine organ comprised of two main types, brown adipose tissue and white adipose tissue. The physiological roles of each type are different, brown adipose tissue is primarily important for heat generation and white adipose tissue for the storage of excess dietary energy. White adipose tissue can be found both subcutaneously and in the abdomen, termed visceral adipose tissue. It has been established that subcutaneous and visceral adipose tissues have different physiological features (Gomez-Hernandez et al., 2016). Visceral fat is involved in other metabolic processes aside from its main function as energy storage, including inflammation (Gomez-Hernandez et al., 2016). The pro-inflammatory cytokines TNF-α and IL-6 are secreted by white adipose tissue (Fruhbeck et al., 2001) and in particular IL-6 expression is found to be up to 3 times higher in visceral fat than other types and distributions of adipose tissue (Fried et al., 1998).

In obesity visceral fat deposits often increase which results in an increased inflammatory response in the adipose tissue (Fain et al., 2004). This can also activate an inflammatory response in the liver, and the combination of the adipose tissue and hepatic inflammation can result in systemic inflammation. The effect of this systemic inflammation on peripheral tissues includes insulin resistance, hypertension and atherosclerosis (Gomez-Hernandez et al., 2016). The link between central obesity, systemic inflammation and vascular disease is well established (Van Gaal et al., 2006). Therefore, as dementia is thought to occur as a result of vascular disease (Crichton et al., 2014) central obesity may be associated with an

increased risk of dementia (Razay et al., 2006), and at least partly mediated by inflammation (Festa et al., 2001).

Clinically, BMI can give an estimation of total body adiposity, with no indication of fat distribution, whereas WC or WHR can give an estimation of visceral adiposity or fat distribution. Obesity is often measured using BMI, however as individuals with increased central obesity are at an increased risk of inflammation mediated vascular diseases such as dementia, WC or WHR may be more clinically relevant measurements.

An alternative biological mechanism to explain these findings may be that the WHR genetic variant may directly, through distribution or utilisation of body fat, influence cognitive impairment through the actions on specific components of inflammation e.g. IL-6. Alternatively, it may also be that the genetic loci of WHR genetic variants may be located proximally close to specific cognitive loci, and so it may also be possible that WHR variants have an impact on the expression of specific genes for cognitive ageing. It is also possible that epigenetics play a role by the modification genes located close to either inflammation or WHR loci.

6.2 Strengths of the Study

The ET2DS was designed as a prospective cohort where cognitive change over time could be assessed along with other risk factors and characteristics of the cohort. Prospective cohorts are advantageous, when compared to retrospective cohorts or cross sectional studies, as they enable observations of incident disease and change in outcomes over time. Despite not being able to infer causality, temporal relationships between risk factor and

outcome can be established through this prospective design that can inform further work that investigates causality. The relatively large sample size recruited at baseline enabled analyses to be adequately powered in order for associations to be detected. The sample recruited at baseline was largely representative of all those invited (Marioni et al., 2010), and due to participants being selected at random from the Lothian Diabetes Register (LDR), we can be confident that the results obtained are generally representative of the local diabetes population. Furthermore, this population included both people living in the city of Edinburgh itself and people living in more rural areas (including smaller towns with generally lower SES) outside the city in the Lothians. This feature of the study allows the results to represent a broad spectrum of people with type 2 diabetes with differing severity of disease, from a range of different areas and socioeconomic backgrounds. For these reasons, the external validity of the study can be accepted to be relatively high and results can be generalised to other regions, and nationally.

Cognitive ability was assessed in the same way at follow-up as it was at baseline, using a comprehensive battery of validated cognitive tests, taking care testing conditions were consistent between participants and between phases of the study. The general cognition factor '*g*', was derived at baseline and year 10 using the same factor loadings and the standardised residual scores were calculated using a method that allowed for a direct case-wise comparison between scores at each time point. All research staff involved in baseline and year 10 clinics received training in physiological examination, interviewing and cognitive testing. Clinical procedures were carried out at year 10 by myself and one other researcher where periodic checks took place every 3 months to ensure consistency between researchers, where one researcher would sit in on the other's appointment at random and give feedback on how the appointment was conducted according to the

standard operating procedures (SOPs). SOPs were developed at year 10 to closely follow procedures at baseline and were strictly adhered to, reducing observer bias.

Incident dementia cases were identified by consulting a variety of sources adopting an inclusive criteria that required a primary source of medical information, such as a clinical diagnosis, along with a secondary source of medical information, such as a self-report. This enabled evidence for a diagnosis to be built and allowed for cases with only one piece of information to be identified and discussed at consensus meetings to determine probable dementia status. This method allowed for everyone with some form of information to be discussed and resulted in a final dementia group to be established based on all available evidence, regardless of whether they attended the year 10 follow-up clinic. The criteria and consensus model for determining the dementia group was conservative in its approach, inferring that everyone in the group has a very high chance of having clinical dementia, however it should be noted that some cases may have been missed for lack of evidence of diagnosis, death before formal diagnosis, personal or family decision to not be formally assessed for stress or emotional reasons, and decision to not to be prescribed or take medications.

Missing data were systematically dealt with where baseline variables were inspected and where missing data were substantial (e.g. HbA1c), original files were consulted to find if these data could be located or if truly missing, data within a specific time frame (e.g. within 6 months of baseline appointment), could be used as a proxy value. Full cognitive data were not available for each participant at both time points, which is problematic when deriving the general cognition variable '*g*'. In deriving '*g*', full data are required when running a principal component analysis (PCA), and so any missing cognitive data would negatively impact on the statistical power of analyses using this variable. Data may be missing for a

number of reasons such as a visual impairment or hearing impairment that impacts on the ability of the participant to carry out specific tests, regardless of their cognitive ability. Other participants may have missing data as a cognitive test is beyond their cognitive capability, they fail to understand instructions, or they anticipate the test being too challenging for them to do. As both these types of missing cognitive data are not the same, any attempt at minimising missing data must be sensitive to the fact that these data may not be missing at random. A multiple imputation method was used to reduce missing data, on a case-wise basis, using other cognitive tests that were not missing to aid in the prediction of the tests that were missing. This allowed for participants of relatively high or low cognitive ability to have a score imputed for missing tests, based on their cognitive ability at a time point. This was done only in people who had completed over half of their cognitive tests, to increase the reliability of the imputation, and was carried out for both baseline and year 10 follow-up phases of the study. This sensitive approach to data imputation was adopted as this would increase the number of cases with a '*g*' score, take into account both cognitive and physical impairments of the cohort and increase power analyses using '*g*' as a variable. Moreover, it could be argued that bias is reduced in the derived final '*g*' variables, as '*g*' would otherwise only be available for the most physically and cognitively healthy, and this would impact on the external validity of any analyses using this variable.

6.3 Limitations of the study

Missing data

The ET2DS has a number of key limitations that need to be acknowledged in order to be able to interpret any findings appropriately. The main limitation, common to most

prospective cohort studies, is around loss to follow-up and missing outcome data. The 'attender vs non-attender' analysis reported in this thesis acknowledges that there was a systematic drop-out in the ET2DS.The retention rate at the year 10 follow-up phase was 55%, which is in line with other studies (Okely and Deary, 2018), and high when taking into account both participant age (Tilvis et al., 2004) and diabetes status (Holman et al., 2008). For analyses of dementia, all participants recruited at baseline were included. To maintain power in analyses on cognition, considerable effort was made to ensure that as many of the surviving original cohort as possible were seen at year 10, through recruitment strategies involving numerous modes of contact and by offering transport to the clinic as well as home visits. This was done to ensure data were collected on as wide a range of participants as possible (taking into account a range of health and economic statuses), enabling results of analyses to be reflective of the true local population. Despite these efforts to minimise missing data, there was loss to follow up in the cohort, which is unsurprising when considering the age and diabetic status of the participants. The main outcome of interest in these analysis is cognitive decline and dementia, which by the nature of the condition is systematically affected by loss to follow-up, and only the most cognitively and physically healthy, on average, were seen at follow-up. It must therefore be acknowledged that in the cognition outcome variables, a systematic attrition will have occurred which may affect the results. The outcome dementia was however less affected by this as all cases were examined throughout the 10 year time frame of the study, and so even if a participant had died, or was still alive but was not able to attend the follow-up clinic, dementia status was still assessed by means of the criteria described. Similarly, as dementia and cognitive impairment are conditions that occur on a spectrum, over an extended period of time, it is also likely that in some cases dementia, or various degrees of pre dementia, will have been prevalent in the cohort at baseline, again affecting the results presented here. In both

scenarios, this would result in a drop in effect size and so any associations that fail to reach statistical significance may be subject to type 2 error, a phenomenon known as left truncation (Cain et al., 2011). The more extreme cases of the cognitive change outcome will also be affected by this and so analyses should be regarded as a snapshot of only the relatively healthy cases.

In linear and logistic regression models, only complete cases are analysed at each stage of the model. This in practice results in more cases being part of the analysis in models adjusted for age and sex, than fully adjusted models, where a case with any of the covariates missing is excluded from the analysis. Therefore, each step in the regression models may not include the exact same cases. A list wise deletion method would have allowed for a more literal and direct comparison between steps of the model, however this would have also resulted in losing a large amount of data, essential for exploring small associations in preliminary models that may have otherwise been missed. A pairwise deletion method was used in this thesis as the principal objective throughout was to investigate associations by building novel models to explore the data, as opposed to testing a known model on this population. The results should therefore be interpreted formally as standalone results for each step in the various models.

Bias and error

This thesis presents the findings of numerous analysis and so a limitation in the results reported is that there is possibility of type 1 error, false positive results, due to multiple comparisons. When deriving the component '*g*', the decision was made to use principle component analysis (PCA) as opposed to factor analysis (FA) as a data reduction technique. The component '*g*' used in this thesis is purely a summary variable, combining the weighted

cognitive test scores, per case, into a single variable. True latent variables, often used and preferred in cognitive psychological research for their ability to represent traits that are difficult to quantify, are derived using FA and take into account testing error. By incorporating error into the derived factor scores, analyses using this latent factor '*g*' would then have to be corrected for multiple testing as it is a new distinct variable, which no longer merely summarises the other cognitive test data. Both forms of '*g*', factor or component, would in practice be fairly similar, however one could argue that a factor when discussed without the context of the other cognitive tests would be more informative in terms of interpretation. A component form of '*g*' was used here as a formal correction for multiple comparisons, such as Bonferroni, would result in a very conservative p-value threshold and also a component form of '*g*' can be explored more directly by looking at the outcomes of analyses using the individual cognitive tests. Moreover, as described above, the cohort is subject to healthy survival bias and some non-dementia cases are likely misclassified, thus the majority of findings at significance level $p<0.05$ are deemed unlikely to be chance findings, therefore results presented here are likely to be accurate reflections of the associations.

Cognitive testing, reliant on a host of skills including cognitive as well as physical abilities, are also susceptible to bias and error. Age increases the intra-individual variability in test performance, and disproportionately so in those of lower ability (Rabbitt et al., 2001), so a systematic error in recoding ability by using only one score per person for each test is possible. Multiple testing, and taking an average of three may overcome this, however results would then be subject to practice effect (Salthouse, 2010). In this thesis, intra-individual variability is minimised by deriving a general cognition component '*g*' as a primary outcome variable, from a number of different testing opportunities that takes into account performance in all 7 tests.

The analysis which incorporates baseline and year 10 variables, despite successfully capturing general cognitive change, does not take into account individual differences in the temporal pattern of cognitive change pathways experienced (Deary et al., 2009). Cognitive measures recorded more frequently, for example every year or 6 months, would provide a more accurate representation of the cognitive change trajectory over time. However similar to the point mentioned above, practice effect would likely skew results if tests were given on a more regular basis.

Study design

As this study was observational by design, any findings reported are only able to acknowledge that specific correlations or associations exist between predictors and outcome. Causal relationships can only be established by using evidence presented from intervention based studies in the form of randomised controlled trials where numerous experimental features are kept constant and often a placebo group is used along with the control group. Although causal associations cannot be determined, the temporal design of data collection over an extended follow-up period does allow for speculation and comment regarding the likely direction of these associations. Namely, that if the risk factor variable was observed at baseline and an outcome variable observed at follow-up, it is likely that the risk factor predicts the likelihood of an outcome and not vice versa. Yet, the notion of reverse causality should not be underestimated in observational research. The age old question of the chicken and the egg, and what came first, is a metaphor that describes this notion well, and even though it may seem initially obvious that a given risk factor likely 'causes' a given outcome to occur, it may well be that other factors, often not easily quantifiable, may in fact be influencing this relationship. In the example of the research

presented in this thesis where specific modifiable risk factors are associated with subsequent cognitive change, it may well be that the severity of follow-up cognitive change may be correlated with, amongst other risk factors, cognitive ability at baseline (or even before, in early adulthood), which may affect lifestyle choices that result in the associations observed. Cognitive reserve theory (Stern, 2002) hypothesises that the greater the neural network, the longer it takes to decline and the later clinical symptoms of cognitive impairment present (Stern, 2012). Similarly, midlife cognitive reserve may have proportional effect on lifestyle choices in midlife.

The issue of confounding was explored by including numerous covariates in multivariable models in an attempt to eliminate the potential confounding effect of these variables. When associations persisted, further investigation is required into possible confounding of elements not measured directly in the ET2DS. This can be achieved in RCTS that keep experimental conditions and exposures consistent. For the longitudinal analyses that used incident dementia as an outcome, associations between baseline variables and dementia outcome are likely affected by when dementia was diagnosed so a major limitation of these analyses is that it was not possible to determine an approximate date of dementia diagnosis for individual cases, which would have allowed for a sensitivity analysis that excluded cases diagnosed within a set time frame (e.g. 2 years) of baseline. This limitation should be taken into account when interpreting the results of these analyses and continued data collection in future years of the ET2DS may be able to address this.

Confounders were chosen to improve the reliability of the models, however a balance between the numbers of confounding variables entered into the model and the power of the model needs to be maintained. The power is impacted by adding more variables into the model and as a result a judgment was made as to which adjustments were included. A

number of variables were not included in the final model but it can be argued that these should have been adjusted for. The level of deprivation as measured by SIMD was not included in the final models used in this thesis as it was deemed a fairly crude measure of an individual's SES, however SES is likely to have effect on both the outcome of interest and predictors. Similarly, hypoglycaemia is also traditionally adjusted for in models with cognitive outcomes, however as the models in this thesis included diabetic medication it was argued that insulin medication would act as a proxy for hypoglycaemia. In all regression models the pros and cons of including specific covariates needs to be considered carefully and it is rarely possible to adjust for everything.

Survivor Bias and the role of competing risks

Survivor bias is a when survivors of a potentially lethal disease are likely to enter a study than the true population (Delgado-Rodriguez and Llorca, 2004). The results obtained through investigating the ET2DS study population used in this thesis is particularly at risk of this type of bias as this particular population exclusively consists of people with type 2 diabetes who have survived until the age of 65 years. It should therefore be acknowledged that upon entering the study, the ET2DS participants are presumably a healthier subgroup of all people with type 2 diabetes as many people with more severe forms of the disease or with multiple comorbidities, will have died before reaching this age.

A 10 year follow up of people aged approximately 65 years at baseline was deemed appropriate for detecting cognitive decline and dementia onset in a cognitively healthy group at baseline. However by selecting an already aged group at baseline the risk of survivor bias may become problematic. Selecting a younger cohort for baseline would reduce survivor bias, however the length of a study to measure the primary outcome in this

cohort would be prohibitively long. When interpreting results obtained from this cohort this bias should be taken into account as it is likely that estimates will lie closer to the null with a smaller effect size than that in the true population, affecting the external validity of the outcomes (Delgado-Rodriguez and Llorca, 2004).

Survivor bias also effects any of the analyses that have cognitive decline as measured at follow-up and should be considered when reading results. Only surviving participants were able to provide cognitive information at follow-up and those that had died during the 10 year course of the study were not taken into account in the results. This must be acknowledged as in essence cognitive change in only the relatively healthy population, who have survived until the age of 75 years, is measured. A large percentage of people with type 2 diabetes will die before this age and these cases are not represented in this analyses.

Survivor bias has a lesser effect on analysis that have dementia diagnosis as an outcome variable. Although there is survivor bias upon entry into the study, there is less survivor bias at follow-up as death certificates and other records were consulted in all study participants, i.e. not only those still attending the clinic at year 10. It should be noted that death certificates do not always include dementia as a cause of death and it is possible that someone who would have gone on to develop dementia dies before any cognitive issues are recorded. Therefore, it is more likely to pick up a dementia diagnosis in those still alive at year 10. By consulting death records and medical records for all people included at baseline active steps were taken to reduce the effect of survivor bias at follow-up, although this cannot be eliminated entirely.

The competing risk of death, where participants die without experiencing the outcome of interest is often a consideration in studies involving older people (Berry et al., 2010). For analyses of cognitive decline, competing risks also include any reason an individual failed to

complete follow-up cognitive testing. The main reason being death, although any disability (e.g. blindness) or comorbidity (e.g. stroke) that meant that testing was not feasible on the day would also be included as a potential competing risk for the measurement of cognitive decline. Competing risks for dementia would presumably be limited to death, discussed previously as reducing the likelihood of diagnosis being recorded. This would result in an underestimation of the incidence of dementia in the study. The impact of death as a competing risk is that the association between risk factor and outcome is weakened as only the healthiest sub-group of the study population is taken into account. Others have shown that, compared to people without diabetes, dementia onset in people with diabetes is earlier although people with diabetes have a higher risk of premature death and failing to take this into account can exaggerate the strength of the association between diabetes and dementia (Davis et al., 2017). This highlights the need to take the competing risk of death into account when investigating dementia in this particular population.

6.4 Comparison to other work

Inflammation and cognitive impairment

The inflammation marker IL-6 was previously shown to be associated with cognitive decline in the general population, and has been linked to a diet consisting of a high intake of red meat and processed and fried foods (Ozawa et al., 2017). Recently, a systematic review on the effect of systemic inflammation on cognitive decline and dementia has shown that increased levels of systemic inflammation markers increased the risk of developing dementia (Darweesh et al., 2018). The inflammatory response has been linked to the pathogenesis of diabetes (Yan et al., 2008). Single nucleotide polymorphisms (SNPs) in the gene for the insulin degrading enzyme (IDE) have been associated with type 2 diabetes

(Karamohamed et al., 2003) and dementia (Bertram et al., 2000), and IL-6 has recently been shown to increase the expression of IDE (Kurauti et al., 2017). Despite a lack of prospective cohort studies investigating the effect of IL-6 on cognitive decline and dementia in people with type 2 diabetes, the results presented in this thesis are in line with the evidence presented from studies in the general population (Singh-Manoux et al., 2014). The results of this thesis aid in building the evidence for a specific role of the inflammatory marker IL-6 in cognitive decline and the potential synergistic role IL-6 and diabetes may play in effects on cognition.

Obesity and cognitive impairment

The results presented in this thesis are supported in part by the findings of previous studies. Others have shown a stronger association of WHR as an obesity variable and cognitive impairment than BMI and WC in the general population (Liu et al., 2018). This recent study included a number of people with type 2 diabetes (26.7%) of which 11.4% were obese as measured by BMI. There may be considerable overlap between these groups and so it would not be unrealistic to hypothesise that if they controlled for diabetes (known to be associated with cognitive impairment), BMI may not be significantly associated with cognitive impairment.

The results of the systematic review on obesity and cognitive decline in type 2 diabetes (Chapter 3) were in line with the results presented in this thesis, as many studies did not find an association with BMI. WHR as an alternative measure of obesity was rarely investigated, however Abbatecola et al. (2010) provided results that are in line with the results of the ET2DS where WHR was associated with cognitive decline while BMI was not. In a further paper, that failed to be identified though the systematic review as it was

incorrectly indexed, by Bruce et al. (2008) it was shown that in their cohort of older people with type 2 diabetes WHR was significantly associated with cognitive impairment, while BMI failed to show a significant association. As a result of identifying this study, the terms used to index this paper were added to the search strategy described in chapter 3 of this thesis, to see if other papers could be identified that may have also met the inclusion criteria. This was carried out on the 20th of August 2018, and resulted in no additional papers being found.

The systematic review identified two studies that explored the association between obesity and dementia in type 2 diabetes. These studies found no association between BMI and dementia in cross-sectional analyses (Espeland et al., 2017) and showed that in longitudinal analyses a higher BMI was associated with a lower risk of dementia (Hu et al., 2012). The result by Hu et al. (2012), was in line with the results of the ET2DS presented in this thesis, and the authors noted that these findings may be due to weight loss in pre dementia, despite noting that associations persisted even after sensitivity analyses were carried out that removed individuals diagnosed within 2 years of baseline. No previous study was identified that investigated the effect of WHR on dementia so the results of this thesis cannot be placed in context of other work. The direction of the association observed in the ET2DS, although not statistically significant, was in line with the results of the cognitive decline analyses, and opposite in direction to the association seen with BMI and dementia, providing further evidence that WHR and BMI measure distinct obesity phenotypes.

Physical (in) activity and cognitive impairment

A comprehensive meta-analysis on the effect of physical activity on cognitive decline in the general population found that increased levels of activity may act as a protective factor on

cognitive decline (Sofi et al., 2011). The association between physical activity and cognitive ability and decline in people with diabetes is yet to be extensively investigated. The results of the studies identified in the systematic review chapter of this thesis are mixed, as some find an association between level of activity and cognitive status, while others do not. The results presented in this thesis provide evidence to support the notion that level of physical activity is related to cognitive ability in diabetes, as noted also by Valiente-Barroso et al. (2015) and Devore et al. (2009). However, the ET2DS does not have the temporal data to support any link with cognitive decline short of dementia. Physical activity and dementia are shown to be associated in the ET2DS, however no other studies could be identified that investigated this in people with diabetes.

The association between sedentary behaviour and cognitive ability or dementia as seen in the ET2DS cannot be placed in context of previous work as no studies investigating this in people with diabetes could be identified. Moreover, studies reporting on sedentary behaviour and cognitive decline and dementia in the general population are also limited in number and in employing valid measures of time spent sitting. One study measuring sedentary time as time spent watching television and time spent on a computer as proxy measure of global sitting behaviour (Hamer and Stamatakis, 2014). This study reported conflicting results between the two sedentary measures, and their association with cognitive impairment, which seemed unsurprising as both activities require different cognitive abilities and skills, where TV watching can be seen as cognitively passive and computer time cognitively active, making the interpretation of their result difficult. A more recent systematic review of sedentary behaviour and cognitive health in the general population found that increased sedentary time was associated with poorer cognitive performance, although it could not identify evidence for the association between sedentary time and cognitive decline or dementia (Falck et al., 2016).

6.5 Conclusions and Further work

The work presented here primarily aimed to determine the association between potentially modifiable risk factors and cognitive impairment, to identify where it may be possible to develop and/or target preventive measures in the future. Overall conclusions and suggestions for further work in this area are listed below:

1. Evidence presented here supports the hypothesis that in people with diabetes there may be an association between obesity and increased cognitive decline during aging, independent of diabetes-related, vascular and inflammatory risk factors. However, this was only evident when obesity was measured by elevated WHR, not by raised BMI. Moreover, results indicated that increased BMI and WC were associated with a *lower* risk of developing dementia. Overall, findings suggest that further work is required to establish the direction and strength of associations between obesity and cognitive decline, preferably including populations free of pre diabetes and using a range of different obesity measures.

2. Increased levels of inflammatory markers in people with diabetes (IL-6 and fibrinogen) may be predictive risk factors for cognitive decline, although diabetes-related and vascular risk factors appear to confound this relationship.

3. Increased levels of IL-6 and decreased levels of CRP were shown to be risk factors for dementia, but only when adjusting for other inflammatory markers, suggesting the possibility of suppressor effects which warrant further investigation.

4. Cross-sectionally, physical inactivity was shown to be associated with poorer cognition and greater levels of dementia in people with diabetes, but further longitudinal work needs to be carried out to establish the temporal nature of this relationship.

5. Models using dementia as an outcome could be developed further to explore the strength and direction of associations. For example, adjustment for a low MMSE (e.g. MMSE <24) could help explore the effect of pre dementia on associations, as could a sensitivity analysis of those people who were diagnosed with dementia a number of years after their baseline assessment.

6. To explore temporal relationships between risk factor and '*g*' further, growth curve analysis could be a useful next step (Deary et al., 2011a). Currently, the ET2DS only has cognitive data on people collected at year 4 (2010/2011), if/when future phases of data collection are to take place, modelling incorporating baseline, year 4, year 10 and future phases would help to confirm the results presented here and would explore associations in more detail over an extended period of time. In addition to this the relationship with the outcome variable dementia could be explored further

by exploring hazard ratios (Atti et al., 2008), which incorporate time to event in the model.

7. Exploration of causality could involve the use of genetic variants for the obesity variables, for example in a Mendelian Randomisation analysis (Lawlor et al., 2008). Exploring the genetic loci of the WHR phenotype and determining if associations between genetic variants of these genes and cognitive outcomes exist could also help in determining why differences in key associations with cognition are observed for WHR and BMI, when both are thought to measure the same phenotype.

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Appendices:

Appendix A

Distribution of selected variables at baseline that were used in models.

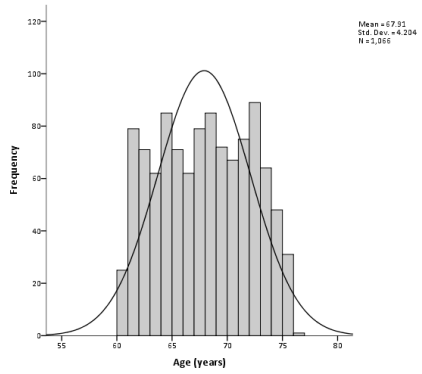
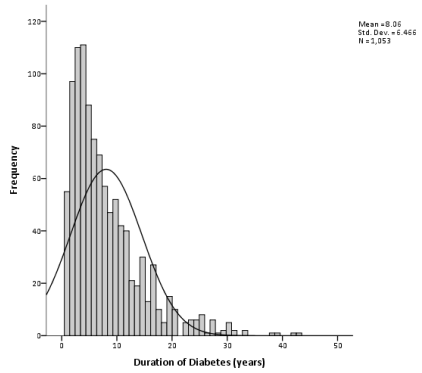


Figure A.1 Distribution of age at baseline



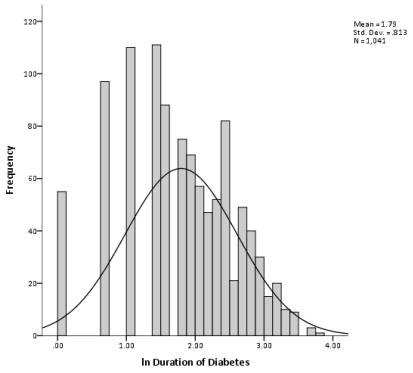


Figure A.2 Distribution of Duration of Diabetes at baseline (before and after natural log transformation)

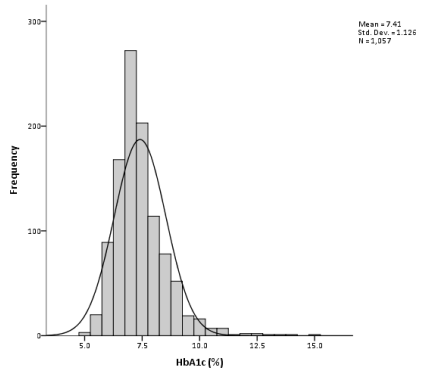


Figure A.3 Distribution of HbA1c at baseline

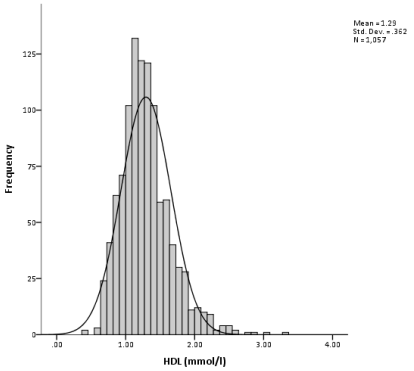


Figure A.4 Distribution of HDL at baseline

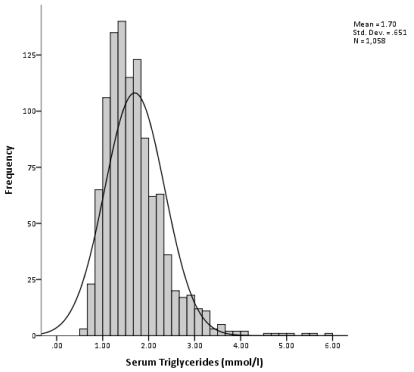


Figure A.5 Distribution of Serum triglycerides at baseline

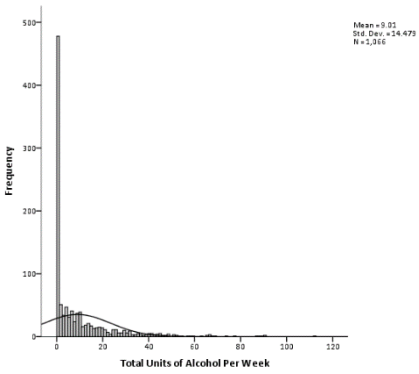


Figure A.6 Distribution of Alcohol units at baseline

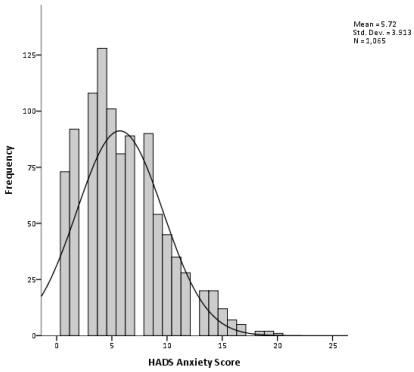


Figure A.7 Distribution of Anxiety at baseline

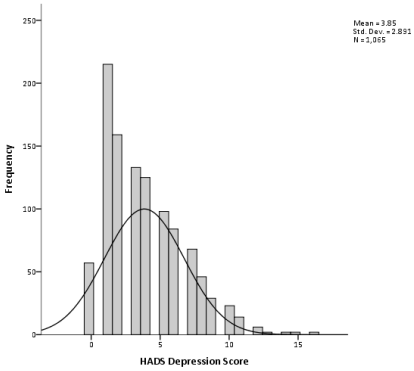


Figure A.8 Distribution of Depression at baseline

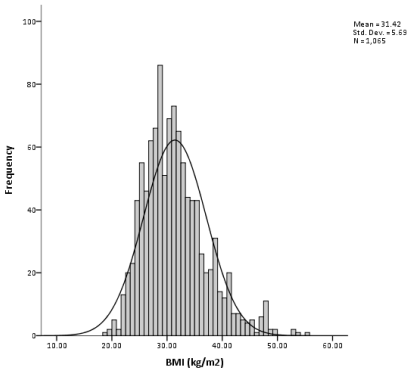


Figure A.9 Distribution of Body mass index at baseline

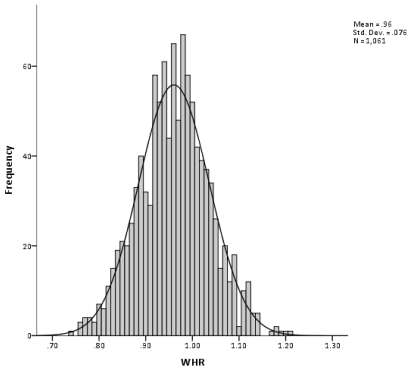


Figure A.10 Distribution of Waist to hip ratio at baseline

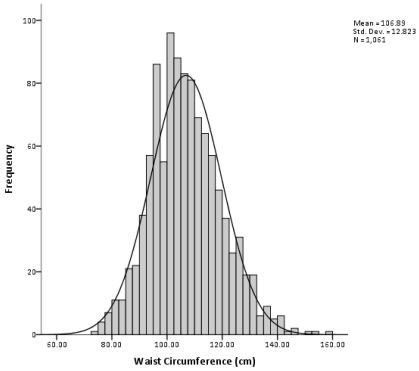


Figure A.11 Distribution of Waist circumference at baseline

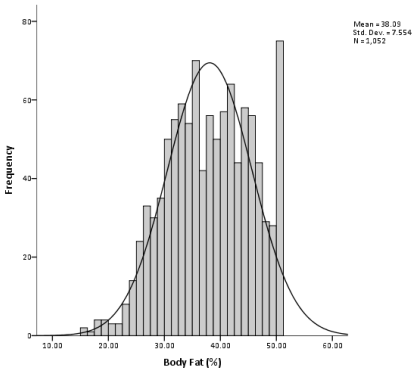


Figure A.12 Distribution of Body fat at baseline

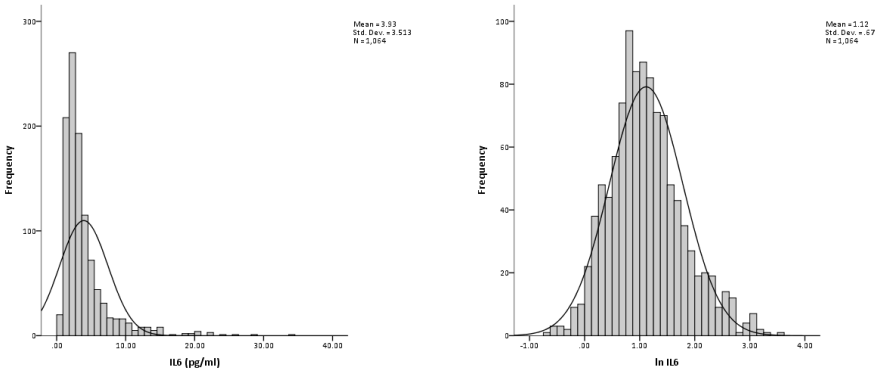


Figure A.13 Interleukin 6 at baseline (before and after natural log transformation)

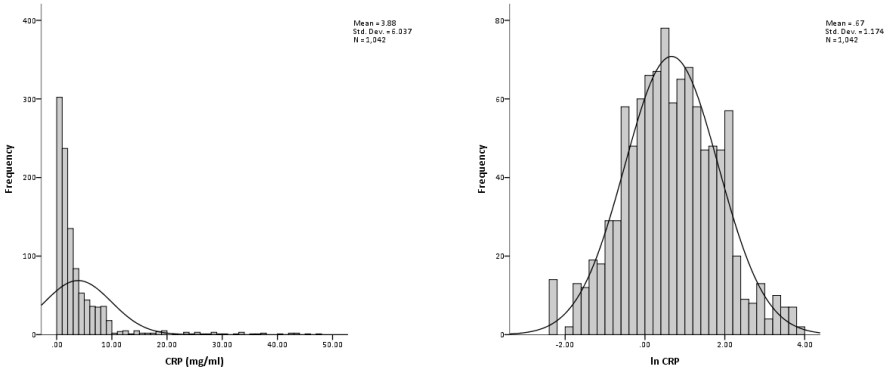


Figure A.14 C- reactive protein at baseline (before and after natural log transformation)

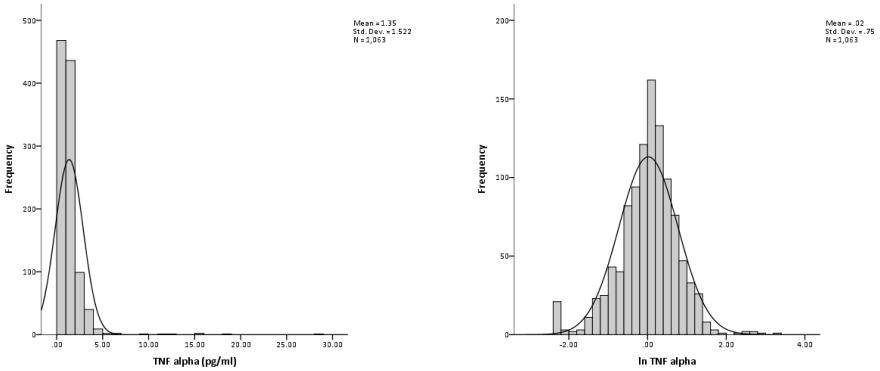


Figure A.15 Tumour necrosis factor alpha at baseline (before and after natural log transformation)

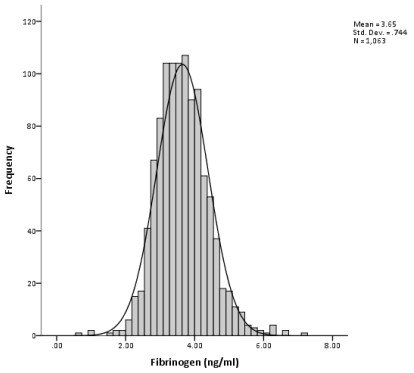


Figure A.16 Fibrinogen at baseline

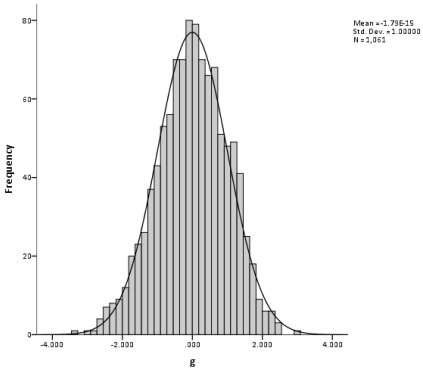


Figure A.17 *g* at baseline

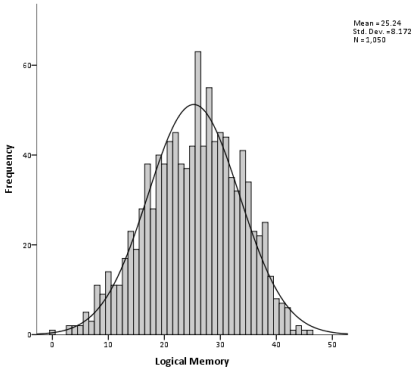


Figure A.18 Logical memory task at baseline

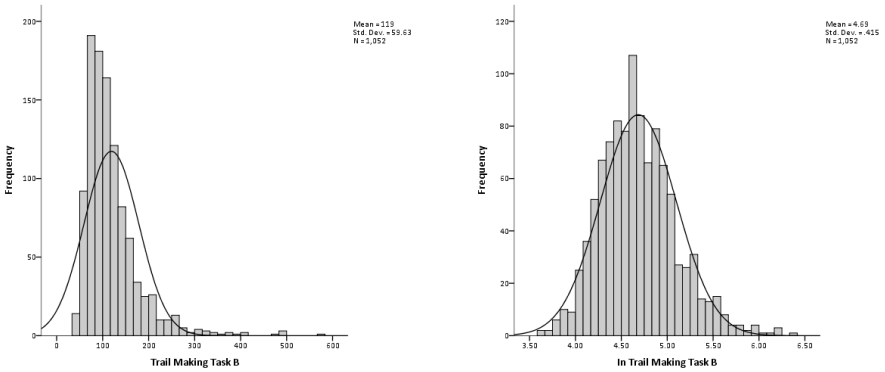


Figure A.19 Trail making task B at baseline (before and after natural log transformation)

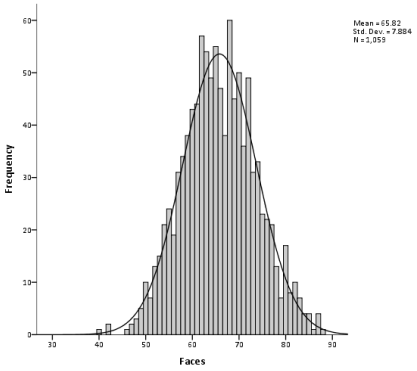


Figure A.20 Faces task at baseline

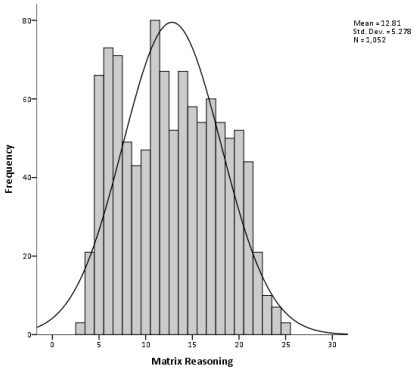


Figure A.21 Matrix reasoning task at baseline

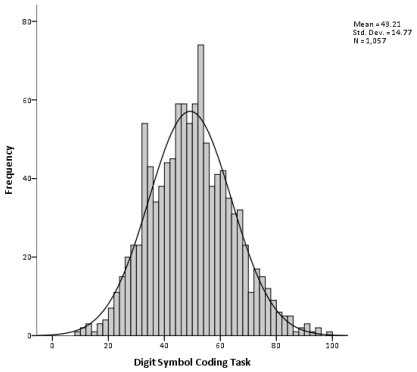


Figure A.22 Digit symbol test at baseline

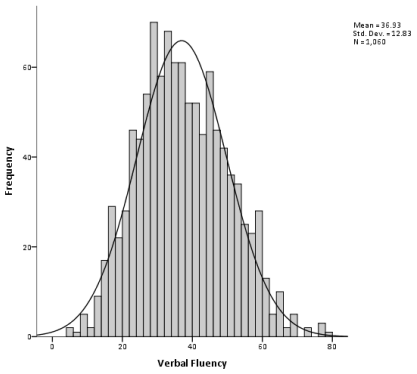


Figure A.23 Verbal fluency task at baseline

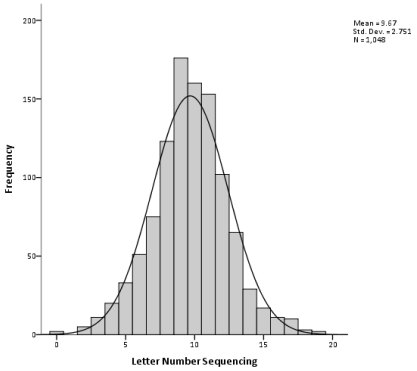


Figure A.24 Letter number sequencing task at baseline

Appendix B

Distribution of selected variables at year 10 follow-up that were used in models.

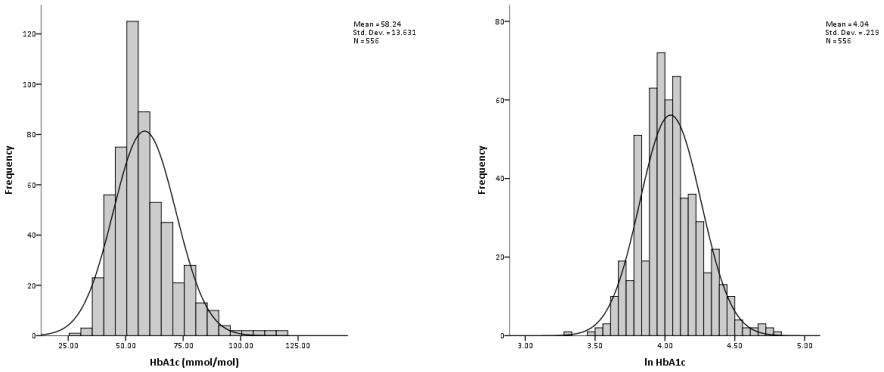


Figure B.1 HbA1c at year 10 follow-up (before and after natural log transformation)

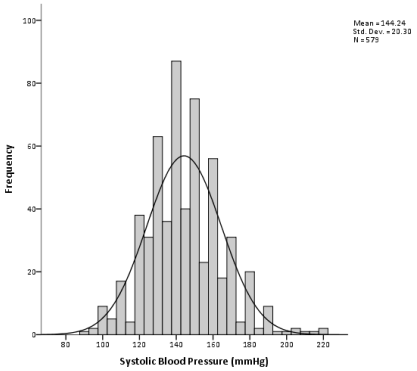


Figure B.2 Systolic Blood pressure at year 10 follow-up

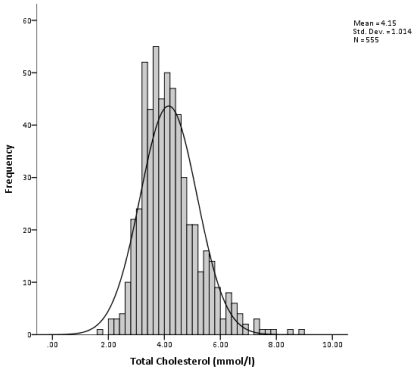


Figure B.3 Total Cholesterol at year 10 follow-up

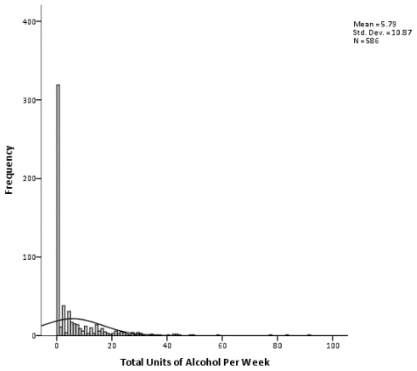


Figure B.4 Alcohol units at year 10 follow-up

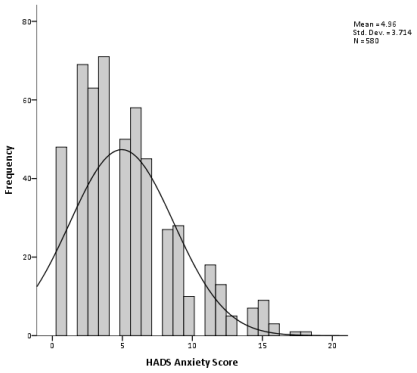


Figure B.5 Anxiety at year 10 follow-up

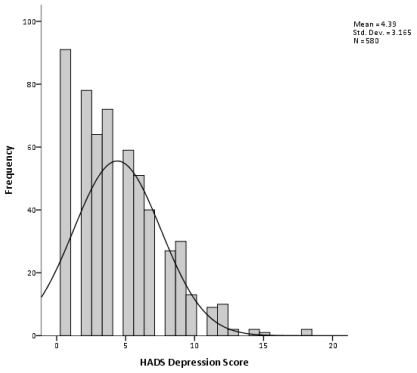


Figure B.6 Depression at year 10 follow-up

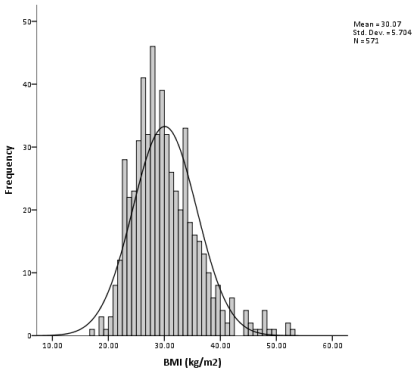


Figure B.7 Distribution of Body mass index at year 10 follow-up

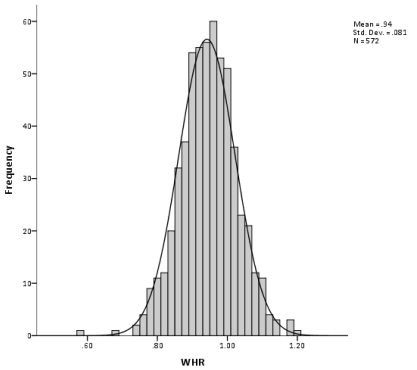


Figure B.8 Distribution of Waist to hip ratio at year 10 follow-up

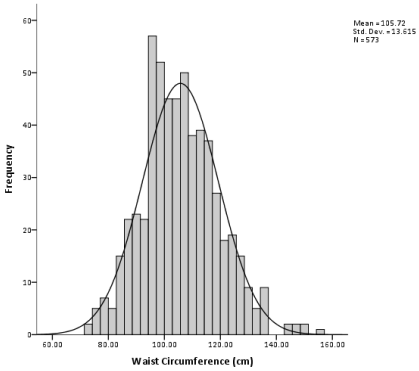


Figure B.9 Distribution of Waist circumference at year 10 follow-up

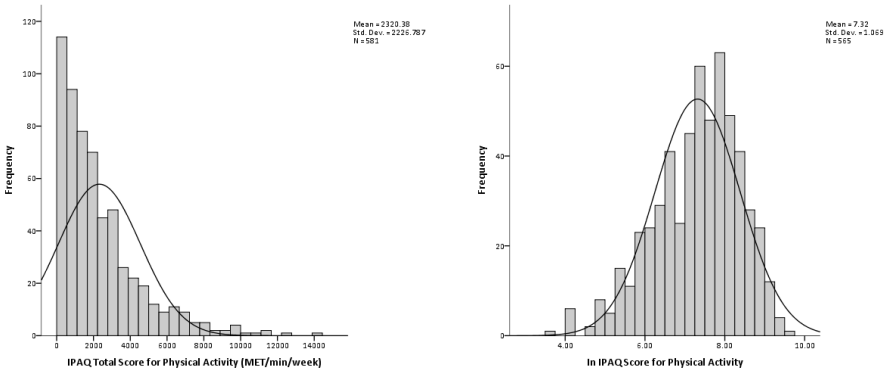


Figure B.10 Distribution of Physical activity score at year 10 follow-up (before and after natural log transformation)

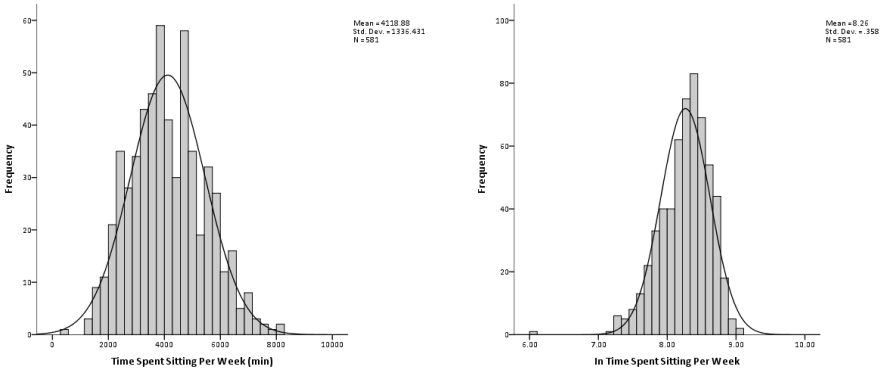


Figure B.11 Distribution of Sedentary time at year 10 follow-up (before and after natural log transformation)

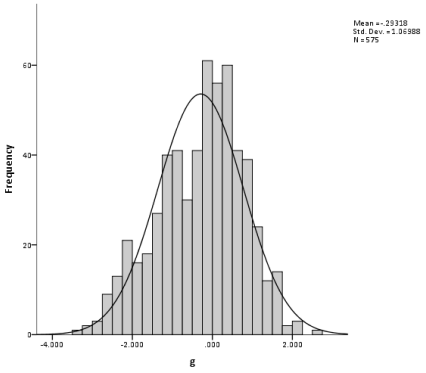


Figure B.12 *g* at year 10 follow-up

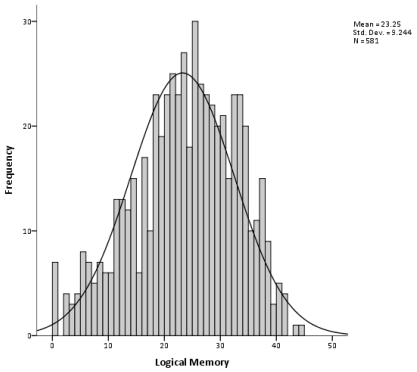


Figure B.13 Logical memory task at year 10 follow-up

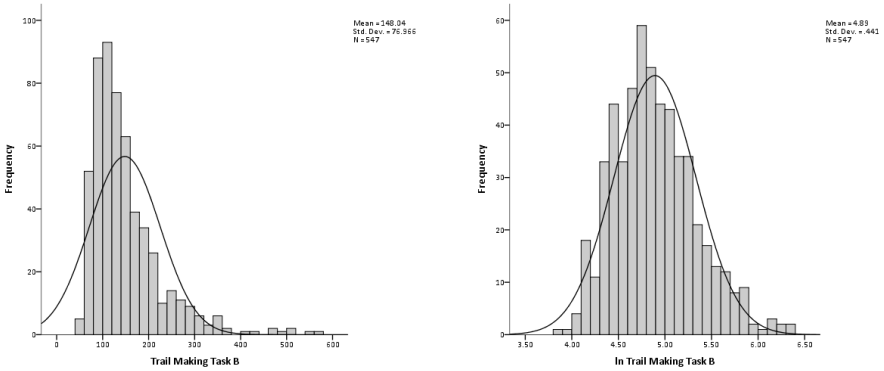


Figure B.14 Trail making task B at year 10 follow-up (before and after natural log transformation)

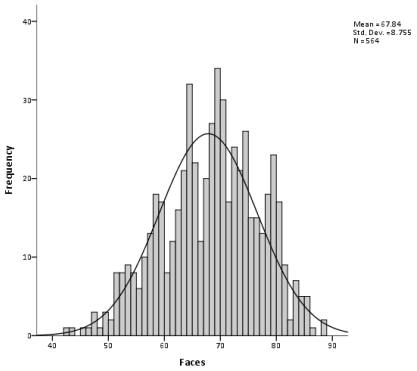


Figure B.15 Faces task at year 10 follow-up

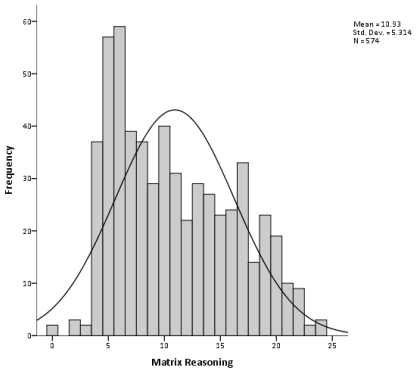


Figure B.16 Matrix reasoning task at year 10 follow-up

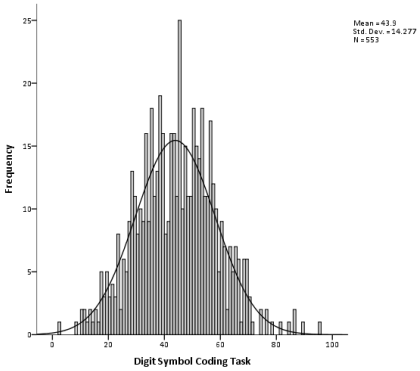


Figure B.17 Digit symbol test at year 10 follow-up

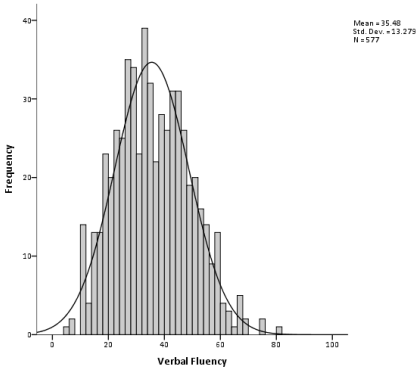


Figure B.18 Verbal fluency task at year 10 follow-up

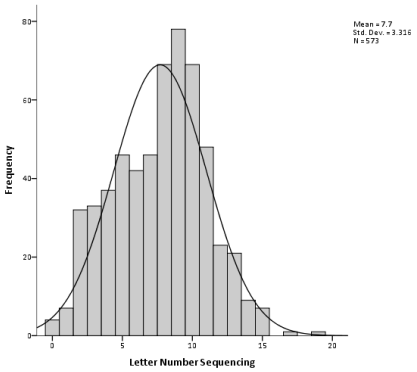


Figure B.19 Letter number sequencing task at year 10 follow-up

Appendix C

Copy of the Ethics form sent to the research ethics committee (REC) and NHS Lothian R&D.

Appendix D

ET2DS Participant newsletter.

Appendix E

ET2DS baseline questionnaire.

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select "Save" and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
The Edinburgh Type 2 Diabetes Study 10 year follow up - Version 1

1. Is your project research?

(•) Yes ( ) No

2. Select one category from the list below:

( ) Clinical trial of an investigational medicinal product

( ) Clinical investigation or other study of a medical device

( ) Combined trial of an investigational medicinal product and an investigational medical device

( ) Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice

(•) Basic science study involving procedures with human participants

( ) Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology

( ) Study involving qualitative methods only

( ) Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)

( ) Study limited to working with data (specific project only)

( ) Research tissue bank

( ) Research database

If your work does not fit any of these categories, select the option below:

( ) Other study

2a. Will the study involve the use of any medical device without a CE Mark, or a CE marked device which has been modified or will be used outside its intended purposes?

( ) Yes (•) No

2b. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation?	( ) Yes	(•) No
b) Will you be taking new human tissue samples (or other human biological samples)?	(•) Yes	( ) No
c) Will you be using existing human tissue samples (or other human biological samples)?	(•) Yes	( ) No

Our Supporters:

The Edinburgh Type 2 Diabetes Study

March 2016

Newsletter from the ET2DS research team:

Contact Details

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Centre for Population Health Sciences
University of Edinburgh
Medical School
Teviot Place
Edinburgh
EH8 9AG

2 Telephone: 0131 650 3242
Email: elds@ed.ac.uk

We would like to take this opportunity to thank you for supporting the Edinburgh Type 2 Diabetes Study (ET2DS). Without your time and support none of the valuable work we are conducting in this study would be possible and so we are very appreciative of your help. We would like to update you on our progress and are happy to report that the study is progressing well. As you will remember, we asked you to return to our follow-up clinic in 2011 and in this newsletter we would like to share some of the results from this so far. Moving forward, as it has now been 10 years since the study began, we are really excited to invite you back for another follow-up clinic this year.

If you have changed your address, phone number or General Practitioner since your last clinic visit, please contact us to update your information using the address or phone number on the left. We will be in touch by letter to invite you personally to the 10 year follow-up clinic between May 2016 and April 2017, so please look out for this and feel free to contact us with any questions you have.

-Professor Jackie Price
(Principal Investigator, on behalf of the ET2DS research team)

EDINBURGH TYPE 2 DIABETES STUDY

BASELINE

QUESTIONNAIRE

PLEASE NOTE: ONE OF OUR RESEARCH NURSES WILL GO OVER THE QUESTIONNAIRE WITH YOU AT THE CLINIC AND MAY ASK A FEW ADDITIIONAL QUESTIONS

THE INFORMATION IN THIS QUESTIONNAIRE IS HIGHLY CONFIDENTIAL AND IS PART OF A MEDICAL RESEARCH STUDY

The information you give in this questionnaire will be treated as strictly confidential and will be available only to your own doctor and the study team. The results of the research will appear only in the form of general statistics from which it will be impossible to identify you as an individual.

Please complete the following:

SURNAME: ……..

FORENAMES: ……..

DATE: ……..

If you have any difficulties in answering some of the questions, you will have a chance to discuss these with a member of the study team.

If you find that the questionnaire is too long for you to complete today, you will be able to take part 2 home with you to complete (we will give you a reply paid envelope to return it to us).

THANK YOU FOR YOUR CO-OPERATION IN THIS STUDY

For Office Use: Study No…....

BASELINE QUESTIONNAIRE

IT IS IMPORTANT TO ANSWER ALL THE QUESTIONS CAREFULLY. PLEASE TAKE YOUR TIME.

PERSONAL HISTORY

1. Please tick one box: Male ☐ Female ☐

2. Enter your date of birth: Day ☐☐ Month ☐☐ Year ☐☐

3. Please tick the box showing your present marital status:

Married and/or living with long-term partner ☐ 1

Single ☐ 2

Widowed ☐ 3

Divorced or separated ☐ 4

4. Please enter your address (including postcode) and telephone no.

Address: ……

……

Postcode: ……..

Telephone no: ……

5. Please enter the details of your GP

GP name: ……

Address:…….

EDUCATION

6. What is the HIGHEST level of education you and your spouse/ex-spouse or long-term partner have completed?

Please tick appropriate boxes:

	You	Spouse/ex-spouse partner
University/college degree course	☐ 1	☐ 1
Other professional/technical qualification after leaving school	☐ 2	☐ 2
Secondary school	☐ 3	☐ 3
Primary school	☐ 4	☐ 4

ETHNICITY

7. What is your ethnic group?

Please choose ONE section from 1 to 5, then tick the appropriate box to indicate your ethnic Group

(i) White

11 ☐ British

12 ☐ Any Other White background, *please write in* _____

(ii) Mixed

21 ☐ White and Black Caribbean

22 ☐ White and Black African

23 ☐ White and Asian

24 ☐ Any Other Mixed background, *please write in* _____

(iii) Asian or Asian British

31 ☐ Indian

32 ☐ Pakistani

33 ☐ Bangladeshi

34 ☐ Any Other Asian background, *please write in* _____

(iv) Black or Black British

41 ☐ Caribbean

42 ☐ African

43 ☐ Any Other Black background, *please write in* _____

(v) Chinese or other ethnic group

51 ☐ Chinese

52 ☐ Any Other, *please write in* _____

CURRENT EMPOYMENT STATUS

8. At the moment, what is the employment status of you and your spouse/ex-spouse or long-term partner?

You		**Spouse/ex-spouse/partner**	
Employed, full-time	☐ 1	Employed, full-time	☐ 1
Employed, part-time	☐ 2	Employed, part-time	☐ 2
Unemployed	☐ 3	Unemployed	☐ 3
Retired	☐ 4	Retired	☐ 4
A Housewife (full-time)	☐ 5	A Housewife (full-time)	☐ 5
Other	☐ 6	Other	☐ 6
please specify ……..		please specify ...……	

MEDICAL HISTORY

Diabetes history

9. When was your diabetes diagnosed (if known)? Year ……..……

10. What treatment do you receive currently for your diabetes?

	Yes	No
(i) Tablets	☐ 1	☐ 2

If 'yes', please give name(s) …….....

	Yes	No
(ii) Insulin injections	☐ 1	☐ 2

If 'yes',

(a) give total number of units per day ……..…units/day
(b) give date (year) when you started insulin year ……

		Yes	No	Don't Know
11.	Have you ever had an episode of low blood glucose (hypoglycaemia) when you have needed **someone else** to treat you eg. give sugary drink or glucagon?	☐ 1	☐ 2	☐ 3

If 'yes', how many times has this **ever** happened?

1-2 ☐ 1
3-4 ☐ 2
5 or over ☐ 3

How many times has this happened **over the past year**?

1-2 ☐ 1
3-4 ☐ 2
5 or over ☐ 3

12. Are you on any regular medical treatment from a doctor as follows:

	Yes	No	Don't Know
Aspirin?	☐ 1	☐ 2	☐ 3
Drugs for angina (including spray)?	☐ 1	☐ 2	☐ 3
Drugs to lower blood pressure?	☐ 1	☐ 2	☐ 3
Drugs to lower cholesterol?	☐ 1	☐ 2	☐ 3

(If you have answered YES to any of these, please give details below)

13. Give names of all current medication if possible (including regular skin creams, eye drops, inhalers, tablets and injections which may or may not be repeat prescriptions):

…… ……....

…… ……....

…… ……....

…… ……....

14. Have you taken any oral steroids, used steroid inhalers or used steroid containing creams or eye drops in the last 3 months?

Yes ☐ 1 No ☐ 2 Don't Know ☐ 3

Vascular Disease

15. Have you ever been told by a doctor that you have or have had any of the following?

		Yes	No	Don't Know
(i)	Heart attack (coronary thrombosis, myocardial infarction)?	☐ 1	☐ 2	☐ 3
(ii)	Angina?	☐ 1	☐ 2	☐ 3
(iii)	Stroke?	☐ 1	☐ 2	☐ 3
(iv)	Hardening of the arteries in the legs?	☒ 1	☒ 2	☒ 3
(v)	High blood pressure?	☒ 1	☒ 2	☒ 3

If you have answered 'yes' to any of the above, please give the year in which the event occurred and/or condition was diagnosed (as near as you can remember) and the name of the hospital/GP surgery where you were/are treated for the condition

Event/condition	Year of event/diagnosis	Hospital/GP surgery where treated
……	……	……
……	……	……

16. Have you ever undergone any of the following procedures/operations?

	Yes	No	Don't Know

(i) An operation or balloon treatment to relieve a blockage in the arteries of your heart (coronary by-pass or angioplasty)? ☐1 ☐2 ☐3

(ii) An operation or balloon treatment to relieve a blockage in the arteries of your leg(s) , other than for varicose veins? ☐1 ☐2 ☐3

(iii) Surgery to remove toes or leg (above or below the knee)? ☐1 ☐2 ☐3

(iv) An operation or balloon treatment to relieve a blockage in the arteries of your neck (carotid surgery/angioplasty/stenting)? ☐1 ☐2 ☐3

If you have answered 'yes' to any of the above, please give the year in which the procedure was performed and the name of the hospital you attended

Procedure/operation	Year performed	Hospital attended
……	…….	…….
……	…….	…….

Liver Condition/Disease

17. Have you ever been told by a doctor that you have or have had any of the following?

		Yes	No	Don't Know
(i)	Hepatitis?	☐1	☐2	☐3
(ii)	Cirrhosis of the liver?	☐1	☐2	☐3
(iii)	Any other disease/medical condition affecting the liver?	☐1	☐2	☐3

If you have answered 'yes' to any of the above, please give the name of the condition, the year in which it was diagnosed (as near as you can remember) and the name of the hospital where you were/are treated for the condition

Name of condition	Year of diagnosis	Hospital where treated
……	…….	…….
……	…….	…….

18. Have you ever had any of the following investigations of your liver

		Yes	No	Don't Know
(i)	Abnormal blood tests of liver function?	☐ 1	☐ 2	☐ 3
(ii)	Liver biopsy?	☐ 1	☐ 2	☐ 3
(iii)	Scan (ultrasound or CT etc.) of the liver?	☐ 1	☐ 2	☐ 3
(iv)	Other investigation of the liver?	☐ 1	☐ 2	☐ 3

If you have answered 'yes' to any of the above, please give the name of the investigation, the year in which it was done (as near as you can remember) and the name of the hospital where the test/investigation was performed

Name of investigation	Year done	Hospital where performed
……	……	……
……	……	……

Other Medical Conditions

		Yes	No	Don't Know
19.	Do you suffer from disease of the thyroid gland?	☐ 1	☐ 2	☐ 3
20.	Do you have any other medical conditions not mentioned above?	☐ 1	☐ 2	

If yes, please specify: ……..

……

……..

ALCOHOL

21. **Current alcohol intake**

(i) Think back carefully over the last seven days. Please write in each column the exact number of alcoholic drinks you consumed on each day during the past week. If none consumed write '0' in the boxes. Try to remember where and who you were with on each day. This may help you remember what you had to drink.

	Pints of beer, lager, cider etc	Single glasses of whisky, vodka, gin etc	Single glasses of martini, wine, sherry, etc
Monday	☐	☐	☐
Tuesday	☐	☐	☐
Wednesday	☐	☐	☐
Thursday	☐	☐	☐
Friday	☐	☐	☐
Saturday	☐	☐	☐
Sunday	☐	☐	☐

(ii) Would you say that last week was fairly typical of what you usually have to drink in a week?

Yes ☐ No ☐

(iii) If last week was not typical, would you normally drink more or less in a week?

More ☐ Less ☐

22. **Alcohol intake over past year**

(i) How often did you have a drink containing alcohol in the past year?

Consider a "drink" to be a can or bottle of beer, a glass of wine, or one cocktail or a measure of spirits (like scotch, gin, or vodka).

never	☐ 1
monthly or less	☐ 2
2 to 4 times a month	☐ 3
2 to 3 times a week	☐ 4
4 to 5 times a week	☐ 5
6 or more times a week	☐ 6

(ii) How many drinks did you have on a typical day when you were drinking in the past year?

0 drinks	☐ 1
1 to 2 drinks	☐ 2
3 to 4 drinks	☐ 3
5 to 6 drinks	☐ 4
7 to 9 drinks	☐ 5
10 or more drinks	☐ 6

(iii) How often did you have 6 or more drinks on one occasion in the past year?

never	☐ 1
less than monthly	☐ 2
monthly	☐ 3
weekly	☐ 4
daily or almost daily	☐ 5

23. Have you or your doctor ever considered that you suffer/have suffered in the past from an alcohol problem/excessive drinking?

Yes	No
☐ 1	☐ 2

SMOKING

Smoking has been linked with many health problems. It is important that you answer the following section as accurately as possible.

24. Do you smoke at present?

Yes	No
☐ 1	☐ 2

If no, proceed to Question 29

25. What do you usually smoke now?

	Yes	No
Cigarettes	☐ 1	☐ 2
Pipe	☐ 1	☐ 2
Cigars	☐ 1	☐ 2

26. How many do you usually smoke now?

Cigarettes per day	…… cigarettes
Oz. tobacco per week	…… oz.
Cigars per week	…… cigars

27. For how many years during your life have you smoked cigarettes? …… years

28. How many cigarettes have you smoked on average per day during the period you have smoked? ……cigarettes

Now proceed to Question 34

29. Have you ever smoked regularly?

Yes	No
☐ 1	☐ 2

If no, proceed to Question 34

30. What did you usually smoke?

	Yes	No
Cigarettes	☐ 1	☐ 2
Pipe	☐ 1	☐ 2
Cigars	☐ 1	☐ 2

31. How much did you smoke on average while you were a smoker?

Cigarettes per day	…… cigarettes
Oz. tobacco per week	…… oz.
Cigars per week	…… cigars

32. For how many years did you smoke cigarettes? …… years

33. If you smoked cigarettes, how long is it since you finally gave up?

……. years …… months

CHEST PAIN

		Yes	No
34.	Do you ever get pain or discomfort in your chest?	☒ 1	☒ 2

IF NO, PROCEED TO QUESTION 40

		Yes	No
35.	Do you get this pain or discomfort when you walk uphill or hurry?	☒ 1	☒ 2

IF NO, PROCEED TO QUESTION 40

		Yes	No
36.	Do you get it when you walk at an ordinary pace on the level?	☒ 1	☒ 2

37. When you get any pain or discomfort in your chest what do you do?

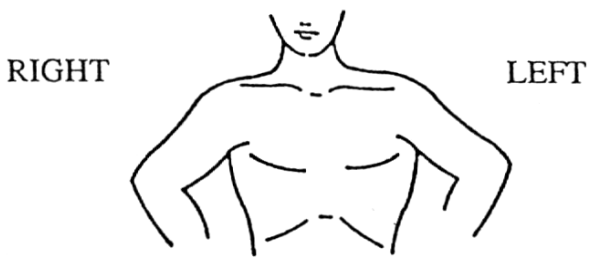
	Tick one
Stop	☒ 1
Slow down	☒ 1
Continue at the same pace	☒ 1

		Yes	No
38.	Does it go away when you stand still or sit down?	☒ 1	☒ 2

How soon?

	Tick one
10 minutes or less	☒ 1
More than 10 minutes	☒ 2

39. Where do you get this pain or discomfort? Mark the place(s) with an 'X' on the diagram



Yes No

40. (i) Have you ever had a severe pain across the front of your chest lasting for half an hour? ☐ 1 ☐ 2

(ii) What was the cause? ……

LEG PAIN

	Yes	No	I am unable to walk
41. Do you get a pain or discomfort in your leg(s) when you walk?	☐ 1	☐ 2	☐ 3

If you answered 'yes' to question 41, please answer the following questions.

	Yes	No
(i) Does this pain ever begin when you are standing still or sitting?	☐ 1	☐ 2
(ii) Do you get it if you walk uphill or hurry?	☐ 1	☐ 2
(iii) Do you get it when you walk at an ordinary pace on the level?	☐ 1	☐ 2
(iv) Does the pain ever disappear while you are still walking?	☐ 1	☐ 2
(v) What do you do if you get it when you are walking?	☐ 1	☐ 2

	Tick one
Stop	☐ 1
Slow down	☐ 2
Continue at same pace	☐ 3

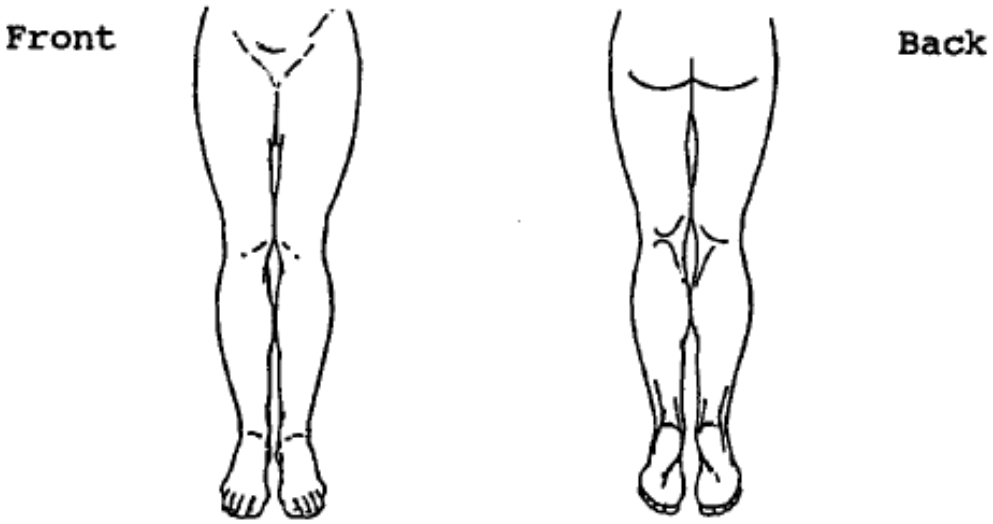
(vi) What happens to it if you stand still?

	Tick one
Usually continues for more than 10 minutes	☐ 1
Usually disappears in 10 minutes or less	☐ 2

(vii) Where do you get this pain or discomfort?

	Yes	No
(a) Do you get this pain in your calf (or calves)?	☐ 1	☐ 2

(b) Please mark the place(s) where you get the pain with 'X' on the diagram below



THANK YOU FOR COMPLETING THIS QUESTIONNAIRE – PLEASE BRING IT WITH YOU TO YOUR APPOINTMENT AT THE WELLCOME TRUST CLINICAL RESEARCH FACILITY

EDINBURGH TYPE 2 DIABETES STUDY

BASELINE QUESTIONNAIRE

Part 2

THE INFORMATION IN THIS QUESTIONNAIRE IS HIGHLY CONFIDENTIAL AND IS PART OF A MEDICAL RESEARCH STUDY

The information you give in this questionnaire will be treated as strictly confidential and will be available only to your own doctor and the study team. The results of the research will appear only in the form of general statistics from which it will be impossible to identify you as an individual.

Please complete the following:

SURNAME: ……..

FORENAMES: ……..

DATE: ……..

THANK YOU FOR YOUR CO-OPERATION IN THIS STUDY

For Office Use: Study No…....

EMPLOYMENT STATUS / OCCUPATION

The following questions refer to your current main job, or (if you are not working now) to your last main job. Please complete for both yourself (I) and for your spouse/ex-spouse or long-term partner (II)

(I) Yourself (Please tick one box only per question)

1. Do (did) you work as an employee or are (were) you self-employed?

Employee ☐

Self-employed with employees ☐

Self-employed / freelance without employees (go to **question 4**) ☐

Housewife (go to **question 4**) ☐

No previous paid employment (excluding housewife) (go to **question 4**) ☐

2. Number of employees

For employees: indicate below how many people work (worked) for your employer at the place where you work (worked). Then go to question 3.
For self-employed: indicate below how many people you employ (employed). Then go to question 4.

1 to 24 ☐ 1 25 or more ☐ 2

3. Do (did) you supervise any other employees?

A supervisor or foreman is responsible for overseeing the work of other employees on a day-to-day basis

Yes ☐ 1 No ☐ 2

4. Please tick one box to show which **best** describes the sort of work you do. (If you are not working now, please tick a box to show what you did in your last job). PLEASE TICK **ONE BOX ONLY**

Modern professional occupations
such as: teacher - nurse - physiotherapist - social worker - welfare officer - artist - musician - police officer (sergeant or above) - software designer ☐ 1

Clerical and intermediate occupations
such as: secretary - personal assistant - clerical worker - office clerk - call centre agent - nursing auxiliary - nursery nurse ☐ 2

Senior managers or administrators
(usually responsible for planning, organising and co-ordinating work and for finance)
such as: finance manager - chief executive ☐ 3

Technical and craft occupations
such as: motor mechanic - fitter - inspector - plumber - printer - tool maker - electrician - gardener - train driver ☐ 4

Semi-routine manual and service occupations
such as: postal worker - machine operative - security guard - caretaker - farm worker - catering assistant - receptionist - sales assistant ☐ 5

Routine manual and service occupations
such as: HGV driver - van driver - cleaner - porter - packer - sewing machinist - messenger - labourer - waiter / waitress - bar staff ☐ 6

Middle or junior managers
such as: office manager - retail manager - bank manager - restaurant manager - warehouse manager - publican ☐ 7

Traditional professional occupations
such as: accountant - solicitor - medical practitioner - scientist - civil / mechanical engineer ☐ 8

EMPLOYMENT STATUS / OCCUPATION (cont.)

(II) Your spouse/ex-spouse/long term partner (Please tick one box only per question)

5. Do (did) he/she work as an employee or is (was) he/she self-employed?

Employee ☐

Self-employed with employees ☐

Self-employed / freelance without employees (go to **question 4**) ☐

Housewife (go to **question 4**) ☐

No previous paid employment (excluding housewife) (go to **question 4**) ☐

6. Number of employees

For employees: indicate below how many people work (worked) for his/her employer at the place where he/she work (worked). Then go to question 3.
For self-employed: indicate below how many people he/she employs (employed). Then go to question 4.

1 to 24 ☐ 1 25 or more ☐ 2

7. Do (did) he/she supervise any other employees?

A supervisor or foreman is responsible for overseeing the work of other employees on a day-to-day basis

Yes ☐ 1 No ☐ 2

8. Please tick one box to show which **best** describes the sort of work he/she does.

(If not working now, please tick a box to show what he/she did in his/her last job).PLEASE TICK **ONE BOX ONLY**

Modern professional occupations
such as: teacher - nurse - physiotherapist - social worker - welfare officer - artist - musician - police officer (sergeant or above) - software designer  1

Clerical and intermediate occupations
such as: secretary - personal assistant - clerical worker - office clerk - call centre agent - nursing auxiliary - nursery nurse  2

Senior managers or administrators
(usually responsible for planning, organising and co-ordinating work and for finance)
such as: finance manager - chief executive  3

Technical and craft occupations
such as: motor mechanic - fitter - inspector - plumber - printer - tool maker - electrician - gardener - train driver  4

Semi-routine manual and service occupations
such as: postal worker - machine operative - security guard - caretaker - farm worker - catering assistant - receptionist - sales assistant  5

Routine manual and service occupations
such as: HGV driver - van driver - cleaner - porter - packer - sewing machinist - messenger - labourer - waiter / waitress - bar staff  6

Middle or junior managers
such as: office manager - retail manager - bank manager - restaurant manager - warehouse manager - publican  7

Traditional professional occupations
such as: accountant - solicitor - medical practitioner - scientist - civil / mechanical engineer  8

EDINBURGH TYPE 2 DIABETES STUDY

BASELINE QUESTIONNAIRE

Part 3

THE INFORMATION IN THIS QUESTIONNAIRE IS HIGHLY CONFIDENTIAL AND IS PART OF A MEDICAL RESEARCH STUDY

The information you give in this questionnaire will be treated as strictly confidential and will be available only to your own doctor and the study team. The results of the research will appear only in the form of general statistics from which it will be impossible to identify you as an individual.

Please complete the following:

SURNAME: ……..

FORENAMES: ……..

DATE: ……..

THANK YOU FOR YOUR CO-OPERATION IN THIS STUDY

For Office Use: Study No…....

STRESS QUESTIONNAIRE

Stress means feeling irritable, filled with anxiety, or having sleeping difficulties as a result of conditions at work or at home.

1. How often have you felt stress at work in the past year?

- Never ☒ 1
- Some periods ☒ 2
- Several periods ☒ 3
- Permanently ☒ 4
- Not working in past year ☒ 5

2. How often have you felt stress at home in the past year?

- Never ☒ 1
- Some periods ☒ 2
- Several periods ☒ 3
- Permanently ☒ 4

3. What level of financial stress do you feel?

- Little or none ☒ 1
- Moderate ☒ 2
- High or severe ☒ 3

4. Have you experienced any of the following in the past year?

- Marital separation or divorce ☒ 1
- Loss of job or retirement ☒ 2
- Business failure ☒ 3
- Violence ☒ 4
- Major intrafamily conflict ☒ 5

Major personal injury or illness ☐ 6

Death or major illness of a close family member ☐ 7

Death of a spouse ☐ 8

Other major stress ☐ 9

None of the above ☐ 10

5. SATISFACTION WITH LIFE SCALE

Below are five statements with which you may agree or disagree. Using a 1-7 scale, indicate your agreement with each statement by ticking the appropriate box next to that item. Please be open and honest in your responses.

The 7-point scale is:

1= Strongly disagree

2= Disagree

3= Slightly disagree

4= Neither agree nor disagree

5= Slightly agree

6= Agree

7= Strongly agree

	1	2	3	4	5	6	7
In most ways my life is close to ideal.	☐	☐	☐	☐	☐	☐	☐
The conditions of my life are excellent.	☐	☐	☐	☐	☐	☐	☐
I am satisfied with my life.	☐	☐	☐	☐	☐	☐	☐
So far I have got the important things I want in life.	☐	☐	☐	☐	☐	☐	☐
If I could live my life again, I would change almost nothing.	☐	☐	☐	☐	☐	☐	☐

6. SUBJECTIVE SOCIAL STATUS

Scotland

Think of this ladder as representing where people stand in Scotland. At the top of the ladder are the people who have the most money, most education, and the most respected jobs. At the bottom are the people who have the least money, least education and the least respected jobs or no job. The higher up you are on this ladder, the closer you are to the people at the very top. The lower you are on this ladder, the closer you are to the people at the very bottom. Where would you place yourself on this ladder? Please place a large "X" on the rung where you think you stand at this time in your life, relative to other people in Scotland.

Community

Think of this ladder as representing where people stand in their communities. People define community in different ways, e.g., including friends, neighbours, or co-workers. Please define it in whatever way is most meaningful to you. At the top of this ladder are the people who have the highest standing in their community. At the bottom are the people who have the lowest standing in their community. The higher up you are on this ladder, the closer you are to the people at the very top. The lower you are on this ladder, the closer you are to the people at the very bottom. Where would you place yourself on this ladder? Please place a large "X" on the rung where you think you stand at this time in your life, relative to other people in your community.

7. PERSONALITY

Below are a number of phrases that describe people's behaviours. Read each statement, and then tick the response that most accurately describes you. Describe yourself as you honestly see yourself. Read each statement carefully, but try not to take too long on each statement, as your first response is likely to be best.

		Very Inaccurate	Moderately inaccurate	Neither accurate/ inaccurate	Moderately accurate	Very accurate
1	I am the life of the party.	1	2	3	4	5
2	I feel little concern for others.	1	2	3	4	5
3	I am always prepared.	1	2	3	4	5
4	I get stressed out easily.	1	2	3	4	5
5	I have a rich vocabulary.	1	2	3	4	5
6	I don't talk a lot.	1	2	3	4	5
7	I am interested in people.	1	2	3	4	5
8	I leave my belongings around.	1	2	3	4	5
9	I am relaxed most of the time.	1	2	3	4	5
10	I have difficulty understanding abstract ideas.	1	2	3	4	5
11	I feel comfortable around people.	1	2	3	4	5
12	I insult people.	1	2	3	4	5
13	I pay attention to detail.	1	2	3	4	5
14	I worry about things.	1	2	3	4	5
15	I have a vivid imagination.	1	2	3	4	5
16	I keep in the background.	1	2	3	4	5
17	I sympathise with others' feelings.	1	2	3	4	5
18	I leave a mess in my room.	1	2	3	4	5
19	I seldom feel blue.	1	2	3	4	5
20	I am not interested in abstract ideas.	1	2	3	4	5
21	I start conversations.	1	2	3	4	5

		Very Inaccurate	Moderately inaccurate	Neither accurate/ inaccurate	Moderately accurate	Very accurate
22	I am not interested in other people's problems.	1	2	3	4	5
23	I get chores done right away.	1	2	3	4	5
24	I am easily disturbed.	1	2	3	4	5
25	I have excellent ideas.	1	2	3	4	5
26	I have little to say.	1	2	3	4	5
27	I have a soft heart.	1	2	3	4	5
28	I often forget to return things to their proper place.	1	2	3	4	5
29	I get upset easily.	1	2	3	4	5
30	I do not have a good imagination.	1	2	3	4	5
31	I talk to a lot of different people at parties.	1	2	3	4	5
32	I am not really interested in others.	1	2	3	4	5
33	I like order.	1	2	3	4	5
34	I change my mood a lot.	1	2	3	4	5
35	I am quick to understand things.	1	2	3	4	5
36	I don't like to draw attention to myself.	1	2	3	4	5
37	I take time out for others.	1	2	3	4	5
38	I neglect my duties.	1	2	3	4	5
39	I have frequent mood swings.	1	2	3	4	5
40	I use difficult words.	1	2	3	4	5
41	I don't mind being the centre of attention.	1	2	3	4	5
42	I feel others' emotions.	1	2	3	4	5
43	I follow a schedule.	1	2	3	4	5
44	I get irritated easily.	1	2	3	4	5
45	I spend time reflecting on things.	1	2	3	4	5
46	I am quiet around strangers.	1	2	3	4	5
47	I make people feel at ease.	1	2	3	4	5
48	I am exacting in my work.	1	2	3	4	5
49	I get overwhelmed by emotions.	1	2	3	4	5
50	I am full of ideas.	1	2	3	4	5

8. ANGRY FEELINGS QUESTIONNAIRE:

(i) Below are a number of statements that people use to describe themselves. Read each statement and then tick the box that indicates how you generally feel or react. There are no right or wrong answers. Do not spend too much time on any one statement. Mark the answer that *best* describes how you *generally* feel or react.

How I generally feel…….

		Almost never	Sometimes	Often	Almost always
51	I am quick tempered.	1	2	3	4
52	I have a fiery temper.	1	2	3	4
53	I am a hotheaded person.	1	2	3	4
54	I get angry when I am slowed down by others' mistakes.	1	2	3	4
55	I feel annoyed when I am not given recognition for doing good work.	1	2	3	4
56	I fly off the handle.	1	2	3	4
57	When I get mad, I say nasty things.	1	2	3	4
58	It makes me furious if I am criticised in front of others.	1	2	3	4
59	When I get frustrated, I feel like hitting someone.	1	2	3	4
60	I feel infuriated when I do a good job and get a poor evaluation.	1	2	3	4

(ii) Everyone feels angry or furious from time to time, but people differ in the ways they react when they are angry. A number of statements are listed below which people use to describe their reactions when they feel *angry* or *furious.* Read each statement and then tick the box which indicates how *often* you *generally* react or behave in the manner described when you are feeling angry or furious. Remember that there are no right or wrong answers. Do not spend too much time on any one statement.

When I am angry or furious, …..

		Almost never	Sometimes	Often	Almost always
61	I control my temper.	1	2	3	4
62	I express my anger.	1	2	3	4
63	I take a deep breath and relax.	1	2	3	4
64	I keep things in.	1	2	3	4
65	I am patient with others.	1	2	3	4
66	If someone annoys me, I'm apt to tell him or her how I feel.	1	2	3	4
67	I try to calm myself as soon as possible.	1	2	3	4
68	I pout or sulk.	1	2	3	4
69	I control my urge to express my angry feelings.	1	2	3	4
70	I lose my temper.	1	2	3	4

		Almost never	Sometimes	Often	Almost always
71	I try to simmer down.	1	2	3	4
72	I withdraw from people.	1	2	3	4
73	I keep my cool.	1	2	3	4
74	I try to soothe my angry feelings.	1	2	3	4
75	I boil inside, but don't show it.	1	2	3	4
76	I control my behaviour.	1	2	3	4
77	I endeavour to become calm again.	1	2	3	4
78	I tend to harbour grudges that I don't tell anyone about.	1	2	3	4
79	I can stop myself from losing my temper.	1	2	3	4
80	I argue with others.	1	2	3	4
81	I reduce my anger as soon as possible.	1	2	3	4
82	I am secretly quite critical of others.	1	2	3	4
83	I try to be tolerant and understanding.	1	2	3	4
84	I strike out at whatever infuriates me.	1	2	3	4
85	I do something relaxing to calm down.	1	2	3	4
86	I am angrier than I am willing to admit.	1	2	3	4
87	I control my angry feelings.	1	2	3	4
88	I say nasty things.	1	2	3	4
89	I try to relax.	1	2	3	4
90	I'm irritated a great deal more than people are aware of.	1	2	3	4

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE – PLEASE RETURN IT TO ONE OF THE CLINIC STAFF BEFORE YOU LEAVE (or in the reply paid envelope from home)