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Relationship between body weight change and incident dementia in older people with type 2 diabetes



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MSc by Research

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Declaration

I, Bo-Jen Chen, declare that this thesis is of my composition and have not been submitted for any other degree or professional qualification.

The Edinburgh Type 2 Diabetes Study, which was the source for the analysis in this thesis, was an established database before I joined the study group. The collection of data and initial data cleaning were completed by other members of the research team. The majority of the statistical approaches on the basis of the database, including the obesity-related grouping methods, were designed and conducted by myself. The only exception were the multivariable survival models, which were modified by myself from the statistical codes of other members of the team.

Signed:

Date: 24 August 2021

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Abstract

Introduction and literature review

Type 2 diabetes mellitus (T2DM) is a chronic illness associated with many late life morbidities, including dementia. Obesity is a common comorbidity of T2DM, with complex mechanisms influencing one another, both causing various adverse health outcomes. Intentional weight loss is often recommended in obese patients. However, despite some evidence pointing out the beneficial effects of losing weight on cognition, there are many observational studies showing that major change in body weight might be related to poorer cognitive outcomes, particularly in older individuals. A systemic review on the relationship between weight change and dementia in the T2DM population was conducted, suggesting that weight loss is associated with increased risk of dementia in older T2DM subjects. However, due to limited existing literature, the topic requires further investigation.

Methods

The Edinburgh Type 2 Diabetes Study (ET2DS) is a longitudinal study of 1066 people with type 2 diabetes, aged 60-75 at baseline, which was followed from 2006 to 2018. The study database consists of obesity related factors at baseline and year 4 follow up, including body mass index (BMI), waist circumference (WC) and waist hip ratio (WHR), as well as a wide range of demographic and biological measurements. Incident dementia during the follow-up period was extracted from health records. Cognitive tests at baseline and year 4 follow-up were used for post-hoc analysis.

The first part of analysis in this study was focused on the relationship between baseline obesity related factors and outcome of incident dementia. In the second part, the individual changes in obesity related factors from baseline to year four were used to predict outcome of incident dementia. Demographic, biological and genetic factors were used as covariables in regression models, and competing risks were considered in survival models.

Results

In the ET2DS population, baseline BMI was negatively associated with incident dementia outcome (HR=0.82 (per 5 kg/m² increase), p=0.091). Hazard ratios of

incident dementia were significantly lower in overweight or obese BMI groups compared to normal BMI group, with or without competing risks considered (HR=0.55, $p=0.037$ in overweight group; HR=0.46, $p=0.010$ in class I obesity; HR=0.40, $p=0.012$ in class II and III obesity). A negative association was also present between WC and incident dementia, but this did not reach statistical significance (HR=0.92 (per 5 cm increase), $p=0.056$). The trend in WHR was inconclusive.

The cox proportional hazard function survival models in the second part of analysis demonstrated that stable or major increase in body weight (defined as over 5% increase in body weight), compared to major decrease, was associated with lower incidence of dementia (HR=0.46, $p=0.003$ in the stable group; HR=0.29, $p=0.002$ in the major increase group). The trend was also present after taking competing risks and other covariables into consideration but this did not reach statistical significance (HR=0.94, $p=0.870$ in the stable group; HR=0.42, $p=0.140$ in the major increase group). There was no obvious association between the waist circumference change and outcome of dementia in the survival models.

In the post-hoc analysis on cognitive test results, the population with incident dementia had significantly poorer cognitive performance in all cognitive domains at baseline and significant decline in domains such as memory and executive function. Both body weight gain and waist circumference increase were associated with better general cognitive factor 'g' at baseline (Association with baseline 'g', $\beta=0.061$, $p=0.016$ in percentage body weight change, $\beta=0.081$, $p=0.003$ in waist circumference change). In terms of the individual cognitive domains, both weight change and waist circumference change were positively associated with executive function at baseline (association with baseline trail making test B, $\beta=0.078$, $p=0.002$ in percentage body weight change, $\beta=0.093$, $p<0.001$ in waist circumference change).

Conclusions

The findings of this study support body weight loss being an early sign of dementia in elder people with T2DM. Although the association between lower body weight and increased risk of dementia did not reach statistical significance in the competing risks survival model, leading to the possibility of the associations being found by chance,

the findings were in line with those from previous studies in both T2DM and older general populations. It has been hypothesized that a steep decrease in body weight may be an early sign of dementia and the finding of poorer baseline general cognitive ability associated with body weight loss in this study supported this hypothesis. There was some limited evidence that differences in executive function may be a possible mediator in the relationship between cognitive decline and body weight loss, with poor nutritional intake and poor glycaemic control in turn leading to poor protein synthesis and sarcopenia in subjects with T2DM. Further investigation is required to identify precise underlying mechanisms.



Lay Summary of Thesis

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Type 2 diabetes mellitus is a chronic disease that affects many people globally. It can cause many health problems, including an increased risk of developing dementia. Obesity is common in people with diabetes and also increases the risk of related health problems. Weight loss is usually recommended in obese people, especially to prevent ill health as they age. However, there have also been studies showing that people who lose a considerable amount of weight have a greater chance of developing dementia. Some people hypothesize that weight loss in older people is a sign of cognitive decline. However, the true relationship between body weight change and dementia in people with type 2 diabetes is unclear.

The Edinburgh Type 2 Diabetes Study includes 1066 people with type 2 diabetes for whom there is data on blood tests, medical history, cognitive ability and development of dementia at different time points during a ten-year follow-up period. Data related to obesity included body mass index (BMI), waist circumference (WC) and waist hip ratio (WHR), recorded at baseline and after 4 years of follow-up and data was available on whether participants were diagnosed with dementia by the end of the full 10-year follow-up. In this research, data were analysed with a number of statistical methods to determine the relationship between change in body weight and dementia in people with type 2 diabetes.

The results showed that people who were lighter (lower BMI) at baseline had a greater chance of developing dementia. People whose body weight stayed at a stable level or increased (over 5% increase in body weight) had a lower chance of developing dementia. However, there was no such obvious findings for waist circumference change. The data also showed the people who gained more weight usually had a better general cognitive function at baseline. It is possible that at a very early stage of dementia, namely many years before the diagnosis is made, body weight loss might be an early sign of dementia in older people with type 2 diabetes. Poor executive function, which was also found to be poorer in people who lost weight during follow up, might be one reason causing poor

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dietary intake, and in turn, resulting in body weight loss. Further research is required to fully understand mechanisms linking weight and dementia in diabetes and to inform clinical practice.

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Chapter 1: Introduction

1.1 Diabetes mellitus and Obesity

1.1.1 Diabetes Mellitus

Type 2 Diabetes Mellitus (T2DM) is a chronic illness characterized by insulin resistance resulting from pancreatic beta-cell dysfunctions. Major risk factors that lead to T2DM include genetic, epigenic, lifestyle factors and the interactions between them. Obesity, alone, is strongly associated with T2DM. The disease itself and related complications, especially in those who are untreated, contributes considerably to global burden of mortality, morbidity and disability-adjusted life years (DALYs). The worldwide prevalence of Type 2 Diabetes has risen dramatically in the recent decades, with an estimated prevalence of one in eleven adults in 2015 (Chatterjee et al., 2017). In Scotland, 5.7% of the population had been diagnosed with Diabetes Mellitus in 2019, of which 87.9% were T2DM (Scottish Diabetes Data Group, 2019).

The diagnosis of T2DM requires repeated testing of either elevated HbA1c $> 6.5\%$, random plasma glucose ≥ 11.1 mmol/L or fasting glucose ≥ 7.0 mmol/L in asymptomatic subjects or at least one of the elevated tests above in symptomatic subjects. HbA1c is a representative of the average blood glucose in the past two to three months, which is used as the main tool of glucose monitoring and treatment target in T2DM patients (N.G.C. 2020).

The common complications of T2DM can be classified into microvascular and macrovascular complications. Incidence, severity, and mortality from cardiovascular diseases are found to be higher in people with T2DM compared to counterparts without T2DM. Other complications include diabetic kidney disease, diabetic-retinopathy, lower-limb amputation, as well as digestive disorders and cognitive dysfunctions (Zheng et al., 2018).

1.1.2 Obesity

The global burden of obesity has increased in the past few decades, along with increased high-calorie food consumption and sedentary lifestyle globally. The prevalence of obesity in Scotland was found to be around 26–28% since 2008

according to Scottish Health Survey (SHeS) (Tod et al., 2017). The mechanism underlying obesity consists of complex interactions between genetic and lifestyle factors (Heymsfield & Wadden, 2017).

The conventional definition of obesity by the National Institute for Health and Care Excellence (NICE, 2014) is a body mass index (BMI) over 30 kg/m², which has been widely used in clinical settings. However, the definition of BMI is insufficient to identify an individual's fat distribution, particularly visceral fat. Thus, emerging emphasis has been put on the use of additional measurements of central obesity, such as waist circumference or waist hip ratio, to assess the status of obesity. This topic will be discussed in the sub-heading 1.1.2.1.

Obesity is associated with many comorbidities, including T2DM, and increased prevalence of (and mortality from) cardiovascular disease. Weight loss, by lifestyle modification (or, if critical, bariatric surgery) is therefore usually recommended to obese subjects to improve the control of comorbidities (Abdelaal et al., 2017). On the other hand, despite theoretical adverse cognitive effects of obesity, the relationship between obesity and dementia remains unclear.

1.1.2.1 Measurement of obesity

Body mass index (BMI) is a well-established and widely used measurement for the definition of obesity in clinical settings. A cut point of 25 kg/m² or above is defined as overweight, and 30 kg/m² or above obese (NICE, 2014). However, body mass index (BMI) does not take the distribution of fat tissue into account. Body fat distribution, particularly centrally distributed fat, is associated with many chronic diseases, including cardiovascular disease, hypertension, and type 2 diabetes (Ross et al., 2020). Therefore, although widely used, BMI alone may be insufficient for predicting clinical outcome.

Suggestions have been made to include at least one indicator of central obesity in addition to BMI in clinical assessments. Waist circumference, for instance, is an efficient and direct way to assess abdominal obesity. For a given BMI, adults with higher waist circumference have been found to have increased adverse health risks. Waist hip ratio (WHR) on the other hand, reflects the morphology of fat

accumulation in an individual, and was shown to be associated with increased risk of death, cardiovascular diseases and T2DM (Ross et al., 2020).

1.1.3 Overweight and obesity in people with diabetes mellitus

The overlap between obesity and T2DM have been well established in previous literature, hence the term “diabesity” (Verma & Hussain, 2017). Subjects with BMI>27.2 kg/m² were found to have a 100% elevated risk of T2DM compared to those with BMI under 27.2 kg/m² (Heymsfield & Wadden, 2017). The prevalence of obesity was also higher in people with T2DM. A study on female nurses suggested that 61% of the cases with T2DM could be attributed to overweight (BMI>25 kg/m²) (Hu et al., 2001). Both conditions increase the risks of various complications such as cardiovascular events. Due to the strong overlap, weight control is often emphasized in people with T2DM. NICE (2015) recommended an initial target weight loss of 5% to 10% in T2DM patients who were overweight.

1.2. Cognitive decline and Dementia

1.2.1 Dementia

Dementia is an increasing problem along with the ageing society. It is estimated that 9% of people over 65 years old in Scotland have been diagnosed with dementia (NHS Health Scotland, 2010). The definition of dementia is a chronic deficit in two or more cognitive domains, with the most common characteristic being a progressive loss of memory (Arvanitakis et al., 2019). The process of cognitive decline prior to the diagnosis of dementia usually occurs gradually over years. Changes in cognitive function were found at a mean of 7.5 years before the diagnosis of Alzheimer's disease in a longitudinal study (Blazer & Wallace, 2016).

There are various aetiologies of dementia, with Alzheimer's disease (AD) and vascular dementia (VD) being the most common aetiologies. Nonetheless, “mixed dementia” is common, usually a combination of one neurodegenerative disease (e.g. Alzheimers disease, Lewy body disease, Frontotemporal dementia) and vascular dementia (Arvanitakis et al., 2019).

The mechanism behind dementia is multifactorial, associated with both genetic factors and various comorbidities, with age being one of the most important risk

factors. The T2DM populations were reported to have a higher relative risk of both AD (RR=1.53) and VD (RR=2.27) compared to general populations (Biessels & Despa, 2018). History of cardiovascular events may be associated with an overall increased future risk of major ischemic cardiovascular or cerebrovascular events, thus leading to increased risk of vascular dementia (Román, 2005). The presence of the genotype Apolipoprotein E (ApoE) $\epsilon 4$ allele was found to increase the risk of Alzheimer's disease, especially among Caucasian subjects. Two copies of ApoE $\epsilon 4$ had more effect than one copy (when compared to no $\epsilon 4$ allele, $\epsilon 4/\epsilon 4$ odds ratio (OR)= 14.9, whilst $\epsilon 2/\epsilon 4$, OR=2.6, $\epsilon 3/\epsilon 4$, OR=3.2) (Liu et al., 2013).

1.2.2 Cognitive impacts of overweight

The adverse impact of obesity on somatic health condition is well documented, but evidence on the impact on cognitive outcomes is limited. Elevated BMI was found to be associated with brain deficits in imaging studies, including generally reduced integrity in white matter and grey matter atrophy in area including temporal, frontal and occipital cortices, hippocampus, thalamus and midbrain (Dye et al., 2017). Decreased blood flow to the prefrontal cortex in adults with elevated BMI had also been found (Willeumier et al., 2011). Obesity had also been reported to associate with poorer performance in cognitive domains including memory and verbal fluency (Gunstad et al., 2010).

However, the actual impact of obesity on cognition, particularly development of dementia is far from conclusive. It had been suggested that mid-life obesity was associated with increased risk of late life AD or VD, but late-life obesity reduced the risk of dementia (Qu et al., 2020). The phenomenon is possibly complicated by cognitive deficit being a risk factor for weight loss in the older population.

1.2.3 Cognitive outcomes in people with diabetes mellitus

Type 2 diabetes is a risk factor for dementia in the people with mild cognitive impairment (MCI), which is defined as having impairment in at least one cognitive domain but do not fulfill the criteria of dementia. Given the altered metabolic status and high prevalence of cardiovascular comorbidities in people with T2DM, the reported estimated risk for different aetiologies of dementia in such population not surprisingly differed from each other. When compared to those without T2DM,

people with T2DM had an estimated relative risk of 1.73 for all-type dementia, 1.53 for AD and 2.27 for VD (Biessels & Despa, 2018). People with T2DM were also found to have poorer performance in specific cognitive domains, including executive function, and in global cognitive scores, even without a significantly greater subsequent decline (Palta et al., 2017).

The relationship between T2DM and dementia is thought to be multifactorial and the factors contributing to the increased dementia risk in T2DM are not fully clear. Increased cardiovascular risk factors, leading to elevated risks of ischemic stroke and small vessel disease in people with T2DM has been one of the explanations suggested for increased risk of VD. Uncontrolled hyperglycaemia may result in glucose toxicity, which leads to vascular damage and potentially affect neurodegenerative processes in the brain. However, tight glycaemic control can be a risk factor for severe hypoglycaemia events, which can lead to fall and admission, as well as induce neuronal cell death and in turn accelerate cognitive decline (Chatterjee et al., 2017, Feinkohl et al., 2014, Biessels & Despa, 2018). The association between self-reported hypoglycaemia events and poorer cognitive function have been reported in the Edinburgh Type 2 Diabetes Study (ET2DS) (Aung et al., 2011). Optimizing T2DM management to minimize hypoglycaemia is especially challenging in patients that are old and complicated with cognitive impairment. Moreover, prolonged hyperinsulinemia and chronic inflammation were also thought to be associated with cognitive impairment in T2DM subjects (Biessels & Despa, 2018).

1.2.4 Domains and Measurement of Cognition

In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), cognitive function was classified into memory, language, executive function, perceptual-motor function, complex attention and social cognition (American Psychiatric Association, 2013). There are many tests targeted on each of the domains, except social cognition (Wang & Dong, 2018).

Among the domains, memory impairment was found to be the most commonly affected cognitive domain in dementia (Arvanitakis et al., 2019). It has also been shown to be the domain most predictive of dementia in mild cognitive impairment

(MCI) subjects. In a cohort study in Dublin, an odds ratio of 1.85 was presented in amnesic versus non-amnesic MCI patients on the risk of progression to dementia from MCI (Glynn et al., 2021). Similarly, another retrospective study on MCI participants found that the population who progressed to dementia were especially associated with impaired memory domain, while those who remained stable or reversed to normal cognition were more likely to be impaired in executive function or attention (Ganguli, 2019). The patterns of decline preceding dementia were proposed to present differently in various domains. A rapid decline following stable performance was found in many functions within the memory domain (delayed recall, working memory, and spatial memory), but not functions such as immediate recall, executive function, and visuo-spatial abilities, which presented a gradual decline throughout follow up (Cloutier et al., 2015).

1.3. Relationship between Weight Change and Cognition

1.3.1 Potential cognitive benefits of intentional body weight loss

Intentional weight loss is often suggested in obese individuals to reduce adverse health events such as cardiovascular diseases. However, the effect of such weight loss on cognitive outcomes is by far inconclusive.

A meta-analysis of randomized-controlled trials and longitudinal studies found that intentional weight loss in people who were overweight or obese was associated with improvements in cognitive domains including attention and memory (Veronese et al., 2017). Similarly, weight loss following bariatric surgery was found to be associated with sustained improvements in memory, executive function and cognitive control (Handley et al., 2016). However, the majority of such studies had a relatively young study population with a low occurrence of dementia. The mean age of the population in the meta-analysis by Veronese et al. (2017) was 50.0 years and only one out of the 20 recruited studies included people aged 65 years or older.

1.3.2 Body weight change as indicators of cognitive decline

Despite the potential benefits of intentional weight loss, weight loss may also be an early indicator of adverse health conditions, including dementia, particularly in the older population.

Unintentional weight loss, defined as more than 5% weight loss within six to 12 months, is often a sign of underlying comorbidities and requires further evaluation in clinical settings (Gaddey & Holder, 2014). Weight loss is one of the major characteristics in the definition of frailty syndrome, which is a common issue among older adults. The components of frailty syndrome included exhaustion, physical inactivity, muscle weakness, slow walking speed and weight loss, and is often associated with complications such as disability and hospital admissions (Xue, 2011).

There is also literature addressing the specific relationship between weight loss and dementia. Subjects with AD were found to be two times more likely to experience a weight loss over 5% than non-AD counterparts (White et al., 1997). It is possible that the incidence of dementia is related to mid-life obesity, while decreased BMI can be an early sign of dementia in the older population. This explanation is supported by findings from the Whitehall II Study, which was conducted in the UK and consisted of BMI data recorded at many time points up to 28 years before the diagnosis of dementia. According to these findings, when compared to the non-dementia population, the mean BMI in those diagnosed with dementia in late life were higher in middle age but declined rapidly and had significantly lower BMI from eight years before the diagnosis of dementia (Singh-Manoux et al., 2018). Another retrospective study on African Americans over 65 years old reported a similar result, showing a significantly lower BMI from six years prior to diagnosis of dementia (Gao et al., 2011).

Compared with literature addressing the relationship between weight loss and dementia in the general population, evidence on the association between weight loss and dementia in the T2DM population is more limited. Given that this was the main topic of my planned data analysis for my thesis, I decided to undertake a detailed review of the literature in this area, the results of which are described in Chapter 2.

Chapter 2: A systemic review on the relationship between body weight change and dementia or cognitive decline in people with Type 2 Diabetes Mellitus

2.1 Aims of Review

To determine the association between body weight change and cognitive decline or new diagnosis of dementia in people with Type 2 diabetes mellitus (T2DM). Also, to identify any potential confounders or mediating variables in the association.

2.2 Search strategy

2.2.1 Keywords

Table 2.1 Keywords used in literature searching

	Keywords (by MeSH terms)
Population	diabetes mellitus
Exposure	body weight changes
Outcome	cognition OR Cognitive Dysfunction OR Cognitive Aging OR dementia OR Vascular Dementia OR Alzheimer Disease OR Neurocognitive Disorders

The keywords were defined by Medical Subject Headings (MeSH) terms.

This review was focused on the population with Type 2 Diabetes Mellitus. In the MeSH tree, “Diabetes Mellitus” included subtypes such as “Diabetes Mellitus, Type 1,” “Diabetes Mellitus, Type 2,” “Diabetes, Gestational,” “Prediabetic State.” I chose the broader term “Diabetes Mellitus” rather than “Diabetes Mellitus, Type 2” in the initial search because of practical reasons including: (1) Some related studies may not specify the subtype of Diabetes Mellitus, since Type 2 Diabetes Mellitus is the most common of all types. (2) Some studies may use terms such as “non-insulin dependent diabetes” or “adult-onset diabetes” Rather than “Diabetes Mellitus, Type 2.” The exclusion of subtypes of Diabetes Mellitus other than type 2 diabetes was carried out in the selection phase.

The term “Body weight changes” was a category within both categories “Diseases” and “physiological phenomena” in MeSH terms. Weight gain and weight loss were both within the category. Considering the unspecified direction of change in our

current knowledge on the topic of this review, use of “Body weight changes” was considered to be sufficient for searching.

The terms related to cognition, on the other hand, was more complex. Both cognitive outcome assessed by neuropsychological/cognitive test measurements and clinical diagnosis of dementia were outcomes of interest in this review. Therefore, terms related to both topics were used. The terms included “Cognition,” “Cognitive Dysfunction” and “Cognitive Aging” in the “Psychological Phenomena” category, and “Dementia” in both “Psychological Phenomena” and “Diseases” categories. “Vascular Dementia” and “Alzheimer Disease” are both subtitles of “Dementia.” I included these terms because they were the two most common subtypes of dementia associated with Diabetes Mellitus and to reduce the chance of missing disease-specific studies which were not connected to other MeSH terms. I also included the term “Neurocognitive Disorders”, a larger category which included “Dementia” and “Cognition dysfunction” in order to identify potential studies which focused on broader outcomes.

2.2.2 Database

Pubmed and Medline, including all studies prior to the date of searching.

2.2.3 Eligibility criteria

Longitudinal studies including 1, 2 and at least one of 3 and 4

1. Population based on people with diabetes mellitus, impaired glucose tolerance or general population with a clear subgroup analysis on people with diabetes mellitus
2. Measurement of body weight, body mass index (BMI) or waist circumference at two or more different time points
3. Assessment of cognition at one or more different time points
4. Data including time of diagnosis of dementia or MCI

Intervention studies with the same criteria as longitudinal studies, PLUS one of the following

1. Intervention focused on lifestyle modification or physiological approach, including exercise, diet adjustment
2. Intervention targeted on body weight loss or body composition (e.g., body fat, waist circumference)
3. Intervention not targeting on body weight, but the relationship between body weight change and cognitive function were recorded and discussed

2.2.4 Exclusion criteria

1. Studies on type 1 diabetes mellitus or gestational diabetes. The mechanism and nature of type 1 diabetes mellitus or gestational diabetes tend to differ from type 2 diabetes mellitus. The relationship with dementia and obesity are also distinct from type 2 diabetes mellitus.
2. Studies on children or adolescents, which did not follow up to the age when age-related cognitive decline or onset of dementia were likely to occur.
3. Studies on specific populations in which obesity and type 2 diabetes were caused by a common etiology, which was not representative of the general type 2 diabetes population (for example, the side effect of atypical antipsychotics).
4. Intervention studies of bariatric surgery unless the studies were followed for more than 5 years after the surgery. The reason to exclude bariatric surgery studies is the general design of such studies. Bariatric surgery is a relatively new intervention for obese people with diabetes, thus leading to a generally short follow up period in such studies, which may not be sufficient to observe long-term cognitive decline. Moreover, there is very likely to be selection bias in these studies, as people who can undergo an elective surgical intervention are required to be in generally good health and are more likely to be at a younger age. This makes the population of the studies unlikely to be representative of the general diabetes population.

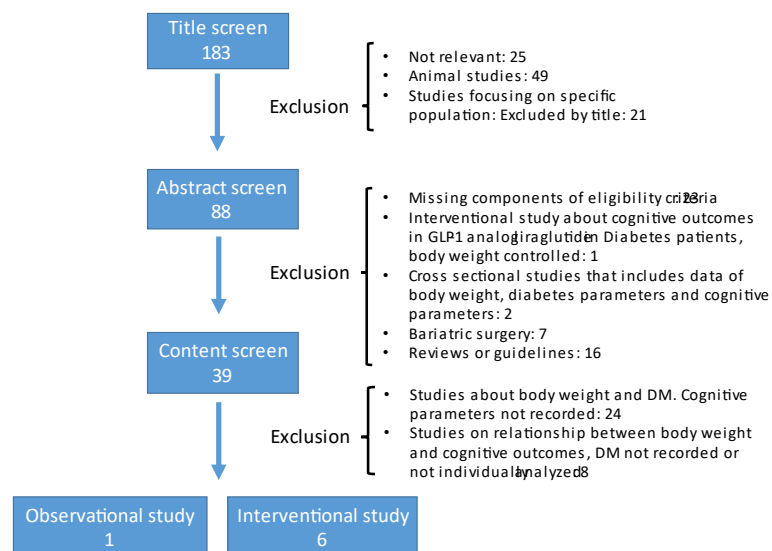
2.3 Results

2.3.1 Studies identified

Article searching was conducted on 17th November 2020 in the databases Pubmed, Medline and Embase, using the following search strategies: The keywords were based on table 1, with small adjustments according to each database design.

- Pubmed search: (diabetes mellitus) AND (Body weight changes) AND (cognition OR Cognitive Dysfunction OR dementia OR Vascular Dementia OR Cognitive Aging OR Alzheimer Disease OR Neurocognitive Disorders)
- Ovid (Medline + Embase): (exclude duplicates of keywords in MESH tree) (exp * Diabetes Mellitus/ OR Diabetes Mellitus.mp) AND (exp * Body Weight Changes/ OR Body Weight Changes.mp) AND ((exp * Cognition/ OR Cognition.mp) OR (exp * Cognitive Dysfunction/ OR Cognitive Dysfunction.mp) OR (exp * Dementia/ OR Dementia.mp) OR (exp * Cognitive Ag?ing/ OR Cognitive Ag?ing.mp))

Figure 2.1 Systemic review: Selection process flow chart



The selection process for articles in this systemic review is recorded in figure 1. In the initial search, 181 articles were found in Pubmed, and 38 were found in Ovid (Medline + Embase). After discarding duplicates, there were 183 different articles in total. Initially, 25 articles were excluded due to content not relevant to the eligibility

criteria. There were also 49 articles on animal studies which were excluded. A further 21 articles were excluded, on review of the title alone, due to focusing on a specific population not relevant to the general population of diabetes, as addressed in the exclusion criteria.

After assessing the abstracts of 88 remaining articles, a total of 49 further articles were excluded. Among the articles excluded, 23 were excluded because of at least one of the essential components missing (T2DM, body weight change, cognition or dementia) according to the eligibility criteria. This included studies focusing on risk factors for the diagnosis of diabetes, and studies on people with diabetes, which did not include longitudinal body weight change or cognitive data as an outcome factor. In addition, there was one intervention study excluded (on cognitive outcomes with the GLP-1 analog liraglutide in people with diabetes), in which body weight was recorded but was used only as a controlling factor in the analysis. There were also two cross sectional studies excluded. Although these studies included data on body weight, diabetes parameters and cognitive parameters, there were no repeated measures to assess change. Seven further excluded articles focused on the cognitive outcome of bariatric surgery in people with diabetes. Also excluded were two guidelines on obesity management, and 14 review articles (five focusing on mechanism, four on diabetes management, three obesity management, one on association between microbiota and diabetes, and one addressing the relationship between diabetes, sarcopenia and frailty).

After screening abstracts, resulting in the exclusions mentioned in the paragraph above, 39 articles remained for full paper screening. Of these, 24 articles discussed the relationship between body weight and type 2 diabetes, but clinical cognitive parameters were not recorded, so were excluded. One of the latter articles was aimed at finding the most ideal lifestyle for preventing type 2 diabetes mellitus in people with obesity and impaired glucose tolerance. Cognitive outcome was one of the goals, but brain imaging was used rather than cognitive functional assessments as an outcome measure in this study. A final eight excluded articles following full-text screening were on the relationship between body weight and cognitive outcomes, but diabetes mellitus was not recorded or not individually analyzed. This

left seven articles included according to the inclusion criteria: Six on intervention studies and one observational longitudinal study.

2.3.2 Summary of Results

Tables 2 and 3 summarize the six articles on intervention studies (Daly et al., 2014, Espeland et al., 2014, Lehtisalo et al., 2016, Rapp, 2017, Espeland et al., 2018a; Espeland et al., 2018b) and the one cohort study (Nam et al., 2019).

2.3.2.1 Characteristics of included studies

Of the six articles on intervention studies, four were part of the Look AHEAD (Action for Health in Diabetes) study (Espeland et al., 2014; Rapp, 2017; Espeland et al., 2018a; Espeland et al., 2018b), which was a single-blind randomized controlled trial conducted by the National Institutes of Health of United States. In this 16-center study, 5145 individuals with overweight and type 2 diabetes were enrolled and divided to the diabetes support and education (DSE) group (n=2575), which received usual medical care, and intensive lifestyle intervention (ILI) group (n=2570), which included usual medical care and an additional intensive 4-year program designed to increase physical activity, with a goal of weight reduction by 7% or more. Body mass index was the main indicator for the initial definition of obesity, primary outcome and long term follow up. A majority of the population (n=3751) had cognitive assessments at 10-13 years after enrollment, with 1091 of them having repeated assessment at either 8-11 or 10-12 years after enrollment.

One of the intervention studies identified was part of The Finnish Diabetes Prevention study (Lehtisalo et al., 2016), which recruited 522 middle-aged (40 to 65 years), overweight (body mass index > 25 kg/m²) participants with impaired glucose tolerance. The participants in the intervention group (n=265) underwent active individualized lifestyle intervention with frequent counselling sessions for an average of four years, while the control group (n=257) received only general health advice at baseline. After the intervention period, the participants of both groups underwent an additional follow up for nine years. In the study, obesity related physiological measurements including body mass index and waist circumference were made. Cognitive assessments were conducted twice, at an average of 13 years and 14 years after the recruitment baseline.

The "Lift for life" protocol is a two-arm randomized controlled trial on middle aged or old people with type 2 diabetes (Daly et al., 2014). The intervention is vitamin D supplements additional to other lifestyle and medical treatments. The outcome variables will include T2DM control, measurements related to body composition and obesity, other metabolic or inflammatory markers, and cognitive outcome. At the time of searching, the results which include cognitive assessments have not yet been published.

The only observational study identified in this review was a cohort study using the database of South Korean National Health Insurance Service-National Health Screening (Nam et al., 2019). There were in total 167,876 people over 40 years old with Diabetes Mellitus identified. Weight changes were monitored for around 2 years after the diagnosis of Diabetes Mellitus.

2.3.2.2 Findings from included studies

Among the studies identified, the Look AHEAD study failed to identify significant cognitive benefits of either intensive lifestyle intervention or weight loss during the intervention period (Espeland et al., 2014, Rapp, 2017). Weight gain was found to be slightly and statistically significantly associated with better cognitive function in a subgroup with repeated cognitive assessments (n=1091). A fitting line with a slope of 0.005 of standard deviation of cognitive function per percent weight change was found ($p=0.03$) (Espeland et al., 2018). The Finnish diabetes prevention study, on the other hand, found the weight pattern associated with the best cognitive outcome was weight loss during intervention phase followed by weight gain in follow up phase (Decrease-Increase group). The group which experienced weight loss throughout the whole study (decrease-decrease group) had the worst cognitive outcome but did not differ significantly from increase-decrease or increase-increase groups. The same finding was also present when change in waist circumference was used, with the significantly better cognitive outcome observed in the Decreased-Increase group (Lehtisalo et al., 2016)

Table 2.2 Interventional studies exploring the relationship between obesity related factors and cognition or dementia (6)

Author (year)	Study design	Population	Intervention	Follow up time	Variables (Body weight)	Variables (Cognition)	Major Outcomes	
							Analysis	result
Daly et al. (2014).	RCT, "Lift for life" protocol	Around 200 50-75 years-old T2DM patients	Progressive resistance training (PRT)	0, 12 and 24 weeks	BMI	Groton maze learning	Not yet published	
					Lean muscle	Detection task		
			[I] 3 months Whey-protein drink plus vitamin D supplements		fat composition	Identification test		
						one-card learning task		
						one back task		
	[C] No additional supplements							
Espeland et al. (2014)	RCT "Look AHEAD study," subgroup analysis	978 (45-76 y/o) T2DM	[I]Intensive lifestyle Intervention (ILI)	Cognition follow up once in 8-9 years	BMI	Rey Auditory verbal learning test	Cognitive outcome in ILI and DSE groups	No significant difference
			[C] Diabetes support and Education (DSE)			speed of processing	Cognitive outcome among overweight patients in ILI group	Significant benefit
						digit symbol coding test		
						modified stroop color and word test		
						Trail-making test part B	Cognitive outcome among obese patients in ILI group	Non-significant deficit
						3MS	Different domains of cognitive outcome in ILI group	Only processing speed in overweight had significant benefit
							BW change and cognitive function	not significantly correlated

Lehtisalo et al. (2016)	RCT, Finnish diabetes prevention study	364 (DPS total 522 (40-65 y/o)), BMI>25, impaired glucose tolerance	4 years intervention period, then follow up	Cognition tested in 13 and 15 years from baseline	BW	The Finnish CERAD-TS battery	Lower baseline BMI and CERAD-TS	Positively associated
			[I] frequent counseling on lifestyle		waist circumference	neuropsychological test battery	Lower baseline waist circumference and CERAD-TS	
			[C] only baseline education		APOE	trial making test A	higher moderate-to vigorous physical activity and CERAD-TS	
							Weight loss between intervention and follow up period predicted and CERAD-TS	Negatively associated (poorer outcome)
							Waist circumference decrease during intervention followed by increase and better CERAD-TS	Positively associated (better outcome)
Rapp et al. (2017)	RCT, Look AHEAD study	3751 with cognitive assessments (Total 5145 (45-76 y/o) T2DM, BMI>25)	[I]Intensive lifestyle Intervention (ILI) for 8-13 years	Cognitive tests 10-13 years after enrollment (once)	BMI	Rey Auditory verbal learning test	Weight change and cognitive function	No significantly associated
			[C] Diabetes support and Education (DSE)			speed of processing	intervention groups and cognitive function	No significantly associated
						digit symbol coding test		
						modified stroop color and word test		
						Trail-making test part B		
						3MS		

Espeland et al. (2018)	RCT, Look AHEAD study	1091 with repeat cognitive assessments. (Total 5145 (45-76 y/o) T2DM, BMI>25)	[I] Intensive lifestyle Intervention (ILI) for 8-12 years	Cognition tested 10-13 years after enrollment (some also have assessments in 8-11 years or 10-12 years)	BMI	Rey Auditory verbal learning test	Weight loss at the end of study among obese patients	Significant higher in the ILI group
			speed of processing					
			[C] Diabetes support and Education (DSE)			digit symbol coding test	Cognitive decline in obese patients	Borderline greater decline in ILI group
						modified stroop color and word test		
						Trail-making test part B	Weight gain and cognitive outcome (slope 0.005)	Slightly positively associated
						3MS		
Espeland et al. (2018)	RCT, "Look AHEAD" study	5145 (45-76 y/o) T2DM, BMI>25	[I] Intensive lifestyle Intervention (ILI)	8-12 years	BMI	MRI (10-12 years after enrollment)	Greater weight loss and cerebral blood flow (CBF)	Positively associated in ILI group but interaction comparing not significant
			[C] Diabetes support and Education (DSE)			Cognition	Greater increases in physical activity and CBF	
						Rey Auditory verbal learning test	CBF among overweight patients in ILI group	Significantly higher
						speed of processing		
						digit symbol coding test	CBF and cognitive function in intervention group	No significant association
						modified stroop color and word test		
						Trail-making test part B	CBF and cognitive function in control group	negative correlation
						MMSE		

Table 2.3. Observational study exploring the relationship between obesity related factors and cognition or dementia (1)

Author, year	Study design	Population	Follow up time	Variables (body composition)	Variables (cognition)	Variables (covariates)	Major Outcomes													
							Analysis	result												
Nam et al. (2019).	Cohort	South Korea, NHIS cohort, DM, >40 y/o, 167876	Average 8.1 years	BMI	Diagnosis of Dementia (AD, VD)	Alcohol	Risk of all cause dementia according to baseline BW	lower in overweight and obese groups												
				Cut points: <18.4 underweight 18.5-22.9 normal 23-24.9 overweight 25-29.9 class I obese >30 class II obese		physical activity			Risk of AD according to baseline BW	significantly higher in underweight patients, lower in overweight and class I obese groups										
						baseline comorbidities					Risk of VD according to baseline BW	No significant association								
													Risk of dementia according to weight change	“U shaped association” higher risk of all dementia in gain>10% (HR:1.38) or loss >10% (HR:1.34)						
															Risk of AD according to weight change	significantly higher in patients > 10% weight loss				
																	Risk of VD according to weight change	No significant association		
																			Subgroup analysis between sex	Men with fluctuating BW have higher risk for VD than women.

In the South Korean observational study (Nam et al., 2019), the author reported a “U-shaped association with dementia” to describe higher risk of all dementia in people undergoing either major weight gain >10% (HR 1.38) or loss >10% (HR 1.34.) Among the dementia types, incidence of Alzheimer’s disease was significantly higher in people experiencing >10% weight loss. Body weight change was not shown to be significantly associated with vascular dementia. Men with fluctuating body weight had higher risk for vascular dementia than women. Of note, the group experiencing a weight gain between 5% and 10% did not have a significant increase in the risk of incident dementia.

Among the studies identified, only the Finnish diabetes prevention study (Lehtisalo et al., 2016) addressed repeated detailed lifestyle measurements, including three-day food record, nutrient intake calculation, and self-reported physical activity (annual leisure-time physical activity assessed by the Kuopio Ischemic Heart Disease (KIHD) risk factor study questionnaire). The Finnish diabetes prevention study was also the only study which used waist circumference in addition to BMI as a major assessment tool.

2.4 Discussion

2.4.1 Findings from the review

According to existing evidence, though limited, the fact that weight loss in people with diabetes might be a predisposing sign of dementia was favored. Stable weight, on the other hand, have been suggested to be beneficial among the general elderly population (Lo et al., 2012). This result is in line with the observational study included in this review, which proposed a “U-shaped” association, with the subgroup with over 10% body weight loss having increased risk of dementia (Nam et al., 2019). Different observations were found in the intervention studies in this review. The Look AHEAD study failed to identify an obvious relationship between weight loss and cognitive outcome. A statistically significant, yet weak positive association, was described between body weight gain and cognitive outcome in the sub-analysis with repeated cognitive tests (Espeland et al., 2018). The Finnish Diabetes Prevention Study, on the other hand, found the weight pattern associated with the best cognitive outcome was weight loss during the intervention phase followed by weight

gain in the follow up phase (Lehtisalo et al., 2016). Of note, only the study by Nam et al. (2019) used a cut-point of 10% for weight change subgroups, while the Look AHEAD study used weight change as continuous variables and The Finnish Diabetes Prevention Study used a cut point of 5% for grouping. Ten percent body weight loss was a well-established sign of adverse health conditions and was a part of some definitions of frailty (Xue, 2011).

The authors of The Finnish Diabetes Prevention Study suggested that the negative association between weight change and dementia may be more likely due to unintentional weight loss being an early sign of pre-clinical dementia, rather than intentional weight loss as part of diabetes management (Lehtisalo et al., 2016). However, differentiating between intentional and unintentional weight loss may be challenging in real world practice, where lifestyle intervention is highly individualized rather than standardized. Thus, the individual effect of a weight-loss targeted intervention, in combination with other factors, on body weight change is difficult to assess.

The patients recruited in intervention studies included in this review were mostly middle aged, while a noticeable proportion of people with diabetes are older (the average age at recruitment was 58.6 ± 6.8 years (intervention), 58.9 ± 6.9 years (control) in the Look AHEAD study, and 55.1 ± 6.8 years in the Finnish Diabetes Prevention Study). The Diabetes Atlas Ninth edition in 2019 by the International Diabetes Federation has estimated a 19.9% prevalence in people aged 75-79 (Saeedi et al., 2019). The small proportion of elderly population in intervention studies might be related to the difficulties of lifestyle intervention among older people. Moreover, the probability of dementia increases with older age. Different observations on dementia and cognitive decline might be seen in elderly populations and the validity of generalizing the included study results to the total population is questionable.

BMI was the most common variable used for obesity definition in the studies. In the Look AHEAD study, waist circumference was recorded at baseline, but not used for analysis in prediction of cognitive decline. The definition of obesity was purely by BMI, and percent weight change was the main predictor considered (Espeland et al., 2018). The Finnish Diabetes Prevention Study also used BMI as the major definition

method for obesity. In the cognitive decline analysis, they included waist circumference (WC) change in addition to body weight change. The findings using WC change and body weight change as the predictor are similar to each other. None of the studies included waist circumference ratio (WHR) as an indicator. There is emerging evidence showing the importance of WC alone, or WHR as an approachable factor to accurately estimate body fat composition or visceral obesity. The concept of visceral obesity has been emphasized in predicting cardiometabolic risk or risk for dementia. (Ross et al., 2020, Luchsinger et al., 2007). The relationship between obesity, weight change and cognitive outcomes in the T2DM population is likely to be better understood if WC change, in addition to body weight change, is analyzed in future studies.

2.4.2 Conclusions, aims and objectives of secondary data analysis

In conclusion, the current literature is inconsistent about the role of weight change in cognitive outcomes. The intervention studies, but not the observational study, favored weight gain to be a positive indicator of better cognitive outcomes. The population is younger in intervention studies. BMI is the most commonly used indicator for obesity. More evidence is required to clarify the relationship between body weight change and cognitive decline in people with T2DM.

In my secondary data analysis, based on the Edinburgh Type 2 Diabetes Study (ET2DS), I aim to:

1. Determine the association between weight and weight change (or waist circumference/WC change) and incident dementia in older people with Type 2 Diabetes mellitus.
2. Explore possible reasons for any relationship between weight change and dementia in this population.

Chapter 3: Methods

3.1 The ET2DS Study Population

The Edinburgh Type 2 Diabetes Study (ET2DS) is a prospective cohort study on subjects with type 2 diabetes (T2DM), aimed at investigating the associations between potentially modifiable risk factors and outcomes such as micro/macrovacular diseases and cognitive decline. The study received full ethical approval from the Lothian Medical Research Ethics Committee and complies with the Declaration of Helsinki (Price et al., 2008).

The study population was randomly selected at baseline, in 2006-2007, from the known patients with T2DM in the Lothian Diabetes Register (LDR), which included around 20,000 patients with T2DM in total. The diagnosis of T2DM was confirmed if the individual was taking oral anti-diabetic agents and/or insulin treatment or had HbA1c level over 6.5% and did not have a history of pancreatic disease. Individuals who refused consent or were unable to receive physical examination or cognitive tests were excluded from the study. A total of 1066 participants were included in the baseline population.

Year 4 follow-up clinics for the participants were scheduled in 2010–2011. By this time, 88 participants had died, nine refused follow-up attendance, 25 were considered not suitable to continue with the study and 112 did not turn up at the follow-up clinic after invitation. This left 831 participants in the population of year 4 follow-up (of which 825 had physiological measurements undertaken and 824 received both physiological measurements and cognitive testing).

3.2 Demographic and clinical data collection

3.2.1 Demographics

Self-reported information including educational attainment, occupation, current employment status of the participant and their spouse, marital status and ethnicity were collected from questionnaires at baseline. Deprivation status was defined by the Scottish Index of Multiple Deprivation (SIMD) according to the participants' postcodes, which was then presented in quintiles (first to fifth quintile, with lower quintiles indicating higher deprivation).

3.2.2 Vascular and diabetes-related risk factors

The duration of diabetes and current treatment for T2DM were recorded using a self-completion baseline questionnaire and confirmed by reviewing health records. The treatment of T2DM was then categorized to (1) lifestyle modification only (2) oral hyperglycaemic agent use without insulin and (3) insulin injection with or without oral medication. HbA1c, blood pressure and lipid profile (including serum total cholesterol and high-density lipoprotein) were measured in the baseline study clinic using physical examination or from a venous blood sample provided at the clinic.

Self-reported smoking and alcohol drinking status was collected by standard questions included in the baseline questionnaire. Smoking status was defined as having a smoking habit at the time (current smoker) or in the past but having quit (ex-smoker) or being a never smoker. The amount of cigarette smoking (in those that were current or ex-smokers) and alcohol drinking were also self-reported and calculated as cigarettes per day or units of alcohol per week, respectively.

3.2.3 Cardiovascular events

History of myocardial infarction or angina was defined using self-reported medical histories plus a relevant ICD code diagnosis in past medical records or at least one other supporting criteria, such as relevant medication use, electrocardiogram findings or WHO chest pain questionnaire. Cerebrovascular events (stroke or transient ischaemic attack) were defined by fulfilling two of three criteria including self-report, doctor diagnosis or a consistent ICD code in clinical records. History of coronary or peripheral artery intervention were also defined by self-report followed by clinical data review. Intermittent claudication was self-reported using an established claudication questionnaire (the Edinburgh Claudication Questionnaire).

3.2.4 Obesity-related variables

Physiological parameters were recorded at baseline and year 4. This included the obesity-related variables which form the focus of this thesis - body height, weight, waist and hip circumference. Body weight and height were used to calculate body mass index (BMI). Waist and hip circumference were both measured twice, and the

averages were calculated to increase the level of accuracy. Waist hip ratio was calculated using waist circumference divided by hip circumference.

3.2.5 Follow-up for dementia and cognitive testing

3.2.5.1 Dementia

The diagnosis of dementia was defined primarily using information from retrieved medical records, which included (1) records from the National Health Service patient management system (TrakCare) searched from Nov 2017 to Feb 2018, (2) ICD-10 codes from hospital discharge records, (3) death certificates codes searched in Feb 2018 and (4) prescribed medications for dementia. At least two records of dementia from the above sources were required for the definition of dementia in this thesis. An alternative was a dementia record from one source plus at least one supportive criterion, including (1) recorded results from mini mental state exam (MMSE) score ≤ 24 , (2) reported dementia status from the participant's caregiver or (3) reported dementia from a general practitioner (GP). The criteria were developed by the ET2DS study team and have been reported previously (Carr et al., 2021).

3.2.5.2 Cognitive testing

A total of nine cognitive tests were administered at both baseline and year 4. These included seven fluid-type cognitive abilities on various domains, one crystalized-type ability (an indication of pre-morbid intelligence) and a screening tool for dementia. Table 3.1 lists the nine cognitive tests performed, with the corresponding domains assessed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) (American Psychiatric Association, 2013, Wang & Dong, 2018). The details and procedures of each cognitive tests were described in [Appendix table 1](#).

Table 3.1 Cognitive tests used in the ET2DS at baseline and year 4

Cognitive Test	Abbreviation	Domains involved (DSM-V)
Mill Hill Vocabulary Scale	MHVS	Premorbid intelligence
Mini Mental State Exam	MMSE	General screening tool for dementia
Logical Memory	LM	Memory
Faces	Faces	Memory, perceptual-motor function
Trial Making Test B	TMTB	Executive function
Matrix Reasoning	MR	Executive function, perceptual-motor function
Digital Symbol Test	DST	Complex attention
Letter Number Sequencing	LNS	Executive function
Borkowski Verbal Fluency Task	BVFT	Executive function, memory, language

DSM-V, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

3.2.5.3. Generalized Cognitive factor

A derived factor 'g' was imputed by the ET2DS team from the seven fluid-type cognitive tests (LNS, BVFT, MR, DST, TMTB, Faces, LM) at baseline and year 4 to reflect the general cognitive function of a participant. Principle component analysis (PCA), which takes into consideration the variances between each of the components, was used to derive the factor 'g.' PCA was imputed with all seven test results at different time points, similar to the approach of Gow et al. (2008) so that the comparison of cognitive ability between different time points were meaningful. The variable 'g' was the main non-dementia cognitive assessment included in the analyses which I performed in this thesis as part of a post-hoc analysis following the main analyses on dementia.

3.2.6 Genetic testing

DNA samples of the participants were extracted at baseline. The single nucleotide polymorphisms (SNPs) rs429358 and rs7412 were used to create a full APOE genotype by the ET2DS team with the results recorded in the ET2DS database used for my analyses.

3.3 Data analysis

3.3.1 Software

Data analyses were conducted on R (version 3.6.3), an open-source software for data analysis.

3.3.2 Selection and derivation of variables

3.3.2.1 Physiological variables

For baseline obesity-related factors, I used three variables to represent the participant's obesity status, which included body mass index (BMI), the most widely used measurement representing overall obesity, and two measurements, waist circumference (WC) and waist hip ratio (WHR) to indicate central obesity. Body mass index (BMI) was calculated using height and weight, with the formula Weight/Height^2 (kg/m²). Waist hip ratio was calculated with Waist circumference divided by hip circumference (cm/cm).

3.3.2.2 Grouping methods for obesity-related physiological factors and changes in obesity-related physiological factors

Obesity-related factors

There were found to be various ways of classifying obesity status in the scientific and clinical literature. The most common classifications were those developed by WHO. Among these, the classification using BMI was well established and associated with various clinical outcomes. However, the clinically valuable cut points for WC and WHR were found to be more controversial (Bosomworth, 2019). The WHO classifications using WC and WHR were only stratified by sex, although a recent consensus statement from the International Atherosclerosis Society (IAS) and the International Chair on Cardiometabolic Risk (ICCR) Working Group on Visceral Obesity suggested that other factors like ethnic groups or BMI should also be considered (Ross et al., 2020). This consensus preferred a classification method for central obesity according to BMI groups, which was developed by Arden and was proposed to be associated with clinical health conditions and cardiovascular morbidities (Arden, 2004) ([appendix table 2](#)). The distribution of the ET2DS

population according to each selected grouping method will be described in the results chapter, as well as the final methods chosen for subsequent analysis.

Changes in Obesity-related Factors

From review of the literature, no definition relating specifically to body weight (BW) or waist circumference (WC) changes were found to have been associated with clinically meaningful health outcomes. Those used most frequently in prior research were therefore chosen.

For BW change, percentage BW change ($100\% \times (\text{year 4 BW} - \text{baseline BW}) / (\text{baseline BW})$) was selected, with a common cut point used in previous research of 5% change further selected when categorizing this variable. However, it should be noted that the meanings of such categorization in clinical studies were not always consistent. For instance, an intentional 5% loss in body weight was recommended for obese individuals to improve insulin sensitivity (Magkos et al., 2016). Other studies suggested that subjects with Alzheimer's disease were nearly 2 times more likely to experience a weight loss over 5% compared with those without (White et al., 1997). Another cut point for body weight loss used in certain studies was 10%, defined as severe weight loss. This definition was often used to indicate a sign of underlying health conditions. A 10% body weight decrease at the age of 60 years was a part of the definition of frailty in the Women's Health and Aging Studies (WHAS) (Xue, 2011). Considering the sample size in the ET2DS population, with only 4% experiencing a weight loss as much as 10%, and only four people within this group having incident dementia, the 10% definition of severe weight change was not used.

For WC, the absolute difference, which was WC at year 4 minus WC at baseline, was used. The evidence on meaningful definitions of waist change was rare. In a cohort study from European Prospective Investigation into Cancer and Nutrition (EPIC), an increased risk of death of 17% in men, and 13% in women was found for every 5cm increase of waist circumference adjusted by BMI (Pischon et al., 2008). Therefore, I chose 5cm as the cut point in grouping for subsequent analysis. The distribution of percentage BW change and WC change in the ET2DS will be presented in chapter 4.

3.3.2.3 Variables used as covariables

Demographics

Basic demographics used in my analyses included (1) sex and age (2) highest education attainment, which is associated with cognitive function (3) SIMD (Scottish Index of Multiple deprivation), used as an indication of social class status, which is likely related to both physical and cognitive function status. Age was used as a continuous variable, sex, education and SIMD were categorical variables.

Status of Diabetes

The following variables were chosen to indicate baseline duration and severity of diabetes: (1) duration since onset (2) HbA1c, which is an indicator of average blood glucose in the 3 months prior to extraction of blood sample (3) medications prescribed to treat diabetes mellitus (including oral hyperglycemic agents and insulin injection).

Comorbidities

Comorbidities common in people with diabetes include hypertension and hyperlipidaemia. For the purposes of my analyses, untreated hypertension was defined as a systolic blood pressure (SBP) over 140 mmHg or diastolic blood pressure over 90 mmHg, as recommended blood pressure control is below 140/90 mmHg in people diagnosed with hypertension (N.G.C. 2019). Recommended lipid profile targets vary between guidelines and individuals, taking into account family histories, comorbidities and cardiovascular event histories (Brown et al., 2020). For the purposes of describing overall lipid status in the ET2DS, I used the general cut point for normal total cholesterol levels of 5 mmol/L or below (National Health Service, UK, 2019).

Cardiovascular and hypoglycaemic events

A number of medical conditions likely to be associated with cognitive abilities were included in my analyses. This included, (1) history of stroke, which may affect cognitive ability via direct brain damage, (2) history of cardiovascular diseases, which indicates the general condition of the vascular system, categorised as a single variable for one or more episodes of intermittent claudication, myocardial infarction,

angina, transient ischaemic attack, coronary or peripheral artery intervention or 'peripheral artery disease' (defined as an ankle brachial pressure index (ABPI) lower than 0.9 (N.G.C. 2019)), and (3) history of hypoglycaemic events, likely to be associated with cognitive prognosis in previous studies (Aung et al., 2012).

Lifestyle factors

Two lifestyle factors were included, (1) smoking history, which has been related to increased risk of dementia (Peters et al., 2008) and (2) alcohol drinking habit, for which heavy intake was found to be associated with brain atrophy and dementia (Tapiwala & Ebmeier, 2018).

Genetic factor

The Alzheimer's disease related genotype Apolipoprotein E (ApoE) was included in my analysis. Since two copies of ApoE ϵ 4 have more effect on dementia than one copy (Liu et al., 2013), APOE genotypes were derived for no copies of ApoE ϵ 4, one copy or two copies for the multivariable analysis.

3.3.2.4 Use of covariables for multivariable analysis

The baseline variables mentioned in section 3.2.3 were used to describe the characteristics of the study population and prior to their possible incorporation in multivariable analyses.

A subset of the baseline variables was subsequently simplified and grouped to be used in multivariable models on the relationship between obesity-related variables and dementia. To reduce the potential problem of overfitting, factors with potential overlap were simplified to a single variable, followed by grouping according to similar causal pathways. The covariable groups were added into the multivariable logistic regressions one by one to identify the effect of each group on the model and were also used in the multivariable survival models.

The final covariable groups used in the logistic regression models included (1) diabetes status: baseline HbA1c and history of hypoglycemic episodes (2) other medical factors: history of stroke, history of cardiovascular diseases, systolic blood pressure and total cholesterol (3) socioeconomic: education attainment and Scottish

Index of Multiple Deprivation (SIMD) (4) lifestyle factors: smoker and alcohol drinker (5) genetic factor: Apolipoprotein E (APOE) genotype.

3.3.2.5 Distribution of continuous variables

The distributions of continuous variables were checked using skewness values or Z scores depending on the sample size. For variables with a sample size larger than 300, skewness value lower than two was defined as normal distribution. Z score was calculated if the sample size was between 50 and 300, with the cut point of normal distribution being 3.29 (Kim, 2013).

If the variables did not meet the definition of normal distribution, transformation was deemed necessary to meet the normal distribution assumptions in regression models. Histograms were performed for such variables, and the method of transformation were chosen accordingly.

3.3.2.6 Dealing with missing data

Data at baseline and year four

Baseline demographics of the population with obesity-related physiological data at year 4 versus the whole population were compared to check for representativeness. The same procedure was applied to the cognitive test results in the post-hoc analysis section.

Explanatory variables

Any individuals with missing values on the main explanatory variables, BMI, WC or WHR at baseline was excluded from the whole study. Similarly, any individual with missing data on weight or waist circumference at baseline or year 4 was excluded from the analysis using changes of obesity-related physiological factors as the explanatory variables. As for other covariates, complete case analysis for all the variables were used in each individual multivariable model.

3.3.3 Statistical analysis

Incident dementia was the main outcome variable. The main explanatory variables included baseline BMI, WC and WHR in the first part of the analysis and the percentage changes in BW and changes in WC in the second part.

3.3.3.1 Significance

I used the cut point $p < 0.05$ for rejecting null-hypothesis, which indicates a 5% probability of incorrectly accepting the alternative hypothesis.

3.3.3.2 Descriptive analysis

The main variables of interest, including obesity-related factors, dementia and other baseline covariables were presented in the descriptive analysis. Mean and standard deviations were presented for normally distributed continuous variables, median and quantiles for other continuous variables and proportions and numbers for categorical variables. Missing data on each baseline variable was also shown. Histograms were presented for non-normally distributed continuous variables.

The proportion of the study population in each group of obesity or weight change were presented, as well as the proportion of participants who died or were diagnosed with dementia by the end of the study.

In the post-hoc analysis, the mean and standard deviations of cognitive test results were presented among the whole population, those who had obesity-related data in year 4 and in the dementia and non-dementia groups.

3.3.3.3 Univariate analysis

Simple correlation between continuous baseline variables and obesity-related variables was performed, as well as calculating the mean values of obesity-related variables according to each categorical variable. The distributions of baseline variables were also presented in the population who had dementia by the end of the study and those who did not. T tests were calculated for differences in continuous variables between the groups and chi-squared tests for categorical variables (or fisher exact test if any category was zero or over 20% of categories had values < 5). The same procedure was performed for the association between baseline covariables, percentage BW change and WC change in the population with obesity-related physiological data at year 4. In addition, Analysis of Variance (ANOVA) was used for continuous variables to test the difference between participants in different percentage BW change or WC change groups.

Survival models with Kaplan-Meier method were used to give an overview of all-cause mortality and dementia free survival over time, according to obesity-related factors and changes in BW or WC.

3.3.3.4 Multivariable analysis

Logistic regression

Logistic regression was the initial multivariable model used for estimating the contributions of obesity-related factors or changes in obesity-related factors and other confounding factors to the binary outcome, dementia. Logistic regression is an established method for identifying the factors contributing to binomial outcomes. In this part of the analysis, the main explanatory variables were used as continuous variables. The grouped covariables (described in section 3.3.2.4) were added into the model one by one to investigate the interaction between the covariables, obesity-related factors and dementia. The main possible drawback of this model includes (1) time of diagnosis not considered (2) competing risk effect of mortality (3) possibility of non-linear relationship not considered.

Survival analysis

Survival models are capable of identifying association with outcomes while considering more complex issues, including time to event and competing risks. I therefore performed survival models in the next stage of my analysis. The models were performed using both continuous values and the groups of physiological measurements, to better demonstrate any possible non-linearity in the relationship between the measurements and outcome.

Two models were used, including the cox-proportional hazard (Cox PH) function and the competing risk sub-distribution hazard function. Different obesity-related variables might have different relationship with all-cause mortality and incident dementia, which may in turn influence the modelling techniques and interpretation, thus competing risk is an important issue to consider. Although all-cause mortality was not the main outcome of interest in this thesis, it may affect the accuracy of models as competing risk. In survival analysis, competing risk analysis should be included in the models if the competing event had a prevalence of 10% or higher than the event of interest (Schuster et al., 2020). The survival models were

performed using both baseline obesity-related factors and changes in obesity-related factors as main explanatory factors. Age and sex were adjusted for in both models. Additional models were performed on the relationship between changes in obesity-related factors and dementia outcome, with adjustment of age, sex and the pre-selected covariables (as mentioned in section 3.3.2.4).

Chapter 4: Results

This chapter contains four main sections. The first section describes the distribution of the variables of interest of the ET2DS population. The second section focuses on analysis and models on the relationship between baseline physiological (obesity-related) factors and dementia outcome, followed by the third section with similar approach on the relationship between change in physiological factors and dementia outcome. Lastly, the fourth section demonstrates the post-hoc analysis of this research, which focuses on cognitive function tests in association with the main obesity-related variables of interest, and the diagnosis of dementia.

4.1 Descriptive statistics on characteristics of study population

In this section, I will present the baseline characteristics of the study population, including the main obesity related variables of interest (body mass index (BMI), waist circumference (WC) and waist hip ratio (WHR)) and various demographics. I will then focus on a detailed description of how BMI, WC and WHR were distributed in the population, and define the grouping methods used in the further analysis

4.1.1 Distribution and descriptive analysis of baseline characteristics

The rationale of distribution identification and transformation of continuous variables was described in the methods chapter. Of all the variables with a sample size larger than 300, only units of alcohol per week had a skewness value greater than two. Z score was calculated for the number of cigarettes per day, which was 5.79, higher than the cut point of 3.29 ([appendix table 3](#)). Thus, I rejected the hypothesis that the two variables were normally distributed. Histograms of the two variables were then drawn ([appendix figure 1](#)). Log transformation was performed for “Total Units of Alcohol per week” because of the exponential distribution pattern. For “Number of Cigarettes per day,” given the right-skewed trend without obvious exponential pattern, square root transformation was performed. Skewness tests were performed again, which were 0 and -0.03, respectively.

Table 4.1.1.1 Baseline characteristics of all participants of the ET2DS (n=1066)

Variable	category	Mean $\pm$ sd or Median (Q1, Q3) or % (n)	Missing
Demographics			
Age (years)		67.91 $\pm$ 4.2	
Sex	Male	51 (547)	0
	Female	49 (519)	
Education	Primary school	1 (7)	0
	Secondary school	55 (581)	
	Professional/ technical	29 (307)	
	University/ college	16 (171)	
SIMD Quintile	1	12 (125)	
	2	19 (199)	
	3	18 (180)	
	4	18 (189)	
	5	32 (331)	
Status of Diabetes			
Duration (years)		8.06 $\pm$ 6.47	13
HbA1c (%)		7.41 $\pm$ 1.13	9
Treatment of diabetes	Diet-controlled	19 (198)	
	Oral medication	64 (681)	
	Insulin injections	17 (186)	
Obesity-related physiological measurements			
Height (cm)		166 $\pm$ 9.2	1
Weight (kg)		86.48 $\pm$ 16.17	1
Body Mass Index (kg/m ²)		31.43 $\pm$ 5.69	1
Waist circumference (cm)		106.9 $\pm$ 12.8	5
Hip circumference (cm)		111.0 $\pm$ 12.0	5
Waist Hip Ratio		0.97 $\pm$ 0.08	5
Other metabolic risk factors			
Systolic Blood Pressure (mmHg)		133.3 $\pm$ 16.4	2
Diastolic Blood Pressure (mmHg)		69.1 $\pm$ 9.0	2
Hypertensive status*	No	65 (697)	2
	Yes	34 (367)	
Antihypertensive treatments	No	17 (186)	7
	Yes	82 (873)	
Total Cholesterol (mmol/L)		4.31 $\pm$ 0.90	9

High Density Lipoprotein (mmol/L)		1.29 ± 0.36	9
Hyperlipidemia status*	No	79 (846)	2
	Yes	20 (211)	
Lipid modification agents	No	14 (152)	2
	Yes	86 (912)	
Medical history			
Cardiovascular disease*	No	50 (532)	4
	Yes	50 (530)	
Stroke	No	94 (965)	8
	Yes	6 (59)	
Hypoglycemic attack	Yes	11 (113)	5
	No	87 (929)	
	Not sure	2 (19)	
Hypoglycemic attack (number of times)	1-2	6 (59)	
	3-4	3 (28)	
	more than 5	3 (27)	
Lifestyle factors			
Smoker	Current	14 (154)	0
	Former	47 (498)	
	Never	39 (414)	
Number of Cigarettes per day (n=154)		16.65 (10, 20)	
Current Alcohol Drinkers	No	19 (205)	9
	Yes	80 (856)	
Total Units of Alcohol per week (n=856)		5.2 (0, 15)	
Genetic factor			
Apolipoprotein E (APOE) genotype	ε2/ε2 or ε2/ε3 or ε3/ε3	73 (744)	43
	ε2/ε4 or ε3/ε4	25 (259)	
	ε4/ε4	2 (20)	

Values are median and 1st and 3rd quantile for Number of Cigarettes per day and Total Units of Alcohol per week, SIMD: Scottish Index of Multiple Deprivation 2006 (quintile 1 is most deprived)

* Hypertensive status is defined as systolic blood pressure <140 mmHg and/or diastolic blood pressure < 90 mmHg * Hyperlipidemia status is defined as total cholesterol < 5 mmol/L

* Cardiovascular disease includes established history of intermittent claudication, myocardial infarction, angina, transient ischaemic attack, coronary or peripheral artery intervention or ankle brachial pressure index below 0.9

The characteristics of the total study population at baseline are shown in table 4.1.1.1. The mean age was 67.91 years, with around half of the population male (male 51%, female 49%). The population had a relatively high level of education, with 43% having achieved highest levels of education (including professional or university degrees) and 55% having completed secondary school. A related trend was seen in the Scottish Index of Multiple Deprivation (SIMD) quintiles, with 32% falling into the least deprived, and only 12% in the most deprived group. The population had been diagnosed with T2DM for an average of 8.06 years, had a mean HbA1c controlled at 7.41 ± 1.13 (%), and the majority (64%) were using oral hypoglycaemic agents but not injected insulin for blood glucose control.

The obesity-related body measurements indicated that the population means were higher (indicating greater levels of obesity) than the definition of normal body composition used by the World Health Organization (WHO). The mean BMI was 31.43 ± 5.69 (kg/m²), WC was 106.9 ± 12.8 (cm) and WHR was 0.97 ± 0.08 , compared with the ranges for normal body compositions used by WHO of 18.5-24.9 for BMI, under 94 cm (male) or 80 cm (female) for WC and 0.9 (male) and 0.85 (female) for WHR (World Health Organization, 2000). Detailed description on the distribution of the obesity related variables is given in section 4.1.2.

Half of the population had a recorded history of cardiovascular disease (50%), including 59 participants with stroke (6%). The population as a whole had a borderline high mean blood pressure (SBP= 133.3 ± 16.4 (mmHg), DBP= 69.1 ± 9.0 (mmHg)). A total of 367 (34%) people had a SBP over 140 mmHg or DBP over 90 mmHg, indicating untreated hypertension (N.G.C. 2019). Eighty-two percent of the total participants (n=873) reported antihypertensive medication use. Mean total cholesterol was 4.31 ± 0.90 mmol/L, with 20% (n=211) of the total population having a cholesterol level of the normal upper limit 5 mmol/L or above (National Health Service, UK, 2019), and 86% (n=912) on lipid modification medications. Eleven percent (n=113) of the population reported at least one episode of hypoglycaemia throughout their lifetime.

Over half of the population were either self-reported current smokers (14%, n=154) or former smokers (47%, n=498). The median number of cigarettes consumed each

day among the current smokers was 16.7 (Q1=10, Q3=20). Eighty percent (n=856) of participants reported drinking alcohol at baseline, with a median of 5.2 (Q1=0, Q3=15) units of alcohol consumed every week.

Within the sub-population of people tested for the Alzheimer's disease related APOE gene (n=963), 2% had two sets and 25% had one set of $\epsilon 4$ allele. This prevalence was similar to the predicted worldwide APOE- $\epsilon 4$ frequency of 13.7% (Liu et al., 2013).

4.1.2 Distribution of obesity-related variables and their categorization into groups

An overview description on different grouping methods for obesity-related variables was described in the methods section. Given that the ET2DS is a diabetic study population, it is likely that the overall distribution of physiological factors would differ from the general population. The percentage of people in different groups, by different classification methods, was therefore explored in detail (table 4.1.2.1) before further analysis by group was undertaken.

As shown in the table, about half of the population fell into at least class I obesity (BMI>30) in the WHO classification by BMI. Only one person fell in the underweight group. Previous studies have suggested that people in the normal or overweight groups have better outcomes than underweight or obese groups. The evidence of poor outcome is stronger among at least class II obesity (Xu et al., 2018). Thus, I used the WHO definitions to group the population into (1) normal (2) overweight (3) class I obesity (4) class II or III obesity in subsequent analysis. The person in the underweight group was excluded when using this grouping method.

For the waist circumference, only 6% (n=59) of people fell into non central obese group by the conventional WHO classification. If using the BMI stratified classification, approximately one third of people fell into the non-central obese group. This might relate to the generally higher BMI in the ET2DS study population. However, a grouping method with only two groups was not sufficient for identifying potentially non-linear associations. Therefore, I chose quantiles for subsequent analysis for WC. As for WHR, only 8% (n=90) of the population fell into the non-central obese group. I chose quantiles for WHR grouping.

Table 4.1.2.1 Distribution of obesity-related variables according to different grouping methods

Classification method	Cut points	Frequency (n)	Percentage (%)
Body Mass Index (BMI) (kg/m²)			
BMI (quantiles)			
Q1	<27.4	258	24
Q2	27.4-30.7	270	25
Q3	30.7-34.5	264	25
Q4	>34.5	272	26
BMI (WHO)			
Underweight	<18.4	1	0
Normal	18.5-24.9	104	10
Overweight	25-29.9	363	34
Class I Obesity	30-34.9	352	33
Class II or III Obesity	>35	244	23
Waist Circumference (WC) (cm)			
WC (quantiles)			
Q1	M: 78-100, F: 73-96	260	24
Q2	M: 100-106.5, F: 96-105	265	25
Q3	M: 106.5-116, F: 105-113.9	269	25
Q4	M: 116-154, F: 113.9-159	266	25
WC (WHO)			
Non-central obese	Male<94, Female<80	59	6
Central obese	Male>94, Female>80	1001	94
WC (BMI stratified) *			
Non central obese		350	33
central obese		710	67
Waist Hip Ratio (WHR)			
WHR (quantiles)			
Q1	M: 0.83-0.96, F: 0.74-0.88	265	25
Q2	M: 0.96-0.99, F: 0.88-0.93	265	25
Q3	M: 0.99-1.04, F: 0.93-0.97	265	25
Q4	M: 1.04-1.22, F: 0.97-1.2	265	25
WHR (WHO)			
Non-central obese	Male<0.9, Female<0.85	90	8
Central obese	Male>0.9, Female>0.85	970	91

WHO: World Health Organization *Definition of BMI stratified WC grouping method is shown in [appendix table2](#).

There were generally high correlations between the different measures of obesity at baseline in the ET2DS population (Table 4.1.2.2). Both waist and hip circumferences were strongly positively correlated with BMI. WHR had a relatively lower correlation with BMI compared to other measures. When looking at the inter-correlations within different sex groups, the correlations between BMI and WHR were higher in male participants. (Male: $\rho=0.393$, $p<0.01$; Female: $\rho=0.114$, $p<0.01$, [appendix table 4](#)) Of note, the correlation between BMI and hip circumference was negative in females but not in males. The concept of WHR reflects central obesity rather than general body weight, thus the findings might imply a different relationship between general and central obesity in different sexes.

Table 4.1.2.2 Inter-Correlation between baseline obesity related physiological factors

	BW	BMI	Waist	Hip
BMI	0.812**			
Waist	0.876**	0.843**		
Hip	0.760**	0.886**	0.763**	
WHR	0.313**	0.099**	0.499**	-0.176**

Values are ρ (Rho) in Pearson correlation. Significance note: *, $p<0.05$, **, $p<0.01$

BW: body weight; BMI: body mass index; Waist: waist circumference; Hip: hip circumference; WHR: waist hip ratio

Table 4.1.2.3 Association between Baseline Obesity Related Variables and Baseline Demographic Characteristics (n=1066)

		BMI		Waist		WHR	
	n	ρ (Rho) / mean $\pm$ sd	p-value	ρ (Rho) / mean $\pm$ sd	p-value	ρ (Rho) / mean $\pm$ sd	p-value
Demographics							
Age (years)		-0.194	<0.001**	-0.161	<0.001**	-0.05	0.105
Sex			<0.001**		0.001**		<0.001**
Male	547	30.35 $\pm$ 4.88		108.20 $\pm$ 12.07		1.00 $\pm$ 0.06	
Female	519	32.57 $\pm$ 6.24		105.55 $\pm$ 13.46		0.93 $\pm$ 0.08	
Education			0.042*		0.256		0.912
Primary school	7	29.49 $\pm$ 3.02		99.94 $\pm$ 10.52		0.95 $\pm$ 0.08	
Secondary school	581	31.68 $\pm$ 5.49		107.32 $\pm$ 12.22		0.97 $\pm$ 0.08	
Professional/technical	307	31.59 $\pm$ 5.84		106.92 $\pm$ 13.04		0.96 $\pm$ 0.07	
University/college	171	30.37 $\pm$ 6.05		105.76 $\pm$ 14.37		0.97 $\pm$ 0.08	
SIMD Quintile			<0.001**		<0.001**		0.067
1	127	32.85 $\pm$ 5.28		110.02 $\pm$ 11.18		0.98 $\pm$ 0.07	
2	208	32.38 $\pm$ 5.72		108.55 $\pm$ 12.6		0.97 $\pm$ 0.08	
3	188	32.24 $\pm$ 6.17		109.11 $\pm$ 13.23		0.97 $\pm$ 0.08	
4	194	31.11 $\pm$ 5.46		106 $\pm$ 13.13		0.96 $\pm$ 0.08	
5	349	30.09 $\pm$ 5.39		104.13 $\pm$ 12.57		0.96 $\pm$ 0.07	
Status of Diabetes							
Duration (years)		0.012	0.690	0.080	0.010 *	0.119	<0.001**
HbA1c (%)		0.052	0.089	0.096	0.002 **	0.124	<0.001**
Treatment			0.004**		<0.001**		<0.001**
Diet-controlled	198	30.26 $\pm$ 4.70		103.24 $\pm$ 10.94		0.95 $\pm$ 0.07	
Oral medication	681	31.60 $\pm$ 5.88		107.25 $\pm$ 12.94		0.96 $\pm$ 0.08	
Insulin injections	186	32.05 $\pm$ 5.80		109.54 $\pm$ 13.49		0.98 $\pm$ 0.08	
Other metabolic factors							
Systolic BP (mmHg)		0.028	0.359	0.015	0.62	-0.011	0.713
Diastolic BP (mmHg)		0.058	0.059	0.094	0.002**	0.118	<0.001**
Hypertensive status*			0.173		0.265		0.974
No	697	31.25 $\pm$ 5.65		106.6 $\pm$ 12.64		0.97 $\pm$ 0.08	
Yes	367	31.75 $\pm$ 5.73		107.53 $\pm$ 13.15		0.97 $\pm$ 0.08	
Hypertensive treatment			<0.001**		<0.001**		0.025*
No	186	29.87 $\pm$ 5.58		103.14 $\pm$ 12.71		0.95 $\pm$ 0.08	
Yes	873	31.78 $\pm$ 5.67		107.72 $\pm$ 12.75		0.97 $\pm$ 0.08	
Cholesterol (mmol/L)*		-0.056	0.07	-0.128	<0.001**	-0.14	<0.001**

HDL (mmol/L)		-0.148	<0.001**	-0.244	<0.001**	-0.287	<0.001**
Hyperlipidemia status*			0.164		0.012*		0.002**
No	846	31.53 ± 5.69		107.38 ± 12.46		0.97 ± 0.07	
Yes	211	30.95 ± 5.45		104.78 ± 13.60		0.95 ± 0.08	
Lipid treatment			0.006**		0.002**		0.046*
No	152	30.21 ± 5.89		103.85 ± 12.79		0.95 ± 0.08	
Yes	912	31.64 ± 5.64		107.41 ± 12.78		0.97 ± 0.08	
Other Medical history							
Cardiovascular disease*			0.03*		<0.001**		<0.001**
No	532	30.87 ± 5.32		105.37 ± 12.11		0.96 ± 0.08	
Yes	530	31.94 ± 5.95		108.36 ± 13.27		0.97 ± 0.07	
Stroke			0.447		0.051		<0.001**
No	1004	31.40 ± 5.69		106.72 ± 12.81		0.96 ± 0.08	
Yes	62	31.97 ± 5.66		110.04 ± 12.67		1.00 ± 0.06	
Hypoglycemic attack			0.932		0.876		0.573
No	929	31.40 ± 5.62		106.92 ± 12.59		0.97 ± 0.08	
Yes	113	31.45 ± 5.90		107.13 ± 13.93		0.97 ± 0.08	
Hypoglycemic attack			0.444		0.564		0.578
0 to 2	59	30.84 ± 5.36		106.22 ± 11.98		0.96 ± 0.07	
2 to 4	28	32.39 ± 6.18		109.66 ± 15.09		0.98 ± 0.09	
more than 4	27	32.11 ± 6.82		107.52 ± 16.73		0.98 ± 0.09	
Lifestyle factors							
Smoker			0.221		0.005**		<0.001**
Current	414	31.43 ± 5.72		105.33 ± 12.68		0.95 ± 0.08	
Former	498	31.65 ± 5.66		108.05 ± 12.60		0.98 ± 0.07	
Never	154	30.73 ± 5.69		107.45 ± 13.54		0.98 ± 0.07	
Cigarettes/ day (n)		0.100	0.219	0.093	0.249	0.082	0.314
Current Alcohol Drinkers			0.007**		0.249		0.125
No	205	32.45 ± 6.02		107.87 ± 12.80		0.96 ± 0.08	
Yes	856	31.19 ± 5.59		106.71 ± 12.84		0.97 ± 0.08	
Units of Alcohol /week		-0.145	<0.001**	-0.057	0.099	0.174	<0.001**
Genetic factors							
APOE genotype			0.065		0.276		0.336
ε2/ε2, ε2/ε3 or ε3/ε3	744	31.54 ± 5.71		106.94 ± 12.48		0.96 ± 0.08	
ε2/ε4 or ε3/ε4	259	31.48 ± 5.56		107.32 ± 13.47		0.97 ± 0.08	
ε4/ε3	20	28.54 ± 4.34		102.58 ± 13.03		0.98 ± 0.08	

Values are (1) Rho in Pearson correlation (for continuous data which are normally distributed, which is the majority of the data presented), (2) Spearman correlation (Continuous data which are not normally distributed: Number of cigarettes per day in smokers and Total Units of Alcohol per week in people with drinking habits), or (3) mean $\pm$ sd in categorical data.

P-values are for (1) correlation in continuous data or (2) t-tests or Analysis of variance (ANOVA) for categorical data

SIMD: Scottish Index of Multiple Deprivation 2006 (quintile 1 is most deprived)

BMI: body mass index; Waist: Waist circumference; WHR: Waist Hip Ratio

BP: blood pressure; HDL: high-density lipoprotein; APOE: apolipoprotein E

* Hypertensive status is defined as systolic blood pressure <140 mmHg and/or diastolic blood pressure < 90 mmHg

* Hyperlipidemia status is defined as total cholesterol < 5 mmol/L

* Cardiovascular disease includes established history of intermittent claudication, myocardial infarction, angina, transient ischaemic attack, coronary or peripheral artery intervention or ankle brachial pressure index below 0.9

Significance note: *, $p<0.05$, **, $p<0.01$

Table 4.1.2.3 demonstrates the associations of the main obesity-related variables with other baseline characteristics, focusing on those characteristics which were used in further analysis. Both BMI and waist circumference (WC) were negatively correlated with age. BMI was higher in females, while WC and WHR were higher in males. BMI and WC were higher in lower SIMD quintiles (more deprived).

The obesity related measures were positively correlated with HbA1c, and the population using insulin injections had the highest average BMI, WC and WHR, followed by those using oral medication. All three measures were negatively correlated with total cholesterol and HDL and were higher in the population taking hypertensive or lipid-lowering medications. All three measures were higher in the participants with cardiovascular diseases while only WC and WHR were higher in those with history of stroke. There was no significant difference in obesity related measures according to history of hypoglycaemic attacks.

In terms of lifestyle factors, WC and WHR were lower in the population with a current smoking habit. The population with a current drinking habit had a lower average BMI. BMI was negatively correlated with the amount of alcohol consumed, while WHR was positively correlated. None of the obesity-related variables were significantly different according to APOE genotypes.

4.2 Relationship between Baseline Obesity Related Physiological Factors and Dementia

This section focuses on the associations between the obesity related physiological factors measured at baseline, including BMI, WC and WHR, and the main outcome of interest, incident dementia. I start by describing overall mortality and incident dementia in the study population. Next, I describe the characteristics of the participants that had or had not been diagnosed with dementia by the year ten follow up. The subsequent section describes the findings from statistical models analyzing the association between baseline obesity and incident dementia.

4.2.1 All-cause mortality and incident dementia in the ET2DS population

In the ET2DS population, 30.1% (n=321) of the ET2DS population had died, which was higher than 9.9% (n=106) who had a recorded diagnosis of dementia by year 10 follow up, or Feb 2018 (table 4.2.1.1). Competing risks of death should be considered in the survival analysis models.

Table 4.2.1.1 Proportion of all-cause mortality and incident dementia in the total population (n=1066)

	All-cause mortality	Incident Dementia
Prevalence %(n))	30.1 (321)	9.9 (105)
Time-to-event (median (Q1, Q3)) (years)	6.38 (3.78, 9.02)	7.08 (4.34, 9.06)

Table 4.2.1.2 shows the distribution of obesity-related variables at baseline according to all-cause mortality or incident dementia by the end of follow up. The central-obesity variables, including WC (mean in participants alive, 106.1 ± 12.7 cm; mean in participants dead, 108.9 ± 13.1 cm, $p < 0.01$) and WHR (alive, 0.96 ± 0.08 ; dead, 0.98 ± 0.08 , $p = 0.01$) were higher in those participants who had died by the end of follow up. This finding was consistent with previous studies addressing cardiovascular risks (Hamer et al., 2017). The difference in mean BMI between groups who had or had not died at the end of the follow-up period was not statistically significant.

In terms of incident dementia, baseline mean BMI was lower among those who were subsequently diagnosed with dementia (mean in dementia group, 29.99 ± 5.21

kg/m² versus mean in non-dementia group, 31.59 ± 5.72 kg/m², p<0.01) while WC and WHR did not show a significant difference between the groups. The trends observed across obesity-related groupings were consistent with findings using the continuous variables. There was no obvious double-peak distribution in the associations with all-cause mortality or incident dementia.

Table 4.2.1.2 Baseline Obesity Related physiological factors according to all-cause Mortality (n=320) and Incident Dementia (n=105)

	Alive (n=745)	Dead (n=320)	p-value	No dementia (n = 960)	Dementia (n=105)	p-value
BMI (kg/m ²)	31.26 ± 5.59	31.83 ± 5.92	0.15	31.59 ± 5.72	29.99 ± 5.21	<0.01*
Underweight	0 (1)	0 (0)	0.72	0 (1)	0 (0)	0.02 *
Normal	10 (74)	9 (30)		9 (85)	18 (19)	
Overweight	35 (262)	32 (101)		34 (324)	37 (39)	
Class I Obesity	33 (244)	34 (108)		33 (321)	30 (31)	
Class II or III Obesity	22 (164)	25 (80)		24 (228)	15 (16)	
Waist (cm)	106.1 ± 12.7	108.9 ± 13.1	<0.01 **	107.2 ± 12.8	104.5 ± 13.0	0.05
Q1	25 (189)	22 (71)	<0.01 **	24 (228)	30 (32)	0.29
Q2	27 (201)	20 (64)		25 (236)	28 (29)	
Q3	25 (188)	25 (80)		26 (245)	22 (23)	
Q4	22 (166)	32 (101)		26 (246)	20 (21)	
Waist hip ratio	0.96 ± 0.08	0.98 ± 0.08	0.01 *	0.96 ± 0.07	0.98 ± 0.08	0.08
Q1	26 (191)	23 (74)	0.08	25 (240)	24 (25)	0.84
Q2	26 (193)	22 (71)		25 (240)	23 (24)	
Q3	26 (190)	23 (75)		25 (239)	25 (26)	
Q4	23 (170)	30 (96)		25 (236)	29 (30)	

Values are mean ± standard deviation or %(n)

BMI: body mass index; WHR: Waist Hip Circumference

Significance note: *, p<0.05, **, p<0.01

The distribution of numbers of deaths of these variables are shown as histograms in the appendix ([appendix figure 1](#)). There were no obvious U-shape distributions or double peak trends in diagnosis of dementia, and I therefore maintained the choice of grouping methods, as discussed in section 2.1, for subsequent analysis.

4.2.2 Baseline characteristics according to incident dementia

Incident dementia is the main outcome of interest in this thesis. In table 4.2.2.1, the baseline characteristics of people who had been diagnosed with dementia by year ten follow up and those who had not are presented.

The people who developed dementia were older at baseline (mean age in dementia group, 69.38 ± 3.96 years versus non-dementia group, 67.75 ± 4.20 years, $p < 0.01$) and had lower educational status (46% had higher qualification in non-dementia group compared to 36% in dementia group, $p = 0.04$). The two groups had similar proportions of current alcohol drinkers, but the non-dementia group had a higher average alcohol consumption per week (6 versus 3.25 units in non-dementia group and dementia group, respectively). The dementia group had a significantly higher prevalence of APOE- $\epsilon 4$ gene (50% ($n = 52$) had at least one allele of APOE- $\epsilon 4$ compared to 23% ($n = 226$) in non-dementia group).

Table 4.2.2.1 Baseline characteristics in people diagnosed with dementia ($n = 105$) and not diagnosed with dementia ($n = 960$) by year 10 follow up

	No dementia ($n = 960$) mean $\pm$ sd, median (Q1, Q3) or %(n)	Dementia ($n = 105$) mean $\pm$ sd, median (Q1, Q3) or %(n)	p- value
Demographics			
Age (years)	67.75 ± 4.2	69.38 ± 3.96	$< 0.01^*$
Sex			0.05
Female	50 (477)	39 (41)	
Male	50 (483)	61 (64)	
Education			0.04*
Primary school	1 (5)	2 (2)	
Secondary school	54 (516)	62 (65)	
Professional/technical	30 (286)	19 (20)	
University/college	16 (153)	17 (18)	
SIMD Quintile			0.22
1	12 (114)	12 (13)	
2	20 (191)	16 (17)	
3	18 (168)	19 (20)	

4	17 (167)	26 (27)	
5	33 (320)	27 (28)	
Status of Diabetes			
Duration of diabetes (years)	7.96 ± 6.39	8.95 ± 7.08	0.18
HbA1c (%)	7.39 ± 1.07	7.54 ± 1.55	0.36
Treatment of diabetes			0.60
Diet-controlled	19 (180)	17 (18)	
Oral medication	64 (615)	62 (65)	
Insulin injections	17 (164)	21 (22)	
Other metabolic risk factors			
Systolic blood pressure (mmHg)	133.24± 16.5	134.1 ± 15.6	0.58
Diastolic blood pressure (mmHg)	69.1 ± 8.9	68.9 ± 9.9	0.84
Hypertensive status *			0.79
No	66 (629)	64 (67)	
Yes	34 (329)	36 (38)	
Hypertensive treatment			0.10
No	17 (161)	24 (25)	
Yes	82 (792)	76 (80)	
Total Cholesterol (mmol/L)	4.32 ± 0.89	4.24 ± 0.97	0.43
high-density lipoprotein (mmol/L)	1.3 ± 0.37	1.27 ± 0.33	0.40
Hyperlipidemia status *			1.00
No	79 (763)	79 (83)	
Yes	20 (190)	19 (20)	
Lipid modification treatment			0.88
No	14 (138)	13 (14)	
Yes	85 (820)	87 (91)	
Medical history			
Cardiovascular disease *			0.11
No	51 (488)	42 (44)	
Yes	49 (469)	57 (60)	
Stroke			0.87
No	94 (905)	93 (98)	
Yes	6 (55)	7 (7)	

Hypoglycemic attack			0.25
No	88 (842)	83 (87)	
Yes	10 (98)	14 (15)	
Hypoglycemic attack (times)			0.09
1-2 times	6 (54)	5 (5)	
3-4 times	3 (25)	3 (3)	
more than 5 times	2 (20)	7 (7)	
Lifestyle factors			
Smoker			0.12
Never	39 (377)	35 (37)	
Former	46 (439)	55 (58)	
Current	15 (144)	10 (10)	
Number of Cigarettes / day	15 (10, 20)	20 (16.25, 20)	0.56
Current Alcohol Drinkers			1.00
No	19 (184)	19 (20)	
Yes	80 (772)	80 (84)	
Total Units of Alcohol / week	6 (0, 16.12)	3.25 (0, 10.88)	0.03*
Genetic factor			
Apolipoprotein E (APOE) genotype			<0.01*
ε2/ε2 or ε2/ε3 or ε3/ε3	72 (694)	48 (50)	
ε2/ε4 or ε3/ε4	22 (213)	43 (45)	
ε4/ε4	1 (13)	7 (7)	

Values are median and 1st and 3rd quantile for Number of Cigarettes per day and Total Units of Alcohol per week

P-value of total units of alcohol per week is performed by t test of log total units of alcohol per week added 1; P-value of number of cigarettes per day is performed by t test of squared rooted number of cigarettes per day

SIMD: Scottish Index of Multiple Deprivation 2006 (quintile 1 is most deprived)

* Hypertensive status is defined as systolic blood pressure <140 mmHg and/or diastolic blood pressure < 90 mmHg

* Hyperlipidemia status is defined as total cholesterol < 5 mmol/L

* Cardiovascular disease includes established history of intermittent claudication, myocardial infarction, angina, transient ischaemic attack, coronary or peripheral artery intervention or ankle brachial pressure index below 0.9

Significance note: *, p<0.05, **, p<0.01

4.2.3 Relationship of baseline obesity measures with incident dementia

In this section, the results from different models used to investigate the relationship between baseline obesity-related variables (BMI, WC and WHR) and incident dementia are described. The models presented are logistic regression, followed by survival analysis with Kaplan-Meier method (KP method), Cox proportional hazard multivariable and competing risk sub-distribution hazard model.

Table 4.2.3.1 Odds ratio of dementia associated with baseline obesity related physiological factors

	BMI (1)		WC (2)		WHR (3)	
Co-variables included	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
+ age + sex	0.82 (0.67-1.01)	0.07	0.93 (0.85-1.01)	0.07	1.02 (0.99-1.05)	0.17
+ diabetes status	0.85 (0.68-1.04)	0.12	0.94 (0.86-1.02)	0.13	1.02 (0.99-1.05)	0.20
+ other medical factors	0.83 (0.66-1.03)	0.09	0.93 (0.85-1.02)	0.11	1.02 (0.99-1.05)	0.21
+ socioeconomic	0.81 (0.65-1.01)	0.07	0.92 (0.84-1.01)	0.08	1.02 (0.99-1.06)	0.21
+ lifestyle factors	0.81 (0.64-1.00)	0.06	0.92 (0.84-1.01)	0.07	1.02 (0.99-1.06)	0.20
+ genetic factors	0.80 (0.63-1.02)	0.07	0.91 (0.82-1.00)	0.05 *	1.02 (0.98-1.05)	0.39

Values are estimated odds ratio for (1) every 5 kg/m² increase in BMI (2) every 5 cm increase in waist circumference (3) every unit increase in WHR multiplied by 100. The model is performed with logistic regression. *p<0.05

BMI: body mass index; WC: waist circumference; WHR: waist hip ratio

Diabetes status: Baseline HbA1c, history of hypoglycemic episodes

Other medical factors: history of stroke, history of cardiovascular diseases, systolic blood pressure, total cholesterol

Socioeconomic: education attainment, Scottish Index of Multiple Deprivation (SIMD)

Lifestyle factors: Smoker, alcohol drinker

Genetic factor: Apolipoprotein E (APOE) genotype

Table 4.2.3.1 demonstrates the odds ratio of dementia according to baseline obesity related physiological factors. Logistic regression was used for this model. A negative trend between BMI and dementia was present but did not reach statistical significance. A negative association between waist circumference and diagnosis of dementia was noted, with an estimated odds ratio (OR) of 0.82 (p=0.07) per 5 kg/m² increase in BMI. Results were similar (OR=0.80, p=0.048) after adjusting for co-

variables related to diabetes status, other medical factors, socioeconomic factors, lifestyle factors and genetic factors.

To give an overview of the incidence of overall mortality and diagnosis of dementia over time, the results of survival analysis for all-cause mortality or incident dementia using Kaplan-Meier method are shown in table 4.2.3.2. A trend of higher overall mortality was present for every unit increase in BMI, WC and WHR, with results for WC and WHR reaching statistical significance (BMI: HR=1.08, $p=0.13$ per 5 kg/m² increase; WC: HR=1.07, $p<0.01$ per 5 cm increase; WHR: 1.11, $p<0.01$ per 0.05 increase). Overall mortality was also higher in higher obesity groups for all three variables. However, only results for the 4th quantile of WC and WHR reached statistical significance.

For dementia free survival, higher BMI and WHR were significantly associated with lower incidence of dementia (BMI: HR=0.78, $p=0.01$ per 5 kg/m² increase, WHR: HR=1.15, $p=0.03$). When grouped, statistical significance was only present for BMI (compared to normal weight, overweight: HR=0.53, $p=0.02$; class I obese: HR=0.51, $p=0.02$; class II or III obese: HR=0.35, $p<0.01$). The trend was inconsistent and not statistically significant for WC, with the lowest risk noted in the third quantile group.

When survival models were performed using the two major types of dementia as the outcome variable (Table 4.2.3.2), both BMI and WC were significantly and negatively associated with Alzheimer's Disease (AD) while WHR was positively associated with vascular dementia (VD). However, the sample size of the two sub-groups of people with dementia who could be most accurately assigned to either AD or VD was very small (only 25 events in each of AD, VD), resulting in very large confidence intervals for the hazard ratios. These results should therefore be treated with the utmost caution.

Table 4.2.3.2 Hazard ratios in all-cause mortality or incident dementia according to different obesity groups using Kaplan-Meier method

	Sample size	Death (n=318)	Dementia (n=102)	AD (n=25)	VD (n=25)
Body Mass Index (WHO classification)					
per 5 kg/m ² increase		1.08 (0.13)	0.78 (0.01) *	0.51 (<0.01) **	1 (1)
Normal	104				
Overweight	363	0.93 (0.72)	0.53 (0.02) *	0.57 (0.25)	0.22 (0.01) *
Obese I	352	1.06 (0.77)	0.51 (0.02) *	0.19 (0.01) *	0.28 (0.03) *
Obese II/III	244	1.14 (0.54)	0.35 (<0.01) *	0.14 (0.01) *	0.48 (0.19)
Waist Circumference (Quantiles)					
per 5 cm increase		1.07 (<0.01) **	0.94 (0.1)	0.82 (0.02) *	1.07 (0.35)
Q1	265				
Q2	262	0.87 (0.41)	0.87 (0.58)	0.67 (0.42)	0.96 (0.95)
Q3	266	1.11 (0.53)	0.70 (0.18)	0.58 (0.3)	0.48 (0.30)
Q4	267	1.52 (0.01)	0.71 (0.22)	0.22 (0.05) *	1.60 (0.38)
Waist Hip Ratio (Quantiles)					
per 0.05 increase		1.11 (0.01) *	1.15 (0.03) *	0.97 (0.84)	1.63 (<0.01) **
Q1	263				
Q2	267	0.93 (0.68)	0.97 (0.96)	0.97 (0.96)	0.97 (0.97)
Q3	265	1.00 (0.99)	1.32 (0.61)	1.32 (0.61)	2.32 (0.22)
Q4	265	1.37 (0.04) *	0.90 (0.86)	0.90 (0.86)	3.87 (0.04) *

Values are hazard ratio (p-value). HR of physiological groups are relative to the first group (Normal for BMI, Q1 for waist and WHR)

HR: Hazard Ratio; *, <0.05, **, <0.01

Estimated cumulative incidence analyses were performed with cox-proportional hazard function and competing risk sub-distribution hazard function. The results are shown in table 4.2.3.3 and figure 4.2.3.1. Death was taken into consideration as a censored competing risk in the competing risk model. Age and sex were included as covariables.

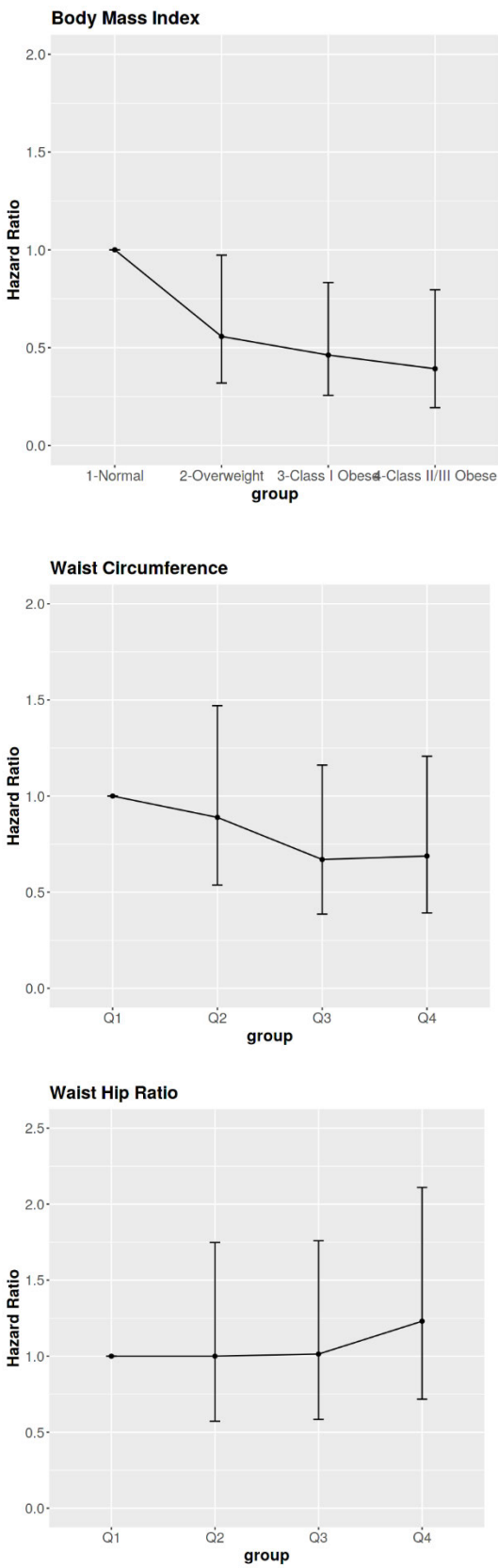
Table 4.2.3.3 Cumulative risk of dementia according to obesity related physiological factors with competing risks considered

	Population (%)	HR (Cox PH multivariable) (p-value)	HR (competing risks multivariable) (p-value)
Body Mass Index (WHO classifications)			
per 5 increase		0.83 (0.67-1.02, p=0.077)	0.81 (0.65-1.00, p=0.055)
Normal	98 (9.7)	1	1
Overweight	346 (34.1)	0.54 (0.31-0.93, p=0.027) *	0.56 (0.32-0.98, p=0.041) *
Obesity I	338 (33.3)	0.48 (0.27-0.85, p=0.012) *	0.46 (0.26-0.84, p=0.011) *
Obesity II / III	233 (23.0)	0.42 (0.21-0.83, p=0.013) *	0.39 (0.19-0.80, p=0.010) *
Waist Circumference (quantiles)			
per 5 cm increase		0.93 (0.85-1.01, p=0.080)	0.91 (0.83-0.99, p=0.036)
Q1	245 (24.1)	1	1
Q2	257 (25.3)	0.89 (0.54-1.48, p=0.657)	0.89 (0.54-1.47, p=0.650)
Q3	260 (25.6)	0.69 (0.40-1.20, p=0.191)	0.67 (0.39-1.17, p=0.160)
Q4	254 (25.0)	0.80 (0.45-1.40, p=0.434)	0.69 (0.39-1.21, p=0.190)
Waist Hip Ratio (quantiles)			
per 0.05 increase		1.10 (0.94-1.28, p=0.221)	1.08 (0.92-1.27, p=0.360)
Q1	254 (25.0)	1	1
Q2	254 (25.0)	0.96 (0.55-1.68, p=0.877)	1.00 (0.57-1.75, p=1.000)
Q3	256 (25.2)	1.00 (0.58-1.75, p=0.988)	1.02 (0.59-1.76, p=0.960)
Q4	252 (24.8)	1.28 (0.75-2.20, p=0.365)	1.23 (0.72-2.12, p=0.450)

Cox PH multivariable: Cox proportional hazard multivariable model

HR: Hazard Ratio; *, <0.05, **, <0.01

Figure 4.2.3.1 Hazard ratio of dementia incidence according to baseline obesity related physiological factors with competing risks considered



In the competing risk model, a negative and consistent association between risk of dementia and obesity assessed by BMI was present. The trend was not statistically significant in the model incorporating BMI as a continuous variable but was when considering groups of overweight or obesity compared to normal weight (compared to normal weight, overweight: HR=0.55, p=0.037; class I obese: HR=0.46, p=0.010; class II or III obese: HR=0.40, p=0.012). The negative trend was also present for WC but was not statistically significant. In the WHR quantile groups, the highest risk fell in the highest quantile group. However, the difference was very small and was not statistically significant. There was no obvious U shape distribution of dementia risk for any of the three variables. The negative trend of higher BMI associated with lower HR for dementia was most obvious between normal and overweight groups, with only slightly lower HR in class I or class II/III obesity groups compared to the overweight group.

Similar models were performed with AD and VD as outcome variables. The trend was similar to that described for the Kaplan Meier method, with the same uncertainty due to very small sample sizes (see [appendix table 5](#)).

In summary, a negative relationship was found between BMI and incident dementia. The findings were consistent in different models and the associations were generally linear when grouping methods were used. Although the sample size was small, this relationship seemed to be more obvious in outcome of AD. A similar trend was present for WC but was less evident. An association between WHR and incident dementia was neither obvious nor consistent.

4.3 Relationship between Changes in Obesity-Related Physiological Factors and Dementia

This section focuses on the changes in body weight and waist circumference from baseline to year four and their relationship with incident dementia (from year four to ten). It starts with a description of the demographics, obesity related factors and other variables in the population who returned for assessment at the year 4 research clinic and for whom it was therefore possible to derive a measure of change in obesity-related variables by this time-point. The distribution of BMI and WC at

baseline and year four in this sub-population is described, followed by a description of change variables used in further analysis. A similar statistical approach to that used in section two was subsequently used to assess the association between the change variables and incident dementia.

4.3.1 Characteristics of the population with data on BMI and WC in year 4 follow-up

Table 4.3.1.1 shows the baseline characteristics of the 825 participants who came to the follow up clinic at year 4 and had data on at least one obesity-related variable, in comparison with the total population. There were no major differences in the variables of interest, including basic demographics, status of T2DM, other underlying diseases, lifestyle, and genetic factors. The baseline obesity-related factors were also not greatly different. The 825 participants were used in subsequent analysis regarding change variables.

Table 4.3.1.2 presents the characteristics and distribution of obesity related physiological factors at baseline and year four in the sub-population with data on BMI and WC in year four. BMI stratified classification rather than WHO classification was used for waist circumference because it was proposed to be a new approach to central obesity, with BMI considered, and the ET2DS population had an overall high BMI. Mean BMI at baseline and year four was not significantly different. The central obesity measures, including waist circumference and WHR were slightly but significantly lower at year four.

Table 4.3.1.1 Baseline characteristics of all participants (n=1066) and those with Year 4 obesity-related data (n=825)

	All participants (n=1066) Mean $\pm$ sd, median (Q1, Q3) or %(n)	Participants with year 4 follow up data (n=825) Mean $\pm$ sd, median (Q1, Q3) or %(n)	P-value
Demographics			
Age (years)	67.91 $\pm$ 4.2	67.69 $\pm$ 4.16	0.25
Sex			0.97
Male	51 (547)	52 (425)	
Female	50 (519)	49 (400)	
Highest education attainment			0.84
Primary school	1 (7)	1 (5)	
Secondary school	55 (581)	53 (439)	
Other qualification	29 (307)	29 (236)	
University/college	16 (171)	18 (145)	
SIMD Quintile			0.50
1	12 (127)	12 (98)	
2	20 (208)	17 (142)	
3	18 (188)	17 (140)	
4	18 (194)	18 (145)	
5	33 (349)	36 (300)	
Status of Diabetes			
Duration of diabetes (years)	8.06 $\pm$ 6.47	7.94 $\pm$ 6.4	0.71
Hba1c (%)	7.41 $\pm$ 1.13	7.4 $\pm$ 1.13	0.86
Treatment of diabetes			0.84
Diet-controlled	19 (198)	19 (160)	
Oral medication	64 (681)	64 (527)	
Insulin injections	17 (186)	17 (137)	
Obesity-related physiological measurements			
Height	166 $\pm$ 9.20	166.22 $\pm$ 8.93	0.60
Weight	86.48 $\pm$ 16.17	86.26 $\pm$ 16.01	0.77
BMI	31.43 $\pm$ 5.69	31.27 $\pm$ 5.59	0.53
Waist Circumference	106.91 $\pm$ 12.82	106.52 $\pm$ 12.56	0.51

Hip Circumference	110.89 ± 11.99	110.58 ± 11.78	0.57
Waist Hip Ratio	0.97 ± 0.08	0.96 ± 0.07	0.84
Other metabolic risk factors			
Systolic blood pressure (mmHg)	133.3 ± 16.4	132.5 ± 15.9	0.28
Diastolic blood pressure	69.1 ± 9.0	68.9 ± 8.9	0.78
Hypertensive status *			0.38
No	67 (556)	65 (697)	
Yes	32 (267)	34 (367)	
Hypertensive treatment			0.38
No	17 (140)	17 (186)	
Yes	82 (680)	82 (873)	
Total cholesterol (mmol/L)	4.31 ± 0.9	4.34 ± 0.9	0.48
High density lipoprotein	1.29 ± 0.36	1.29 ± 0.36	0.88
Hyperlipidemia status *			0.87
No	79 (653)	79 (846)	
Yes	20 (167)	20 (211)	
Lipid modification treatment			0.71
No	14 (112)	14 (152)	
Yes	86 (713)	86 (912)	
Medical history			
Cardiovascular diseases *			0.23
No	50 (532)	53 (435)	
Yes	50 (530)	47 (386)	
Stroke			0.56
No	94 (1004)	95 (783)	
Yes	6 (62)	5 (42)	
Hypoglycemic attack			0.43
No	87 (929)	89 (733)	
Yes	11 (113)	9 (78)	
Hypoglycemic attack (times)			0.52
1-2 times	6 (59)	5 (43)	
3-4 times	3 (28)	3 (21)	
More than 5 times	3 (27)	2 (13)	

Lifestyle factors			
Smoker			0.64
Current	39 (414)	40 (333)	
Former	47 (498)	47 (384)	
Never	14 (154)	13 (108)	
Number of Cigarettes / day	15 (10, 20)	15 (8, 20)	0.42
Currently Drinking			0.15
No	19 (205)	17 (137)	
Yes	80 (856)	83 (686)	
Total Units of Alcohol/ week	5.2 (0, 15)	6 (0, 16.48)	0.74
Genetic factor			
Apolipoprotein E (APOE)			0.88
ε2/ε2 or ε2/ε3 or ε3/ε3	70 (744)	71 (584)	
ε2/ε4 or ε3/ε4	24 (259)	24 (194)	
ε4/ε4	2 (20)	2 (17)	

Values are median and 1st and 3rd quantile for Number of Cigarettes per day and Total Units of Alcohol per week

P-value of total units of alcohol per week is performed by t test of log total units of alcohol per week added 1; P-value of number of cigarettes per day is performed by t test of squared rooted number of cigarettes per day

SIMD: Scottish Index of Multiple Deprivation 2006 (quintile 1 is most deprived)

* Hypertensive status is defined as systolic blood pressure <140 mmHg and/or diastolic blood pressure < 90 mmHg

* Hyperlipidemia status is defined as total cholesterol < 5 mmol/L

* Cardiovascular disease includes established history of intermittent claudication, myocardial infarction, angina, transient ischaemic attack, coronary or peripheral artery intervention or ankle brachial pressure index below 0.9

Significance note: *, p<0.05, **, p<0.01

Table 4.3.1.2 Obesity related physiological factors and obesity groups at baseline and Year 4 in the sub-population with obesity-related data at year 4 (n=825)

	Baseline mean $\pm$ sd or % (n)	Year 4 mean $\pm$ sd or % (n)	p-value
Body mass index (BMI) (kg/m ²)	31.27 $\pm$ 5.59	31.45 $\pm$ 5.74	0.52
WHO classification			0.61
Underweight	0 (1)		
Normal	9 (78)	9 (77)	
Overweight	36 (297)	37 (305)	
Class I Obesity	33 (273)	30 (248)	
Class II or III Obesity	21 (176)	23 (190)	
Waist circumference (cm)	106.52 $\pm$ 12.56	105.73 $\pm$ 13.12	0.21
BMI stratified classification			<0.01 **
Not Central Obese	33 (271)	40 (329)	
Central Obese	67 (552)	59 (489)	
Waist hip ratio	0.96 $\pm$ 0.07	0.95 $\pm$ 0.08	0.01 *
WHO classification			<0.01 **
Not Central Obese	9 (73)	11 (94)	
Central Obese	91 (750)	88 (729)	

WHO: World Health Organization; Significance note: *, p<0.05, **, p<0.01

4.3.2 Change in obesity-related variables and their categorization into Groups

This section presents categorization of changes in body weight and waist circumference and their association with baseline obesity-related physiological factors and other population characteristics.

Table 4.3.2.1 describes body weight (BW) and waist circumference (WC) changes, including by groups used in subsequent analysis. The rationale for grouping was described in the methods chapter. The proportion of the population in each group is also shown.

As describe in the method chapter, the cut point of 5% for BW change and 5 cm for WC change were selected according to previous literature and the distribution of such values in the ET2DS population. The majority of the population (according to

the selected definition of stable), maintained a stable body weight and waist circumference from baseline to year four (63% stable BW, 58% stable WC). Only 16% of the population experienced a major BW loss, while 24% experienced a major decrease in WC.

Table 4.3.2.1 Percentage weight change and waist circumference change in the population with year 4 obesity-related data (n=825) including by weight change groups

Variable	Definition	mean $\pm$ sd or % (n)
Body weight change	Year 4 - baseline	0.2 $\pm$ 5.83
Percentage weight change	(Year 4 – baseline) / baseline * 100%	0.35 $\pm$ 6.84
Weight change groups		
Major weight loss	Over 5% weight loss	16 (135)
Stable body weight	Less than 5% change	63 (516)
Major weight gain	Over 5% weight gain	20 (169)
Waist circumference change	Year 4 - baseline	-0.77 $\pm$ 6.61
Waist change groups		
Major waist decrease	Over 5cm decrease	24 (194)
Stable waist circumference	Less than 5cm change	58 (482)
Major waist increase	Over 5 cm increase	17 (140)

Table 4.3.2.2 Inter-correlations between obesity related physiological factors AT baseline, year four and the changes in between (n=825)

Variables at baseline	BW Change	WC Change
Body weight (BW)	-0.079*	-0.029
Body Mass Index (BMI)	-0.113**	-0.094**
Waist Circumference (WC)	-0.06	-0.172****
Waist Hip Ratio (WHR)	0.016	-0.100**

Values are p(Rho) in Pearson correlation; BW change: body weight change (Year 4 BW – baseline BW); WC change: waist circumference change (Year 4 WC – baseline WC); Significance note: *, p<0.05, **, p<0.01, ***, p<0.001. ****, p<0.0001

Table 4.3.2.2 shows the association between baseline obesity-related variables and BW change or WC change. BW change was negatively correlated with BMI at

baseline, but not with WC or WHR. WC change, on the other hand, was negatively correlated with baseline BMI, WC and WHR.

The associations between baseline characteristics of the study population and both BW change and WC change are presented in table 4.3.2.3. Male participants had a significantly larger percentage weight loss compared to female (mean BW loss in males, -1.50 ± 6.97 % versus females, -0.10 ± 6.18 %). Participants with a history of cardiovascular disease experienced a greater decrease in WC (mean WC change, -1.3 ± 7.2 cm versus -0.3 ± 6.0 cm, $p=0.041$). Participants who did not have an alcohol drinking habit also experienced a more obvious percentage weight loss compared to those who did (mean $\pm$ SD, -2.05 ± 7.80 % versus -0.53 ± 6.28 %), with a positive correlation between the amount of drinking and weight gain ($Rho=0.11$, $p=0.001$). There were no statistically significant associations with other demographic characteristics.

The baseline characteristics in different weight change or waist circumference groups are shown in the appendix ([appendix table 6](#), [appendix table 7](#)). In general, the trends were consistent with those using continuous variables of change. There were more females in the major weight loss group (41% of males experienced a major weight loss versus 59% of females, $p=0.02$). Participants with stable body weight had a lower proportion requiring insulin injections (14% in stable group, compared to 22% in weight increase group and 19% in decrease group, $p=0.02$). The stable body weight group also had a higher proportion only treated by diet (22% in stable group, compared to 14% in weight increase group and 16% in weight decrease group, $p=0.02$). People who underwent major weight loss had higher initial measures of overweight/obesity, including BMI (mean BMI 32.95 ± 5.98 kg/m² in weight decrease group, compared to 30.88 ± 5.06 kg/m² in stable group and 30.92 ± 6.44 kg/m² in increase group, $p=0.03$) and WC (mean WC 108.9 ± 12.6 in weight decrease group, compared to 105.9 ± 11.8 in stable group and 106.1 ± 14.1 in increase group, $p<0.01$). Mean WHR at baseline was higher in the stable weight group (0.97 ± 0.07 compared to 0.96 ± 0.07 in the increase group and 0.96 ± 0.08 in the decrease group, $p=0.02$). There were less people who reported an alcohol drinking habit in those who experienced a major body weight loss during follow up (76% reported a current

drinking habit in BW loss group, compared to 83% in the increase group and 85% in the stable group, $p=0.03$).

The characteristics were similar when grouped according to waist circumference change status. The people whose waist circumference had changed by year four were more likely to be female, had higher baseline BMI, waist circumference or hip circumference, and had a higher alcohol consumption.

Table 4.3.2.3 Association between baseline characteristics and change in obesity related variables (n=825)

		Percentage Body weight change (%)		Waist circumference change (cm)	
	n	rho / mean ± sd	p-value	rho / mean ± sd	p-value
Demographics					
Age (years)		-0.039	0.269	-0.025	0.466
Sex			0.106		0.002 **
Male	425	0.73 ± 5.97		-0.10 ± 6.18	
Female	400	-0.05 ± 7.64		-1.50 ± 6.97	
Education			0.312		0.747
Primary school	5	-0.33 ± 3.82		-1.67 ± 5.97	
Secondary school	439	0.61 ± 7.30		-0.87 ± 6.71	
Other qualification	236	-0.35 ± 6.29		-0.92 ± 6.60	
University/college	145	0.73 ± 6.24		-0.24 ± 6.37	
SIMD Quintile			0.78		0.583
1	98	0.25 ± 6.99		-0.46 ± 6.02	
2	142	0.58 ± 7.68		-1.58 ± 6.94	
3	140	0.84 ± 6.75		-0.45 ± 6.79	
4	145	0.47 ± 7.11		-0.55 ± 7.11	
5	300	-0.01 ± 6.28		-0.75 ± 6.29	
Status of Diabetes					
HbA1c (%)		0.010	0.781	-0.012	0.742
Duration of Diabetes (years)		0.021	0.546	0.022	0.539
Treatment of Diabetes			0.276		0.904
Diet-controlled	160	0.00 ± 5.61		-0.69 ± 5.90	
Oral medication	527	0.25 ± 7.1		-0.85 ± 6.88	
Insulin injections	137	1.19 ± 7.11		-0.59 ± 6.38	

Other metabolic risk factors					
Systolic blood pressure (mmHg)		0.031	0.372	0.015	0.678
Diastolic blood pressure (mmHg)		0.026	0.458	0.053	0.132
Hypertensive status *			0.596		0.700
No	556	0.27 ± 6.54		-0.83 ± 6.69	
Yes	267	0.56 ± 7.43		-0.64 ± 6.45	
Hypertensive treatment			0.406		0.640
No	140	-0.08 ± 6.44		-0.56 ± 6.47	
Yes	680	0.43 ± 6.94		-0.84 ± 6.65	
Total cholesterol (mmol/L)		0.045	0.195	0.014	0.688
High density lipoprotein (mmol/L)		-0.009	0.809	-0.030	0.392
Hyperlipidemia status *			0.155		0.716
No	653	0.17 ± 6.9		-0.80 ± 6.62	
Yes	167	1.00 ± 6.63		-0.60 ± 6.60	
Lipid modification treatment			0.581		0.302
No	112	0.02 ± 6.71		-1.33 ± 5.95	
Yes	713	0.40 ± 6.86		-0.69 ± 6.70	
Medical history					
Cardiovascular disease *			0.126		0.041*
No	435	0.69 ± 5.95		-0.33 ± 6.01	
Yes	386	-0.06 ± 7.73		-1.29 ± 7.22	
Stroke			0.93		0.553
No	783	0.35 ± 6.82		-0.74 ± 6.57	
Yes	42	0.45 ± 7.21		-1.43 ± 7.36	
Hypoglycemic attack			0.442		0.541
No	733	0.42 ± 6.91		-0.72 ± 6.59	
Yes	78	-0.15 ± 6.10		-1.20 ± 6.53	
Hypoglycemic attack (times)			0.22		0.462
1-2 times	43	-1.07 ± 5.53		-2.08 ± 6.82	
3-4 times	21	0.13 ± 6.21		-0.72 ± 5.55	
more than 5 times	13	2.27 ± 7.58		0.3 ± 6.92	
Lifestyle factors					
Smoker			0.09		0.071
Never	333	-0.28 ± 6.66		-1.39 ± 6.57	
Former	384	0.73 ± 6.50		-0.25 ± 6.70	
Current	108	0.96 ± 8.33		-0.72 ± 6.28	

Number of Cigarettes / day		-0.035	0.723	0.039	0.686
Currently Drinking			0.319		0.038 *
No	137	-0.34 ± 9.13		-2.05 ± 8.00	
Yes	686	0.49 ± 6.30		-0.53 ± 6.28	
Total Units of Alcohol/ week		0.054	0.159	0.11	0.004 **
Genetic factor					
Apolipoprotein E (APOE)			0.627		0.944
ε2/ε2 or ε2/ε3 or ε3/ε3	584	0.44 ± 6.48		-0.69 ± 6.45	
ε2/ε4 or ε3/ε4	194	0.22 ± 7.92		-0.73 ± 7.04	
ε4/ε4	17	1.89 ± 8.14		-1.23 ± 5.43	

Values are median and 1st and 3rd quantile for Number of Cigarettes per day and Total Units of Alcohol per week

P-value of total units of alcohol per week is performed by t test of log total units of alcohol per week added 1; P-value of number of cigarettes per day is performed by t test of squared rooted number of cigarettes per day

SIMD: Scottish Index of Multiple Deprivation 2006 (quintile 1 is most deprived)

* Hypertensive status is defined as systolic blood pressure <140 mmHg and/or diastolic blood pressure < 90 mmHg

* Hyperlipidemia status is defined as total cholesterol < 5 mmol/L

* Cardiovascular disease includes established history of intermittent claudication, myocardial infarction, angina, transient ischaemic attack, coronary or peripheral artery intervention or ankle brachial pressure index below 0.9

Significance note: *, p<0.05, **, p<0.01

4.3.3 Relationship between change in obesity related physiological factors and diagnosis of dementia

In this section, I will briefly describe the associations of all-cause mortality and incident dementia with changes in obesity-related variables. Then I will focus on the findings from the statistical models investigating the relationship between changes in BW or WC and incident dementia.

For the purposes of the analyses on the change in physiological variables before the established diagnosis of dementia, four people who were diagnosed with dementia before year four follow up were excluded. This left 78 cases of incident dementia and 743 people without dementia included in subsequent analysis.

Table 4.3.3.1 Changes in obesity related physiological factors according to all-cause mortality (n=176) and incident dementia (n=78)

	Live (n=645)	Death (n=176)	p-value	No dementia (n = 743)	Dementia (n=78)	p-value
Percentage BW change	0.45 ± 6.74	-0.31 ± 7.16	0.34	0.46 ± 6.62	-0.99 ± 8.53	0.15
Major weight loss	15 (97)	22 (38)	0.09	15 (113)	28 (22)	0.01 *
Stable body weight	64 (415)	57 (100)		63 (468)	60 (47)	
Major weight gain	20 (130)	20 (36)		21 (157)	12 (9)	
WC change	-0.76 ± 6.51	-0.85 ± 6.90	0.87	-0.69 ± 6.56	-1.62 ± 6.86	0.25
Major waist decrease	24 (152)	23 (41)	0.91	24 (178)	19 (15)	0.24
Stable waist	59 (381)	56 (99)		57 (427)	68 (53)	
Major waist increase	17 (108)	18 (31)		17 (129)	13 (10)	

BW: body weight; WC: waist circumference; Significance note: *, <0.05

In the ET2DS population with data on obesity-related variables at both baseline and year 4 (n=825), 176 people had died by year 10 and 78 were diagnosed with dementia. Body weight and WC change according to all-cause mortality and incident dementia are presented in table 4.3.3.1. The mean percentage weight change and waist circumference change did not differ between participants who had died and those who were still alive by year 10. There were a higher proportion of people who experienced a major weight loss in the dementia group compared to the non-dementia group (28% in dementia group versus 15% in non-dementia group, p=0.01).

The baseline characteristics of people who had or had not been diagnosed with dementia by year 10 for the population with weight change data, are shown in the appendix ([appendix table 8](#)). Similar to findings in the whole population ([table 4.2.1.1](#)), the subjects with incident dementia had an older mean age, had lower mean BMI at baseline and had a higher prevalence of APOE-ε4 gene.

Table 4.3.3.2 Odds ratio of dementia associated with change in obesity related physiological factors

Continuous values (including decrease and increase)				
	Body weight increase		waist circumference increase	
Co-variables included	OR (95% CI)	p-value	OR (95% CI)	p-value
BW change + age + sex	0.85 (0.71-1.02)	0.08	0.89 (0.75-1.07)	0.20
_ + diabetes status	0.85 (0.71-1.02)	0.08	0.90 (0.75-1.08)	0.26
_ + other medical factors	0.87 (0.73-1.04)	0.14	0.91 (0.76-1.10)	0.34
_ + socioeconomic factors	0.87 (0.72-1.04)	0.13	0.92 (0.76-1.10)	0.32
_ + lifestyle factors	0.87 (0.73-1.05)	0.15	0.93 (0.77-1.12)	0.41
_ + genetic factors	0.91 (0.76-1.09)	0.34	0.99 (0.82-1.21)	0.95
_ + baseline BMI or WC	0.91 (0.75-1.09)	0.30	0.97 (0.80-1.19)	0.77
Absolute values of amount of change				
	Body weight change		waist circumference change	
Coefficients	OR (95% CI)	p-value	OR (95% CI)	p-value
WC change + age + sex	1.10 (0.87-1.36)	0.39	0.97 (0.72-1.27)	0.85
_ + diabetes status	1.10 (0.86-1.36)	0.43	0.96 (0.71-1.26)	0.78
_ + other medical factors	1.08 (0.84-1.35)	0.51	0.94 (0.69-1.25)	0.70
_ + socioeconomic factors	1.08 (0.84-1.35)	0.52	0.95 (0.70-1.25)	0.71
_ + lifestyle factors	1.09 (0.85-1.36)	0.48	0.94 (0.69-1.24)	0.69
_ + genetic factors	0.97 (0.73-1.24)	0.83	0.80 (0.56-1.10)	0.20
_ + baseline BMI or WC	0.97 (0.73-1.24)	0.83	0.81 (0.57-1.12)	0.23

Values are estimated change of odds ratio by (1) every 5% increase in body weight (2) every 5 cm increase in waist circumference (3) absolute value of (1) or every 5% change in body weight (4) absolute value of (2) or every 5 cm change in waist circumference. The model is performed with logistic regression.

diabetes status: Baseline HbA1c, history of hypoglycemic episodes

other medical factors: history of stroke, history of cardiovascular diseases, systolic blood pressure, total cholesterol

Socioeconomic: education attainment, Scottish Index of Multiple Deprivation (SIMD)

Lifestyle factors: Smoker, alcohol drinker

Genetic factor: Apolipoprotein E (APOE) genotype

BW: body weight; BMI: body mass index; WC: waist circumference

In logistic regression models (table 4.3.3.2), there were no statistically significant associations of either BW or WC with dementia. I did the same analysis with the absolute amount of change, regardless of increase or decrease, and there were no obvious V shape associations.

Results from the initial overview of all-cause mortality or incident dementia according to change in BW or WC, undertaken using Kaplan-Meier method, are shown in table 4.3.3.3. The stable BW group had a lower incidence of all-cause mortality compared to the major weight loss group (HR=0.66, p=0.03). There was no statistically significant trend in risk of death according to change in WC. The incidence of dementia was lower in the major BW gain group (HR=0.30, p<0.01), as well as the stable BW group (HR=0.30, p<0.01) compared to the major BW loss group. The risk of incident dementia appeared higher in the stable WC group but this did not reach statistical significance.

Table 4.3.3.3 Hazard ratios in all-cause mortality or incident dementia according to changes in obesity related physiological factors using Kaplan Meier method

	Death (n= 815, number of events=		Dementia (n= 815, number of events=	
	HR	p value	HR	p value
BW (per 5% increase)	0.94	0.28	0.84	0.04 *
Major weight loss (n=133)	1	-	1	-
Stable body weight (n=510)	0.66	0.03 *	0.51	0.01 *
Major weight gain (n=163)	0.74	0.20	0.30	<0.01 *
WC (per 5 cm increase)	0.98	0.78	0.90	0.21
Major WC decrease (n=191)	1	-	1	-
Stable WC (n=478)	0.94	0.76	1.42	0.23
Major WC increase (n=137)	1.03	0.90	0.91	0.81

BW: body weight; WC: waist circumference; HR: Hazard Ratio; significance note: *, <0.05

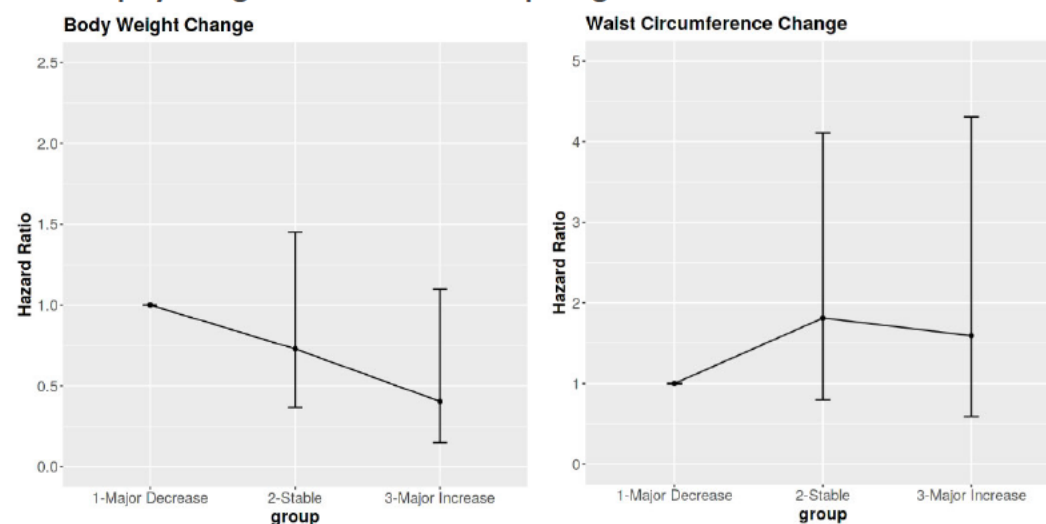
Table 4.3.3.4 Cumulative risk of dementia (n=78) according to change in physiological factors with competing risks considered

	n (%)	HR (Cox PH multivariable)	HR (competing risks multivariable)
Body weight			
Per 5% body weight increase		0.84 (0.71-1.00, p=0.048) *	0.92 (0.68-1.24, p=0.590)
Body weight change			
Major weight loss	133 (16.5)	1	1
Stable body weight	510 (63.3)	0.46 (0.28-0.77, p=0.003) **	0.66 (0.34-1.29, p=0.230)
Major weight gain	163 (20.2)	0.29 (0.13-0.63, p=0.002) **	0.38 (0.14-1.03, p=0.057)
Waist circumference			
Per 5 cm waist increase		0.89 (0.76-1.06, p=0.194)	0.98 (0.78-1.24, p=0.900)
Waist circumference change			
Major WC decrease	191 (23.7)	1	1
Stable waist circumference	478 (59.3)	1.36 (0.77-2.42, p=0.294)	1.65 (0.76-3.59, p=0.200)
Major WC increase	137 (17.0)	0.87 (0.39-1.94, p=0.737)	1.49 (0.57-3.89, p=0.410)

HR: Hazard Ratio, Cox PH multivariable: Cox proportional hazard multivariable model

Values are adjusted with age and sex, WC: waist circumference, significance note: *, <0.05, **, <0.01

Figure 4.3.3.1 Hazard ratio of dementia incidence according to change in obesity related physiological factors with competing risks considered



Values are hazard ratio from competing risks multivariable model

Values are adjusted with age and sex

As shown in table 4.3.3.4 and figure 4.3.3.1, the cumulative incidence of dementia was further estimated with the cox-proportional hazard (Cox PH) function and the competing risk sub-distribution hazard function. Age and sex were adjusted in this model. No statistically significant associations were found when using BW change or WC change as continuous co-variates. When using the grouping methods for change variables, a different trend of the effect on risk of dementia was found, with BW increase associated with lower risk of dementia, while WC increase was associated with higher risk. The hazard ratio for major BW gain compared to BW loss was borderline significant (HR=0.38, $p=0.057$). A higher hazard ratio was observed for stable WC or WC increase when compared to WC decrease (stable: HR=1.65, $p=0.200$; increase: HR=1.49, $p=0.410$). However, due to the inconsistent trend and wide confidence intervals, this finding was far from conclusive.

The same survival models using Cox PH and sub-distribution hazard function were performed with inclusion of other covariates, aimed at identifying further explanatory factors for the relationship between weight or waist change and dementia. In these models, the selected baseline variables as mentioned in the methods section were included as covariates, which included HbA1c, history of hypoglycemic episodes, history of stroke, history of cardiovascular diseases, systolic blood pressure, total cholesterol, education attainment, Scottish Index of Multiple Deprivation (SIMD), smoker, alcohol drinker and Apolipoprotein E (APOE) genotype. Additionally, baseline BMI was used as covariate in the weight change model, and baseline waist circumference was used in the waist change model. Baseline BMI and WC were included respectively to reduce the potentially different meanings of changes in individuals with different obesity status.

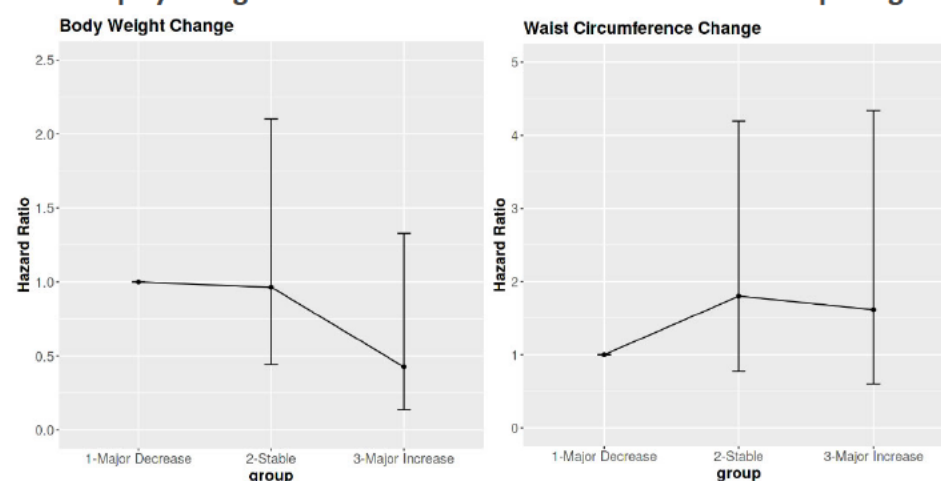
Table 4.3.3.5 Cumulative risk of dementia (n=71) according to change in physiological factors with competing risks and other covariates considered

	n (%)	HR (Cox PH multivariable)	HR (competing risks multivariable)
Body weight			
Per 5% body weight increase		0.97 (0.94-1.01, p=0.155)	0.98 (0.93-1.04, p=0.540)
Body weight change			
Major weight loss	123 (16.3)	1	1
Stable body weight	475 (62.9)	0.55 (0.31-0.98, p=0.043)	0.94 (0.43-2.04, p=0.870)
Major weight gain	157 (20.8)	0.31 (0.14-0.73, p=0.007) **	0.42 (0.13-1.33, p=0.140)
Waist circumference			
Per 5 cm waist increase		1.00 (0.96-1.03, p=0.886)	1.00 (0.95-1.05, p=0.990)
Waist circumference change			
Major decrease	169 (22.6)	1	1
Stable waist circumference	448 (59.9)	2.00 (1.00-4.01, p=0.051)	1.87 (0.82-4.28, p=0.140)
Major increase	131 (17.5)	1.29 (0.53-3.16, p=0.578)	1.70 (0.63-4.58, p=0.300)

HR: Hazard Ratio, Cox PH multivariable: Cox proportional hazard multivariable model,

Values are adjusted with age, sex, baseline HbA1c, history of hypoglycemic episodes, history of stroke, history of cardiovascular diseases, systolic blood pressure, total cholesterol, education attainment, Scottish Index of Multiple Deprivation (SIMD), smoker, alcohol drinker, Apolipoprotein E (APOE) genotype and baseline body mass index for body weight change or baseline waist circumference for waist circumference change, significance note: *, <0.05, **, <0.01

Figure 4.3.3.2 Hazard ratio of dementia incidence according to change in obesity related physiological factors with other covariables and competing risks considered



Values are hazard ratio from competing risks multivariable model.

Values adjusted are identical to that in table 4.3.3.5

The multivariable results are presented in table 4.3.3.5 and figure 4.3.3.2. Complete case analysis was used in this analysis, thus missing data on any of the covariables were excluded. This led to 71 dementia events in total. The different trends in association between dementia risk and both BW change and WC change were still present, similar to findings presented in table 4.3.3.4. Although not significant, the trend was still negative for body weight. The weight gain group had the lowest risk of dementia (when compared to major BW decrease, stable weight: HR=0.94, p=0.87; major increase: HR=0.42, p=0.13) while the difference between stable weight group and weight loss group was not obvious. The groups with stable WC and WC increase had higher HR for dementia but were not conclusive due to very wide confidence intervals.

In summary, in this section, a negative association between BW increase and incident dementia was found. Although not statistically significant in all models, trends were generally consistent. The negative association was linear in the association between weight change and dementia, with weight gain associated with the lowest HR for dementia, followed by stable weight, and weight loss was associated with higher HR for dementia. On the other hand, no significant association between WC change and dementia was found.

In the next section, I will describe my post-hoc analysis. This was done to explore possible reasons for the relationship between BW (and BW change) and incident dementia in relation to possible pre-existing cognitive deficits in people who both develop dementia and those who experience weight loss following such deficits. I describe findings from cognitive testing in the ET2DS population and the association of test results with both obesity-related variables and dementia.

4.4 Association of cognitive test results with obesity-related variables and with incident dementia - post-hoc analysis

In this section, I will start with a brief description of cognitive test results recorded in the ET2DS population. The relationship between cognitive test results and obesity related physiological factors will then be presented, followed by a description of

cognitive performance in people who had or had not been diagnosed with dementia by year ten.

4.4.1 cognitive test Results

The majority of the total ET2DS population received cognitive testing at baseline, as did the majority of those who returned to the year 4 follow up. A total of nine cognitive tests on different cognitive domains were recorded. The general cognitive function 'g' was imputed from the fluid-type cognitive test results and served as a major indicator of each participant's overall cognitive function.

The baseline cognitive test results in the total population and in those who had test results at year four are presented in table 4.4.1.1. Overall, the sub-population who had data on cognitive tests at year 4 had a better mean general cognitive function, 'g', at baseline (0.12 ± 0.93 compared to 0.00 ± 1.00 in the total population). Regarding the individual tests, better average results were obtained by the sub-population with year 4 cognitive data in five out of nine tests. These tests included MHVS (Mill Hill Vocabulary Scale), MMSE (Mini Mental State Exam), TMTB (Trail Making Test B), MR (Matrix Reasoning) and LNS (Letter Number Sequencing).

Table 4.4.1.1 Baseline cognitive tests in the total population (n=1066) and those attending year 4 follow-up clinic (n=825)

	All participants (max n=1063)	Year 4 follow up (max n=824)	p-value
G	0.00 ± 1.00	0.12 ± 0.93	0.007 **
MHVS	30.93 ± 5.23	31.49 ± 5.05	0.020 *
MMSE	28.30 ± 1.89	28.48 ± 1.64	0.030 *
Memory	25.24 ± 8.17	25.90 ± 7.95	0.079
TMTB	104 (81, 138)	101 (79, 132)	0.030 *
Faces	65.82 ± 7.88	66.36 ± 7.66	0.131
MR	12.81 ± 5.28	13.36 ± 5.23	0.025 *
DST	49.21 ± 14.77	50.46 ± 14.36	0.063
BVFT	36.93 ± 12.83	37.78 ± 12.56	0.149
LNS	9.67 ± 2.75	9.94 ± 2.64	0.031 *

Values are mean $\pm$ standard deviation. T test of TMTB is performed with log TMTB.

MHVS, Mill Hill Vocabulary Scale; MMSE, Mini Mental State Exam; LM, Logical Memory; TMTB, Trail Making Test B; MR, Matrix Reasoning; DST, Digit Symbol Test; BVFT, Borkowski Verbal Fluency Test; LNS, Letter Number Sequencing. Significance note: *, $p < 0.05$, **, $p < 0.01$.

Table 4.4.1.2 Inter-Correlations Between Baseline Cognitive Tests

	MHVS	MMSE	Memory	TMTB	Faces	MR	DST	BVFT	LNS
MMSE	0.384								
Memory	0.352	0.286							
TMTB	-0.323	-0.337	-0.248						
Faces	0.229	0.235	0.217	-0.184					
MR	0.448	0.341	0.226	-0.434	0.203				
DST	0.332	0.282	0.217	-0.587	0.218	0.349			
BVFT	0.414	0.298	0.203	-0.363	0.186	0.356	0.363		
LNS	0.360	0.343	0.258	-0.454	0.120	0.366	0.342	0.427	
G	0.549	0.461	0.494	-0.768	0.406	0.662	0.727	0.657	0.679

Values are ρ (Rho) in Pearson correlation. All significance values are < 0.01 .

MHVS, Mill Hill Vocabulary Scale; MMSE, Mini Mental State Exam; LM, Logical Memory; TMTB, Trail Making Test B; MR, Matrix Reasoning; DST, Digit Symbol Test; BVFT, Borkowski Verbal Fluency Test; LNS, Letter Number Sequencing.

The inter-correlations between the cognitive tests at baseline are shown in table 4.4.1.2. All the test results were positively correlated with each other. (Note: In the TMTB test, higher scores indicated poorer performance, so the direction of correlation was also positive.) The high inter-correlations support the representativeness of 'g' to overall cognitive performance.

Each test had a different scale and distribution. The majority of the test results were normally distributed ([appendix table 9](#)). The units for the trail making test B (TMTB) were a measure of the duration of time it took for participants to complete the test, which was a positively skewed distribution, with higher values indicating a worse cognitive function. Log transformation followed by negative transformation was thus computed. Standardizing procedures were then performed for all the cognitive tests, with 0 meaning the mean at baseline, 1 meaning the standard deviation and positive scores indicating better cognitive performance (for instance, a standardized value of 1 indicates the performance was one standard deviation better than the mean of baseline). Table 4.4.1.3 presents the original and standardized values for cognitive

tests at baseline, year 4 and change. The reason for standardization was to visualize the amount and direction of cognitive decline in a more straightforward manner. Standardization for g was not performed due to g being already a standardized derived factor.

Table 4.4.1.3 Cognitive test results in the population with year four cognitive follow-up (n=825), at baseline and year four

	Baseline		Year 4 follow up		Change	p-value
	Original	standardized	Original	standardized	standardized	
G	0.12 ± 0.93	-	0.01 ± 0.97	-	-0.19 ± 1.31	0.021 *
MHVS	31.49 ± 5.05	0 ± 1	30.73 ± 4.94	-0.15 ± 0.98	-0.17 ± 0.47	0.002 **
MMSE	28.48 ± 1.64	0 ± 1	28.34 ± 1.76	-0.08 ± 1.07	-0.09 ± 1.04	0.109
LM	25.90 ± 7.95	0 ± 1	27.28 ± 8.29	0.17 ± 1.04	0.19 ± 0.87	0.001 **
TMTB	113.08 ± 53.14	0 ± 1	122.02 ± 62.69	-0.16 ± 1.06	-0.21 ± 0.78	0.001 **
Faces	66.36 ± 7.66	0 ± 1	69.24 ± 8.45	0.38 ± 1.10	0.37 ± 0.93	<0.001 **
MR	13.36 ± 5.23	0 ± 1	11.59 ± 5.22	-0.34 ± 1.00	-0.34 ± 0.81	<0.001 **
DST	50.46 ± 14.36	0 ± 1	50.26 ± 14.00	-0.01 ± 0.97	-0.04 ± 0.69	0.774
BVFT	37.78 ± 12.56	0 ± 1	36.88 ± 12.78	-0.07 ± 1.02	-0.08 ± 0.62	0.153
LNS	9.94 ± 2.64	0 ± 1	8.94 ± 2.89	-0.38 ± 1.09	-0.4 ± 1.00	<0.001 **

Values are mean ± standard deviation.

Standardized values: Zero means the mean at baseline, one means the standard deviation at baseline, and positive scores indicates better cognitive performance (for instance, a standardized value of 0.5 indicates the performance is one standard deviation better than the mean of baseline).

Change is calculated using standardized test results. P-value is performed with paired T tests on the standardized test results.

Significance note: *, p<0.05, **, p<0.01

MHVS, Mill Hill Vocabulary Scale; MMSE, Mini Mental State Exam; LM, Logical Memory; TMTB, Trail Making Test B; MR, Matrix Reasoning; DST, Digit Symbol Test; BVFT, Borkowski Verbal Fluency Test; LNS, Letter Number Sequencing.

The means for most cognitive tests, including 'g', had significantly declined by year four, with a few exceptions. The changes in mean test scores for MMS, DST and BVFT did not reach statistical significance, while the scores for logical memory and faces had improved.

4.4.2 Relationship between cognitive performance and obesity-related physiological factors

Table 4.4.2.1 demonstrates the association between obesity related factors at baseline and the cognitive test results at baseline, at year four and for change between these different time points, assessed using age and sex adjusted linear regression. The general cognitive factor 'g' at both baseline and year four were negatively associated with the three obesity related factors. However, the changes of g were not associated with either of these factors.

The associations differed between individual tests. There seemed to be associations with WC and WHR in a wider range of tests compared to BMI. All the associations were negative. MR and DST at baseline and year four were negatively associated with all three baseline obesity-related variables, as well as a number of cognitive tests at year 4, including MHVS, MMSE, BVFT and LNS. MHVS and MMSE were associated with WHR at baseline, but not BMI or WC. The changes in MMSE were negatively correlated with baseline WC and WHR (WC: $\beta = -0.036$, $p=0.015$, WHR: $\beta = -0.072$, $p=0.010$), while the changes in LNS were negatively correlated with baseline BMI and WC (BMI: $\beta = -0.110$, $p=0.001$, WC: $\beta = -0.047$, $p=0.001$). The changes of remaining tests were associated with neither of the baseline obesity-related variables.

The associations between cognitive tests and percentage BW change or WC change were performed with sex and age adjusted linear regression, as shown in table 4.4.2.2. The general cognitive status 'g' at baseline was positively correlated with BW change and WC change, indicating that better general cognitive function at baseline was associated with increase in BW or WC from baseline to year 4 (BW change: $\beta=0.061$, $p=0.016$, WC change: $\beta=0.081$, $p=0.003$). However, 'g' at year four or the changes of 'g' from baseline to year four were not associated with BW or WC change.

In terms of the individual cognitive tests, TMTB had strong and consistent associations with the changes in values, both at baseline (BW change: $\beta=0.078$, $p=0.002$, WC change: $\beta=0.093$, $p<0.001$) and year 4 (BW change: $\beta=0.082$,

p=0.002, WC change: beta =0.1115, p<0.001). The changes in TMTB, on the other hand, did not show significant correlations with BW change or WC change. DST and LNS at both baseline and year 4 were also positively associated with WC change, while only DST was associated with percentage BW change at year 4. MHVS at year 4 was also positively associated with WC change at year 4, with a borderline significance.

The cognitive tests according to BW change and WC change groups are shown in appendices, to visualize any non-linearity that might be missed in models using continuous variables ([appendix table 10](#), [appendix table 11](#)). The findings were consistent with those using BW and WC changes as continuous variables. The major BW loss group had the lowest mean 'g' at baseline compared to stable BW or BW increase groups (BW loss, -0.08 ± 0.96 , stable BW, 0.15 ± 0.93 , BW gain 0.22 ± 0.89 , p=0.009). However, no significant difference in 'g' was found between WC change groups. TMTB was the only test whose results significantly differed between BW change groups, with the BW gain group having the best results at baseline (median in BW increase group = 96.5, BW stable = 100.5, BW decrease = 100, p=0.001) and year 4 (median in BW gain group = 103.62, BW stable = 106.68, BW loss = 111.83, p=0.002).

Table 4.4.2.1 Association between baseline obesity related variables and cognitive performance

	n	Body Mass Index (per 5 increase)	Waist Circumference (per 5 cm increase)	Waist Hip Ratio (per 0.05 increase)
Baseline				
G	798	-0.079 (0.014) *	-0.038 (0.008) **	-0.122 (<0.001) **
MHVS	814	-0.060 (0.063)	-0.027 (0.059)	-0.101 (<0.001) **
MMSE	824	-0.036 (0.263)	-0.011 (0.44)	-0.055 (0.040) *
LM	816	0.011 (0.738)	0.015 (0.293)	-0.033 (0.212)
TMTB	817	-0.053 (0.099)	-0.030 (0.030) *	-0.123 (<0.001) **
Faces	821	-0.042 (0.187)	-0.025 (0.068)	-0.059 (0.026) *
MR	816	-0.067 (0.034) *	-0.032 (0.022) *	-0.078 (0.003) **
DST	822	-0.089 (0.005) **	-0.042 (0.002) **	-0.101 (<0.001) **
BVFT	822	-0.053 (0.104)	-0.026 (0.071)	-0.078 (0.004) **

LNS	816	0.017 (0.596)	0.002 (0.872)	-0.050 (0.062)
Year 4				
G	742	-0.101 (0.004) **	-0.054 (0.001) **	-0.069 (0.019) *
MHVS	814	-0.091 (0.004) **	-0.036 (0.010) *	-0.088 (0.001) **
MMSE	818	-0.070 (0.044) *	-0.044 (0.004) **	-0.122 (<0.001) **
LM	815	<0.001 (0.993)	0.007 (0.621)	-0.033 (0.237)
TMTB	796	-0.064 (0.060)	-0.036 (0.014) *	-0.126 (<0.001) **
Faces	817	-0.040 (0.250)	-0.022 (0.146)	-0.036 (0.214)
MR	818	-0.090 (0.005) **	-0.042 (0.003) **	-0.082 (0.002) **
DST	796	-0.119 (<0.001)	-0.059 (<0.001) **	-0.134 (<0.001) **
BVFT	816	-0.083 (0.012) *	-0.043 (0.003) **	-0.091 (0.001) **
LNS	785	-0.093 (0.009) **	-0.046 (0.003) **	-0.101 (0.001) **
Change				
G	731	-0.002 (0.962)	-0.007 (0.751)	0.057 (0.151)
MHVS	804	-0.019 (0.200)	-0.005 (0.456)	0.005 (0.677)
MMSE	818	-0.038 (0.260)	-0.036 (0.015) *	-0.072 (0.010) *
LM	806	-0.021 (0.470)	-0.011 (0.377)	0.001 (0.961)
TMTB	790	-0.006 (0.814)	-0.004 (0.706)	-0.006 (0.778)
Faces	814	0.004 (0.902)	0.002 (0.851)	0.018 (0.482)
MR	810	-0.027 (0.312)	-0.012 (0.313)	-0.006 (0.792)
DST	796	-0.016 (0.489)	-0.011 (0.286)	-0.031 (0.105)
BVFT	813	-0.032 (0.106)	-0.018 (0.037)	-0.017 (0.308)
LNS	777	-0.110 (0.001) **	-0.047 (0.001) **	-0.051 (0.067)

Values are beta (p-value) by linear regression model. Adjusted with age and sex.

Values of cognitive test results are standardized to the mean and standard deviation at baseline.

TMTB are transformed to minus log before standardization. A positive value in beta indicates a positive correlation between both values. (For instance, -0.094 in BMI and MHVS is interpreted as higher BMI is associated with worse performance in MHVS.) G is standardized to all cognitive tests.

Significance note: *, p<0.05, **, p<0.01

MHVS, Mill Hill Vocabulary Scale; MMSE, Mini Mental State Exam; LM, Logical Memory; TMTB, Trail Making Test B; MR, Matrix Reasoning; DST, Digit Symbol Test; BVFT, Borkowski Verbal Fluency Test; LNS, Letter Number Sequencing.

Table 4.4.2.2 Association between body weight or waist circumference change and cognitive performance

	n	Percentage body weight change (per 5 increase)	Waist circumference change (per 5 cm increase)
Baseline			
G	798	0.061 (0.016) *	0.081 (0.003) **
Mill Hill Vocabulary Scale (MHVS)	814	<0.001 (0.992)	0.037 (0.164)
Mini Mental State Exam (MMSE)	824	-0.002 (0.935)	0.014 (0.604)
Logical Memory (LM)	816	0.028 (0.279)	0.034 (0.209)
Trail Making Test B (TMTB)	817	0.078 (0.002) **	0.093 (<0.001) **
Faces	821	-0.008 (0.764)	-0.015 (0.577)
Matrix Reasoning (MR)	816	0.005 (0.850)	0.050 (0.059)
Digit Symbol Test (DST)	822	0.040 (0.111)	0.059 (0.021) *
Borkowski Verbal Fluency Test (BVFT)	822	0.014 (0.574)	0.005 (0.838)
Letter Number Sequencing (LNS)	816	0.027 (0.284)	0.066 (0.013) *
Year 4			
G	742	0.017 (0.559)	0.038 (0.211)
Mill Hill Vocabulary Scale (MHVS)	814	0.013 (0.594)	0.053 (0.043) *
Mini Mental State Exam (MMSE)	818	0.001 (0.966)	0.031 (0.273)
Logical Memory (LM)	815	-0.010 (0.710)	0.042 (0.127)
Trail Making Test B (TMTB)	796	0.082 (0.002) **	0.115 (<0.001) **
Faces	817	0.006 (0.827)	0.009 (0.761)
Matrix Reasoning (MR)	818	0.020 (0.437)	0.036 (0.167)
Digit Symbol Test (DST)	796	0.056 (0.023) *	0.075 (0.003) **
Borkowski Verbal Fluency Test (BVFT)	816	0.016 (0.537)	0.027 (0.320)
Letter Number Sequencing (LNS)	785	0.041 (0.151)	0.075 (0.014) *
Change			
G	731	-0.054 (0.166)	-0.049 (0.234)
Mill Hill Vocabulary Scale (MHVS)	804	0.016 (0.176)	0.022 (0.076)
Mini Mental State Exam (MMSE)	818	0.004 (0.876)	0.018 (0.515)
Logical Memory (LM)	806	-0.026 (0.250)	0.017 (0.475)
Trail Making Test B (TMTB)	790	0.001 (0.956)	0.010 (0.627)

Faces	814	0.010 (0.688)	0.021 (0.397)
Matrix Reasoning (MR)	810	0.012 (0.581)	-0.017 (0.439)
Digit Symbol Test (DST)	796	0.013 (0.461)	0.012 (0.510)
Borkowski Verbal Fluency Test (BVFT)	813	0.001 (0.958)	0.020 (0.219)
Letter Number Sequencing (LNS)	777	0.022 (0.419)	0.009 (0.741)

Values are beta (p-value) by linear regression model. Adjusted with age and sex.

Values of cognitive test results are standardized to the mean and standard deviation at baseline.

TMTB are transformed to minus log before standardization. A positive value in beta indicates a positive correlation between both values. (for instance, -0.094 in BMI and MHVS is interpreted as higher BMI is associated with worse performance in MHVS.) G is standardized to all cognitive tests.

Significance note: *, $p < 0.05$, **, $p < 0.01$

4.4.3 Relationship between cognitive function and incident dementia

Cognitive test results in the dementia and non-dementia groups are shown in [Appendix table 12](#). The general cognitive function 'g' was lower in the dementia group both at baseline and year 4, but not the change in between. Regarding the individual tests, the standardized values of results showed a consistent trend of the people with incident dementia having poorer cognitive functions in all available tests at the two time points. As for the change values, the tests which had a significantly greater decline in the dementia population included MMSE, LM, TMTB, DST and LNS.

Adjusting for age and sex, logistic regression for incident dementia as the outcome variable was performed with explanatory variables defined as cognitive test results at baseline, year ten and the changes in between. As shown in table 4.4.3.1, most cognitive tests at baseline and year 4 were negatively associated with incident dementia. Baseline LM, Faces and MR also had a similar trend but did not reach statistical significance. Regarding the changes in cognitive tests, decline in MMSE, LM, TMTB, DST and LNS were associated with incident dementia.

In summary, the post-hoc analysis explored the association between cognitive function and both obesity-related physiological factors (including weight change) and incident dementia. General cognitive factor 'g' at baseline and year 4 were negatively associated with baseline BMI, WC and WHR. On the other hand, better baseline 'g' was associated with BW gain and WC increase, while change in 'g' was not associated with either BW change or WC change. TMTB, which was an indicator

of executive function, was constantly positively associated with BW gain. As expected, poorer cognitive function measured using the cognitive tests was associated with increased risk of subsequent development of frank dementia.

Table 4.4.3.1 Odds ratios of incident dementia associated with cognitive tests at baseline, year four and change values

	Baseline		Year four		Change	
	beta	p value	beta	p value	beta	p value
G	-0.526	<0.001 **	-0.666	<0.001 **	-0.117	0.227
Mill Hill Vocabulary Scale (MHVS)	-0.282	0.018 *	-0.265	0.037 *	0.058	0.830
Mini Mental State Exam (MMSE)	-0.436	<0.001 **	-0.569	<0.001 **	-0.301	0.008 **
Logical Memory (LM)	-0.215	0.083	-0.648	<0.001 **	-0.527	<0.001 **
Trail Making Test B (TMTB)	-0.490	<0.001 **	-0.616	<0.001 **	-0.422	0.008 **
Faces	-0.208	0.098	-0.267	0.019 *	-0.107	0.407
Matrix Reasoning (MR)	-0.187	0.138	-0.345	0.010 *	-0.196	0.192
Digit Symbol Test (DST)	-0.320	0.015 *	-0.692	<0.001 **	-0.635	0.002 **
Borkowski Verbal Fluency Test (BVFT)	-0.341	0.007 **	-0.414	0.001 **	-0.196	0.318
Letter Number Sequencing (LNS)	-0.509	<0.001 **	-0.684	<0.001 **	-0.334	0.008 **

Values are beta and p-value in logistic regression. Outcome variable was incident dementia, the models were all adjusted with age and sex.

Values of cognitive test results are standardized to the mean and standard deviation at baseline.

TMTB are transformed to minus log before standardization. A positive value in rho indicates a positive correlation between both values (for instance, -0.094 in BMI and MHVS is interpreted as higher BMI is associated with worse performance in MHVS.) G is standardized to all cognitive tests.

Significance note: *, p<0.05, **, p<0.01

Chapter 5: Discussion

In this chapter, I will describe the findings of this thesis, including in comparison with previous studies on similar topics. I will discuss the strengths and also the limitations of the study, including those potentially responsible for sources of chance, bias or confounding which may have affected the observed associations. I will also discuss the possibility of a biological relationship between weight and dementia, including the potential direction of such a relationship (drawing on findings from the post-hoc analysis) and possible underlying mechanisms. Finally, I will make suggestions for further research in this area.

5.1 Summary of main results and comparison with other studies

5.1.1 Main ET2DS Results

This study analyzed the longitudinal association between obesity-related physiological factors and development of dementia in older people with type 2 diabetes. The main findings included a negative relationship between BMI at baseline and incident dementia (higher BMI associated with lower risk of dementia) and a negative relationship between BMI change from baseline to year 4 and incident dementia (weight loss associated with greater risk of incident dementia). These findings were further explored using a post-hoc analysis to assess whether weight change was associated with poorer cognitive function at baseline. This suggested that better general cognitive function 'g' at baseline, but not the change of 'g', was associated with weight increase from baseline to year 4.

5.1.2 Relationship between obesity and subsequent development of dementia

The relationship between obesity related measurements and cognitive outcomes, including dementia, have been investigated in numerous previous research studies. Such studies, however, differed in their study populations and designs. In this section, I will compare the findings from the ET2DS on the association between obesity related variables measured at baseline and incident dementia with other similar studies, starting with the results related to BMI (a general obesity factor), and moving on to the factors associated with central obesity, including WC and WHR.

5.1.2.1 Higher baseline BMI associated with lower risk of incident dementia

In the ET2DS, the median time-to-event (first diagnosis of dementia) from baseline was 7.08 years. A negative and generally linear relationship between baseline BMI and incident dementia was found. Similar findings have been reported in previous studies, in both general and T2DM populations. A cohort study among older people within the Kungsholmen project, with a follow up period of 9 years, suggested lower risks of dementia among those that were overweight or obese (BMI>25) at baseline (Atti et al., 2008). A similar result was found in an observational study on a T2DM population conducted in Korea, which reported a negative trend between baseline BMI and risk of dementia over an average 5.5 years follow up (Nam et al., 2019).

Some previous studies have described a non-linear relationship between BMI and incident dementia. For instance, in a meta-analysis on a total of 589,647 participants, middle age obesity (BMI>30 kg/m² in 35 to 65-year-olds) was related to higher relative risk of late life dementia (RR=1.33) while risk of dementia in underweight participants was also elevated (RR=1.39). However, in this study, some of the observed associations were thought to be due to residual confounding (Albanese et al., 2017). A longitudinal study by Luchsinger et al. (2007) on a population with older participants also reported that the lowest risk of dementia fell in the third quartile BMI group (BMI between 26.3 and 29.6) compared to other groups.

The inconsistent associations of BMI with dementia reported in previous studies might be, at least in part, explained by differences in study populations and designs. One possibly important factor is differences in ages at baseline and follow up time. For instance, the population in a study by Ravona-Springer et al. (2013), which reported an increased risk of dementia among people with obesity at baseline had a relatively young baseline age (40-70 years old). Luchsinger et al. (2007) reported a different trend in association in people younger than 76 compared with those older than 76 in a longitudinal study. As discussed previously, significant BMI decline has been observed prior to the development of dementia, including from eight years prior to the diagnosis of dementia in a model derived from a UK population, and six years in an African American population (Singh-Manoux et al., 2018, Gao et al., 2011). In the ET2DS, the age range of the ET2DS population is rather old, with a

mean age of 67.9 years at baseline, and the median time-to-dementia from baseline was 7.1 years, such that a decrease in BMI being an early sign prior to an established diagnosis of dementia is likely. This is discussed further below.

The characteristics of each study population may also have an influence on differing results, including the distribution of BMI. In the cohort study by Atti et al. (2008), for example, overweight and obese participants were included in the same group for statistical analysis because of very small numbers of obese participants (64 participants, with only 15 diagnosed with dementia). This may lead to a biased result as the obese population, compared to the overweight population, has been shown to have a more obvious association with mortality and morbidity due to a variety of non-communicable diseases in previous studies (Abdelaal et al, 2017; Xu et al, 2018). Of note, the ET2DS population had only one person fulfilling the underweight definition, making identification of the incident dementia risk in underweight people in this population not possible.

The distribution of differing dementia aetiologies in different study populations may also affect the results, with the role of obesity and weight change in dementia development potentially differing between AD and VD. The negative association between baseline BMI and incident dementia in the ET2DS was more obvious for AD. However, due to the small population with pure aetiology of AD or VD (25 persons having the diagnosis of AD and VD, respectively), the power of this analysis was very low and the finding far from conclusive. Nonetheless, there have been similar results reported in previous studies. In the Korean cohort study among T2DM population, a significant association with baseline BMI was present for the risk of AD, while the risk of VD was not related to BMI (Nam et al., 2019). The longitudinal study on older participants by Luchsinger et al. (2007) also pointed out that while the lowest risk of AD fell in the BMI range 26.3-29.6, the BMI range 23.4-26.2 had the lowest risk of “dementia associated with stroke.”

5.1.2.2 Associations between central obesity measurements and incident dementia

In the ET2DS, the negative association between BMI and incident dementia was consistent with findings for WC, although despite a borderline statistical significance when using continuous measurements for WC, the differences between WC groups

in risk of dementia were not significant. The association between WHR and incident dementia, on the other hand, although suggesting a positive direction of association, was not statistically significant.

There have been fewer studies investigating WC or WHR as indicators for dementia risk, especially in the T2DM population. Baseline WC was negatively associated with cognition in the Finnish Diabetes Prevention Study (Lehtisalo et al., 2016). Regarding studies on the general population, the Whitehall II Study found a similar relationship of WC and WHR with diagnosis of dementia to that for BMI, with a statistically significant negative association seen from 8 years prior to diagnosis. A Korean cohort study also found that isolated abdominal obesity increased the risk of dementia among people within normal range of BMI (Cho et al., 2019).

In the longitudinal study by Luchsinger et al. (2007), people with WC in the fourth quantile had higher risk for “dementia associated with stroke” but not AD or all-type dementia. This is largely in line with findings in the ET2DS, which revealed that the fourth quantile of WC had a non-significant higher risk of vascular dementia (HR=1.53, p=0.430) but not of AD or all-type dementia. The participants in the fourth quantile of WHR in the ET2DS population had significantly higher risks of vascular dementia compared to the first quantile (HR=3.65, p=0.050, CI=1.00-13.28). As mentioned before, the small sample size decreased the power of these findings.

Emerging studies have emphasized the role of isolated central obesity in predicting all-cause mortality or cardiovascular disease (Bosomworth, 2019). Therefore, despite the drawback of the small sample size, the trends found in the ET2DS might reflect important differences in mechanisms underlying the effect of obesity and central obesity on different types of dementia. This warrants further investigation in larger studies.

5.1.3. Relationship between weight change and development of dementia

Review of the literature reported earlier in this thesis found that in people with T2DM, an association between body weight loss and incident dementia was evident. Findings from the ET2DS were consistent with this, with a higher risk of dementia in participants experiencing major weight loss compared to the group with stable

weight or major weight gain. However, the statistical significance reduced remarkably after adjusting for multiple baseline covariables and considering competing risks. The weight gain group, on the other hand, was found to have a lower risk of dementia compared to the other groups. The relationship between weight gain and dementia was inconclusive in previous studies.

In the next sections, I discuss the relationship between weight loss and dementia found in the ET2DS compared with previous literature in more detail, followed by the role of weight gain on dementia. I will discuss the findings from the post hoc analysis on cognitive changes, including in relation to both weight change and incident dementia in the ET2DS and discuss how this might assist understanding of the earlier findings.

1.3.1 Body Weight loss associated with higher risk of Incident Dementia

In the ET2DS, and consistent with previous studies on populations with type 2 diabetes (Nam et al., 2019), people who experienced weight loss over 5% had a higher risk of incident dementia compared to those who remained stable in body weight, although the relationship decreased after adjusting for multiple covariables and considering competing risks. The effect of waist circumference change on incident dementia was not significant or consistent among models.

A relationship between weight loss and diagnosis of dementia has also been demonstrated in research on the general population, despite the use of different cut points for weight loss. The trends were found among a variety of different geographical and ethnic groups. In a longitudinal study by Luchsinger et al. (2007), conducted in New York city, a higher dementia risk (HR 1.9) was predicted by weight loss (defined as weight loss over 1 kg in five years). The Whitehall Study, in a British population, also found an increased risk of death from dementia in people who reported more than 7.5 kg weight loss over 30 years from baseline (Allen et al., 2019). Similar trends have also been found in the Asian population. For instance, the Ohsaki Cohort 2006 Study suggested that older Japanese people who experienced over 3.5 kg weight loss had a higher risk of incident disabling dementia. A similar negative effect was presented in a cohort study in Korea, the population with a

weight loss over 5% within two years had increased risk of dementia (Park et al., 2019).

The significance of the negative association between body weight loss and dementia in the ET2DS decreased when taking competing risks into consideration and further reduced when adjusted for multi-covariables. This implies that the true relationship between weight loss and dementia may be obscured by death events in the real world, as overall mortality and dementia have shared risk factors. Moreover, the relationship between BW loss and dementia have potentially multiple confounders and mediators.

There were fewer studies on the relationship of WC change with cognitive outcomes. In the Finnish Diabetes Prevention Study, the finding for WC change and cognitive outcomes was similar to that of BW, that is, a waist circumference decrease during intervention followed by increase after intervention was related to better outcome in cognitive test results (Lehtisalo et al., 2016).

Significant lower WC as well as BMI was observed from eight years prior to diagnosis of dementia in the Whitehall II Study (Singh-Manoux et al., 2018). While the BMI findings are in line with the results in the ET2DS, including timeframes (the ET2DS had a median time-to-event of 7.08 years from baseline and four-year interval between body weight measurements), compared with the significant decline of WC prior to dementia found in the Whitehall II Study, the association between decrease in WC and dementia was not as prominent as BW loss in the ET2DS.

In the Whitehall II Study (Singh-Manoux et al., 2018), despite being from similar ethnic groups (based in the United Kingdom), participant characteristics differed from those of the ET2DS. The ET2DS included only people with T2DM, and participants were on average more obese. The baseline mean BMI in the ET2DS was $31.4 \pm 5.7 \text{ kg/m}^2$ while in the Whitehall II Study, the mean baseline BMI was 26.1 kg/m^2 and 25.5 kg/m^2 in the groups with dementia and without dementia, respectively. It is possible that the role of WC change differs between the general populations and the T2DM population, or in people with different baseline body compositions (obese or not obese). Despite having a higher BMI in general, older

T2DM subjects had been reported to have a higher risk of sarcopenia than people without T2DM, which was proposed to be related to reduced protein synthesis resulted from insulin resistance (Umegaki, 2016). This implies that subjects with T2DM can be more prone to muscular tissue loss without reduction in visceral fat than people without T2DM. More studies focusing on this specific issue within weight change research is required.

1.3.2 The Role of Body Weight gain on Risk on Incident Dementia

In the ET2DS, the group which experienced a BW gain over 5% had a lower risk of dementia compared with the stable BW group and BW loss group. There was no significant trend identified in any of the presented models on WC increase.

The role of weight gain had been inconsistent among previous studies (Lehtisalo et al., 2016, Espeland et al., 2018, Nam et al., 2019). The interventional studies either failed to identify a conclusive association (Lehtisalo et al., 2016), or favored a weak positive relationship of weight gain and cognition (Espeland et al., 2018). On the other hand, the observational study by Nam et al. (2019) demonstrated a significantly increased risk of dementia in the “major weight gain” group, defined as over 10% weight gain in 2 years, but not the group experiencing a weight gain between 5% and 10%. However, the occurrence of experiencing this amount of weight loss was rare in older people. The group experiencing a weight gain above 10% in the study by Nam et al. (2019) only composed 3% of the study population. Similarly, only 4% (n=26) of the ET2DS population experienced a weight gain over 10%, which was insufficient to address the incidence of dementia.

The impact of weight gain on cognitive outcomes in the general population is also unclear. Most previous studies failed to identify a significant association between weight gain and dementia (Allen et al., 2019; Lu et al., 2020). One of the few studies finding a significant trend was a cohort in Korea, stating that 10% weight gain was associated with increased risk of dementia (Park et al., 2019). The Whitehall Study (Allen et al., 2019), on the other hand, did not find a significant increase in risk of dementia even in the group experiencing a weight gain over 7.5 kg. Although percentage weight change wasn't used as a predictor in this article, according to the baseline characteristics presented, the majority of participants fell into the 65 kg to

74.99 or 75kg to 84.99 kg group, thus a 7.5 kg change might be similar to a 10% change in body weight in this population. The difference might be related to ethnic groups. However, the population used in this sub-analysis in the ET2DS, as mentioned previously, was too small to identify the risk of incident dementia in the population with this amount of weight change.

1.3.3 Cognitive Decline in general and in Different Cognitive Domains

In the post-hoc analysis, the results of cognitive tests at different time points were described along with their association with baseline obesity related factors, changes in these factors and dementia outcomes. A derived general cognitive factor 'g' was used to indicate the general cognitive function of each participant. At baseline, 'g' was found to be positively associated with BW change or WC change from baseline to year 4 while the change of 'g' from baseline to year 4 was not associated with BW change or WC change.

Given the rule of temporal precedence in causal studies, a poorer 'g' at baseline preceding associated BW loss or WC decrease, while change in 'g' was not associated with changes in BW or WC, favors the explanation of poorer cognition resulting in decreases in BW or WC in the ET2DS population. Also, 'g' at baseline was significantly associated with incident dementia, which can be interpreted as an early sign of dementia. Thus, the relationship between BW loss or WC decreases and dementia could be explained by BW and WC being a sign of cognitive decline preceding the established diagnosis of dementia.

Among the cognitive tests, the results of TMTB at baseline, which was an indicator of executive functions, had the most consistent and significant positive relationship with BW change or WC change. The pattern of decline in executive functions was found to be gradual rather than rapid (as in memory functions) prior to the established diagnosis of AD (Cloutier et al., 2015). This is in line with the findings in the ET2DS for TMTB but not logical memory (LM) at baseline being negatively associated with incident dementia, thus further supporting BW loss being an early sign of dementia.

There is evidence that the characteristics of cognitive impairment in people with T2DM differ from the general population. In the Ginkgo Evaluation of Memory Study, participants with T2DM had lower baseline executive function and global cognition domain scores, but no significantly greater decline over the median 6.1 years follow up (Palta et al., 2017). Considering the consistent significant associations of TMTB with both weight change and dementia in the ET2DS, the role of executive function in T2DM on weight change and dementia may be distinct from the general population. Further studies are required to investigate this relationship.

5.2 Strengths and limitations

5.2.1 Strengths

The ET2DS was a relatively large cohort of people with T2DM, having data on obesity-related factors (BMI, WC and WHR) and various cognitive test results at different time points, as well as accurate time of dementia diagnosis during follow up. The cohort design and source of participants, who were recruited randomly from the Lothian Diabetes Register (LDR), made the population highly representative of T2DM patients in the local population. The main outcome variable, dementia, was obtained from multiple sources, including medical records, which reduced the chance of selection bias related to relying on research follow up clinic data.

The relationship between weight change and cognitive outcomes, including dementia, in old age is inconclusive in previous studies, possibly due to inconsistencies in study designs and the multifactorial underlying mechanisms. To my knowledge, no current cohort study on T2DM population had analysis on weight change, dementia and cognitive tests in one population. The detailed data on cognitive tests and obesity-related factors at different time points allowed me to better investigate the directions of statistical associations and potential reasons for these associations. The detailed data on demographics, status of diabetes, past medical history, self-reported lifestyle factors and the dementia-related genotype APOE enabled statistical models fully adjusted for a wide range of potentially confounding and/or mediating covariables.

Competing risks analysis were used to reduce the often-overlooked influence of death on observed outcome risks in studies on older populations. The biggest strength of the sub-distribution hazard function used in this study was the ability to investigate the effect of multiple covariates and identify the risk for “all people at risk” even if the person had died of other disease. The major drawback with this method is regarding interpretation. The hazard ratio presented in each model can only be interpreted as “directions and relative quantity of effect” rather than the real increased risk of the event. Of note, the size of hazard ratios in different models cannot be compared directly. Nevertheless, sub-distribution hazard function was the ideal model for estimating actual risks of particular events (Austin & Fine, 2017).

5.2.2 Limitations

Chance

One drawback of this study was limited power, which may have been, at least in part, responsible for a lack of significance in the final model considering competing risks. In the competing risk sub-distribution hazard model adjusted for age and sex, a borderline p value of 0.057 was present in the HR of major weight gain group compared to the major weight loss group. Thus, despite the negative association between BW change and dementia consistently found in various models, it is possible that the associations were found by chance. Nevertheless, the general cognitive function ‘g’ was lower in the BW loss group than BW gain group both at baseline and year 4. Given dementia being a slow progressive disease with common preceding mild cognitive impairment, poorer cognitive function over time was compatible with increased risk of dementia in the same group. This consistency makes the associations found merely by chance less likely.

Confounding and mediating factors

Despite the significant negative association between weight loss and dementia found in some models, the p-value increased after adjusting for multi-covariables and competing risks. The presence of confounders or mediators was undeniable. The covariables were selected based on previous literature rather than their univariable associations with changes in obesity-related factors and dementia. Cautious selection as well as derived variables were used to reduce the risk of overfitting.

However, given the complexity of the mechanism under T2DM, weight change and dementia, with many shared risk factors, the possibility of over adjustment is arguable.

Moreover, there is still a possibility of unincluded confounders or mediators (i.e. residual confounding). For instance, the lifestyle factors at baseline only included smoking and drinking habits. However, both in theory and findings from previous interventional studies, the nature of intentional weight loss and unintentional weight loss can differ dramatically from each other. Due to the lack of data on eating habits and physical activities at baseline, I was unable to differentiate intentional or unintentional weight changes in the analysis.

Bias

Although the recruitment process was designed to represent the T2DM population at the local area, selection bias was still present in the population who came to follow-up clinic at year 4, which differed slightly from the total population. This is often inevitable in prospective data collection, especially considering the old age and high prevalence of comorbidities in the ET2DS population. The difference was particularly obvious in terms of cognitive functions at baseline (those who had obesity-related factor data at year 4 had a significantly better general cognitive function than the total population).

Moreover, although the size of the whole population was reasonably large, sample sizes were small in certain sub-groups, including underweight at baseline, weight gain over 10% and dementia etiologies of AD or VD, respectively. Thus, some potential non-linear relationships may have not been possible to visualize, such as previously reported U-shaped relationships in weight change and dementia, with increased risk in people with both weight loss and weight gain over 10%. Given the different underlying mechanisms of each dementia aetiology, particularly AD and VD, which were reported to have opposite relationships with weight change in some previous studies, using dementia as a single outcome variable may also reduce the likelihood of identifying significant associations statistically. However, as mixed-type dementia is relatively common in T2DM subjects, using dementia as single outcome variable can be more straightforward to apply to clinical settings.

5.3 Potential explanation for association between body weight change and dementia

In this study, body weight loss was found to be related to increased risk of dementia and was favored to be an early sign of cognitive decline prior to the diagnosis of dementia, as the general cognitive factor 'g' at baseline was positively associated with body weight change. Given 'g' being negatively associated with BMI at baseline, the relationship between baseline BMI and dementia outcome can also be explained by body weight loss being an early sign of cognitive decline.

As mentioned previously, body weight loss being an early sign preceding dementia is favored by various literature. In fact, body weight loss was found to be a common feature in clinical dementia patients. White et al. (1996) reported that 30-40% of AD patients were likely to experience a weight loss over 5% in a mean follow up time of 1.05 ± 0.12 years. Moreover, higher risk of malnutrition was found in patients with dementia, which may result in a decline in body weight (Franx et al., 2017).

The relationship between weight change and cognition itself is thought to be multifactorial. There are various theories exploring the relationship between weight loss and poor cognition, ranging from as simple as "forgetting to eat" due to poor memory function to complex biological mechanisms such as hypermetabolism (Franx et al., 2017). The complex relationship can be seen in the fact that the association between BW loss and dementia was affected by multiple confounders or mediators in this thesis.

On the other hand, the mechanism of weight loss associated with cognitive dysfunction in T2DM subjects may differ from the general population. In the ETDS, the negative relationship was found between BW loss and dementia, but not WC decrease and dementia. Thus, the observed reduction in body composition is likely to have occurred mainly in peripheral muscular tissues, rather than visceral fat. In other words, the BW loss presented in this thesis may imply a status of sarcopenia, which can result from a vicious cycle of physical inactivity and poor nutrition (Cruz-Jentoft et al., 2017). The biological mechanism of sarcopenia in older adults has not been fully understood but is thought to be associated with poor protein synthesis

due to insulin resistance. Similarly, high level of insulin resistance in older T2DM subjects was thought to be the cause of their high prevalence of sarcopenia (Umegaki, 2016). This may result in T2DM subjects being more prone to muscular tissue loss related to physical inactivity and poor nutrition status caused by cognitive dysfunction.

Trail making test B (TMTB), an indicator of executive function, was found to be associated with BW change in this thesis, with the better TMTB at baseline associated with increase in body weight from baseline to year 4. Executive function has been found previously to be lower in T2DM subjects than the general population (Palta et al., 2017). Interestingly, while hyperglycemia might lead to decreased executive function, executive function was also a proposed predictor of better compliance and glycemic control (Zhao et al., 2020). To my knowledge, no previous studies have reported a poor executive function preceding weight loss in a T2DM population. It is possible that poor executive function, as an early sign of dementia, led to poorer blood glucose control, which in turn exacerbated the risk of sarcopenia (resulted from insulin resistance) and resulted in the associated weight loss.

5.4 Conclusion and suggestions for further research

In the ET2DS, body weight loss was associated with increased risk of dementia in older people with T2DM. There was evidence that at least part of this association was due to a range of confounders or mediators including glycaemic control, cardiovascular disease history and APOE genotype. The association between poorer baseline cognitive function and subsequent weight loss favors weight loss, particularly sarcopenia, being an early sign of dementia in T2DM subjects, with executive function playing a potentially important role. The findings suggest that weight loss, when observed in clinical older T2DM patients, can indicate early cognitive decline which subsequently develops into frank dementia.

Further research on the relationship between weight change and dementia is required for the T2DM population. Different aetiologies, including Alzheimer's disease and vascular dementia can be used as different outcome variables to differentiate the pathways toward these two diseases. More lifestyle factors,

particularly eating habit and physical activity should be included to differentiate intentional and unintentional weight change. Studies on individual cognitive tests in relationship with dementia, as well as other biomarkers is also warranted to investigate the possibly unique pathway of preceding weight loss towards dementia in people with T2DM.

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Appendix

Appendix Table 1. Description of cognitive tests performed in the ET2DS

<i>Mill Hill Vocabulary Scale (MHVS)</i> The results of the Mill Hill Vocabulary Scale (MHVS) have been suggested to be independent of current cognitive status in subjects with dementia, thus was served as an estimation of pre-morbid intelligence (O'Carroll & Gilleard, 1986). During the test, the participants were instructed to select the synonyms of a given group of words out of six options. A total of 43 groups of words were given in the task and one point was given for each correct answer. The maximum score for this test was 43.
<i>Mini Mental State Exam (MMSE)</i> The Mini Mental State Exam (MMSE) is a short, yet comprehensive test with coverage on many cognitive domains including orientation, immediate and short-term memory, attention, calculation, language and praxis (Lancu & Olmer, 2006). It has been widely used in clinical scenarios both as a screening tool for dementia or follow-up for cognitive decline in dementia patients, although it is insensitive as a measure of cognitive decline in the general population. The total score of MMSE is 30 and a score lower than 24 is a common cut point for cognitive impairment (Lancu & Olmer, 2006).
<i>Logical Memory (LM)</i> Logical memory is a part of the Wechsler Memory Scale 3rd Edition UK version (WMS-III) (Tulsky et al., 2003), which implies the overall immediate and short-term verbal memory of the participant. During the test, the participant listened to a story with 25 key components. The task was to recall the 25 components immediately after listening to the story as well as approximately 40 minutes afterwards. One point was given to a correctly recalled component. The scores of immediate recall and short-term recall were then added together, with a maximum score of 50 points.

Faces

As a part of the Wechsler Memory Scale 3rd Edition UK version (WMS-III), the faces test is representative of overall non-verbal memory (Tulsky et al., 2003). The ability of identifying faces is also a part of the perceptual-motor cognitive function (Wang & Dong, 2018). In the test, the participant was presented with 24 pictures of faces, each for around two seconds, and was required to identify the faces out of 48 pictures (including 24 presented faces and 24 faces new to the participant). The participant was required to answer to each picture whether they have seen it before. The task was performed both immediately after initial exposure to the 24 pictures and after a delay of around 20 minutes. Each point was given to a correct recall and the maximum score is 96 points.

Trail Making Task B (TMTB)

Trail Making Task B (TMTB) is an indicator of executive function, which includes the ability of planning, decision-making and cognitive flexibility (Salthouse et al., 2000, Wang & Dong, 2018). In the task, the participant was given a paper with randomly placed encircled numbers, 1-13, and letters, A-L. The participants were required to draw a continuous line connecting all the encircled characters in a specified order (for instance, 1-A-2-B-3-C.....) as fast as possible. The participants had a chance to practice ensuring they fully understood the task. Correction was pointed out whenever the participant made a mistake, and the task would continue from the previous correct point. The result of TMTB is presented as time of completion (seconds) with no upper limit and a higher number indicates poorer performance.

Matrix Reasoning (MR)

The Matrix Reasoning (MR) of non-verbal reasoning is a part of the Wechsler Adult Intelligence Scale 3rd Edition (WAIS-III). Completion of MR requires various aspects of cognitive ability, including abstract reasoning, executive function as well as visual acuity and perceptual-motor function (Salthouse et al., 2003). During the test, the subject was given a paper with several printed pictures and the task was to choose a picture out of five choices which matches best with the geometric

sequence on the paper. Two chances of practicing followed by 26 tasks were completed, with one point given for a correct answer. The test would be terminated if errors were made in at least four out of five consecutive items. The maximum score for MR is 26.

Digit Symbol Test (DST)

The Digit Symbol Test (DST) is also a part of the WAIS-III, which measures the processing speed (an indicator of complex attention) of the participant (Wang & Dong, 2018). During the task, the participant was given a paper with symbols with corresponding digits 1-9 at the top, and the same symbols with blank boxes at the bottom. The task was to fill in as many blank boxes with correct corresponding digits as possible within 120 seconds. The total score is calculated from the numbers of correct digits placed within the limited time, with a maximum score of 133.

Letter Number Sequencing (LNS)

Letter Number Sequencing (LNS) is another subset of the WAIS-III, assessing working memory, which is also a part of executive function (Wang & Dong, 2018). The test required the participant to listen to a number of numbers and letters in a random order and recall the characters in numbers in numerical order followed by letters in alphabetical order. The test started with one number and one letter, and a new digit (number or letter) was added after every three trials. The test would end if three consecutive incorrect answers were produced by the participant, or reached a maximum of eight digits, thus has a maximum score of 21.

Borkowski Verbal Fluency Task (BVFT)

The Borkowski Verbal Fluency Task (BVFT) indicates the subject's executive function, semantic memory and part of the language cognitive domain. The test involves production of words in a given phonemic category (beginning with C, F or L) determined by the tester (Borkowski et al., 1967). One point is given for a produced word within 3 x 60 seconds. There is no upper limit in achievable scores.

Appendix Table 2. Definition of Central Obesity According to BMI-stratified Waist Circumference Groups

Waist circumference (cm)	Normal weight (18.5 to 24.9 kg/m ²)	Overweight (25 to 29.9 kg/m ²)	Obese I (30 to 34.9 kg/m ²)	Obese II and III (≥35 kg/m ²)
Men	≥90	≥100	≥110	≥125
Women	≥80	≥90	≥105	≥115

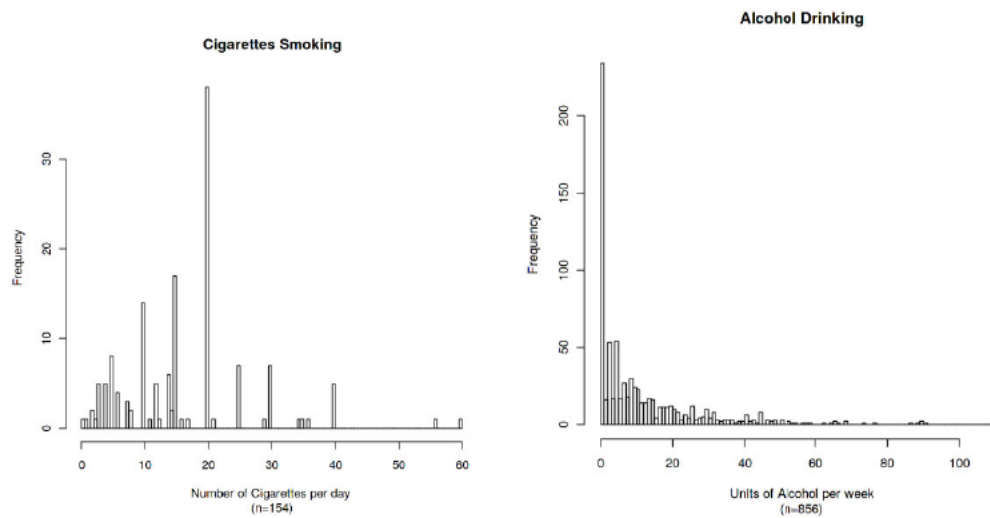
Appendix Table 3. Skewness values of the Baseline Characteristics

Age	Waist circumference (cm)	Hip circumference (cm)	Waist Hip Ratio	Height (cm)	Weight (kg)	BMI (kg/m ²)	SBP (mmHg)
0	0.38	1.04	0.04	-0.01	0.61	0.86	0.54
DBP (mmHg)	HbA1c (%)	Total Cholesterol (mmol/L)	HDL (mmol/L)	Duration of diabetes (years)	Alcohol /week (unit)	Cigarettes / day (n)	
0.18	1.65	1.02	1.01	1.59	2.33*	1.12 * [1]	

[1] Z score = 5.79

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, HDL: high-density lipoprotein

Appendix Figure 1. Histogram of Baseline Smoking (Cigarettes per day) and Baseline Alcohol Drinking (Units per week)



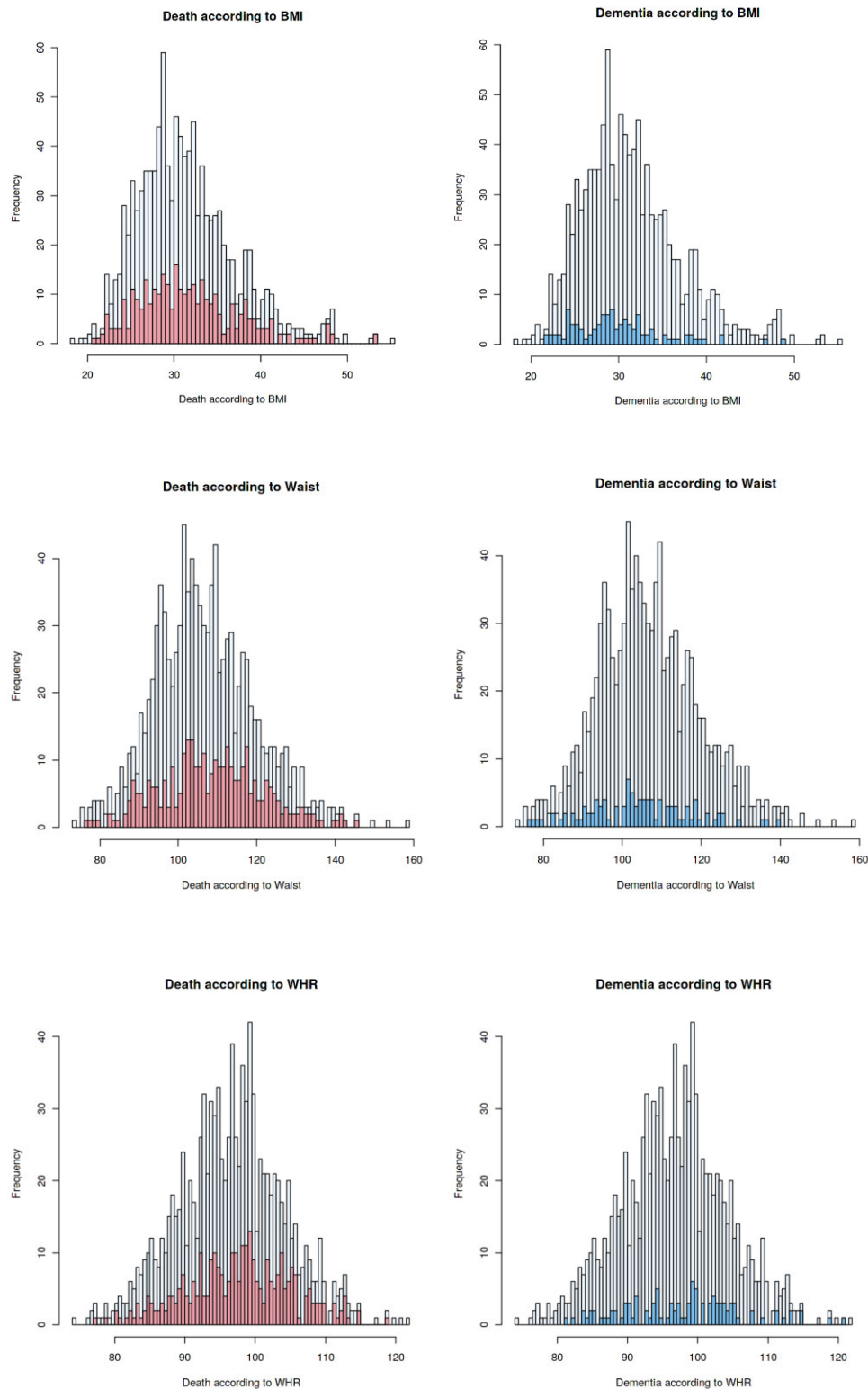
Appendix Table 4. Inter-correlations of Baseline Obesity-related Physiological variables in defferent sex groups

	BW	BMI	Waist	Hip
Male				
BMI	0.898**			
Waist	0.888**	0.892**		
Hip	0.868**	0.856**	0.839**	
WHR	0.365**	0.393**	0.614**	0.088*
Female				
BMI	0.918**			
Waist	0.878**	0.883**		
Hip	0.898**	0.897**	0.815**	
WHR	0.108*	0.114**	0.440**	-0.157**

Values are ρ (Rho) in Pearson correlation. Significance note: *, $p < 0.05$, **, $p < 0.01$

BW: body weight; BMI: body mass index; Waist: waist circumference; Hip: hip circumference; WHR: waist hip ratio

Appendix Figure 2. Histograms on Distribution of number of deaths and Number of Demantia Diagnosis according to mortality outcomes.



White bars, total population; red bars, numbers of deaths; Blue bars, numbers of dementia diagnosis.

**Appendix Table 5. Cumulative Risk of types of Dementia according to Obesity
Related Physiological Factors with Competing Risks and genetic factor Considered**

	All dementia types (n=102)	Alzheimer's disease (n=25)	Vascular dementia (n=25)
Body Mass Index (WHO classifications)			
Per 5 kg/m ²	0.82 (0.66-1.03, p=0.091)	0.52 (0.32-0.84, p=0.007)	1.07 (0.61-1.85, p=0.820)
Normal	1	1	1
Overweight	0.55 (0.31-0.97, p=0.037) *	0.67 (0.23-1.95, p=0.470)	0.55 (0.31-0.97, p=0.037) *
Obesity I	0.46 (0.25-0.83, p=0.010) *	0.21 (0.05-0.77, p=0.019) *	0.46 (0.25-0.83, p=0.010) *
Obesity II / III	0.40 (0.20-0.82, p=0.012) *	0.16 (0.03-0.91, p=0.039) *	0.40 (0.20-0.82, p=0.012) *
Waist Circumference (quantiles)			
per 5 cm increase	0.92 (0.84-1.00, p=0.056)	0.82 (0.70-0.97, p=0.023) *	1.04 (0.85-1.27, p=0.700)
Q1	1	1	1
Q2	0.80 (0.48-1.33, p=0.390)	0.60 (0.23-1.61, p=0.310)	0.95 (0.30-3.01, p=0.930)
Q3	0.70 (0.41-1.21, p=0.200)	0.58 (0.21-1.59, p=0.290)	0.37 (0.07-1.87, p=0.230)
Q4	0.67 (0.38-1.17, p=0.160)	0.20 (0.04-1.01, p=0.051)	1.53 (0.53-4.45, p=0.430)
Waist Hip Ratio (quantiles)			
per 0.05 increase	1.07 (0.91-1.27, p=0.390)	0.92 (0.68-1.23, p=0.570)	1.65 (1.17-2.32, p=0.004) **
Q1	1	1	1
Q2	1.00 (0.57-1.76, p=1.000)	1.02 (0.33-3.19, p=0.970)	1.07 (0.22-5.32, p=0.930)
Q3	0.97 (0.57-1.67, p=0.920)	1.29 (0.44-3.74, p=0.640)	2.02 (0.51-8.08, p=0.320)
Q4	1.18 (0.69-2.04, p=0.550)	0.80 (0.25-2.63, p=0.720)	3.65 (1.00-13.28, p=0.050) *

Values are hazard ratio (95% confidence interval, p value), using competing risk sub-distribution hazard function. Significance note: *, <0.05, **, <0.01.

Appendix Table 6. Characteristics in People in Different weight change Groups

	BW gain	BW stable	BW loss	
	mean ± sd, median (Q1, Q3) or %(n)			p-value
Demographics				
Age (years)	67.63 ± 4.09	67.75 ± 4.15	67.6 ± 4.36	0.66
Sex				0.02 *
Male	51 (86)	54 (281)	41 (55)	
Female	49 (83)	46 (235)	59 (80)	
highest education attainment				0.13
Primary school	0 (0)	1 (4)	1 (1)	
Secondary school	61 (103)	52 (266)	51 (69)	
Other qualification	24 (41)	28 (146)	35 (47)	
University/college	15 (25)	19 (100)	13 (18)	
SIMD Quintile				0.68
1	12 (20)	12 (62)	11 (15)	
2	18 (30)	17 (86)	19 (26)	
3	21 (35)	15 (79)	19 (25)	
4	19 (32)	18 (91)	15 (20)	
5	31 (52)	38 (198)	36 (49)	
Status of Diabetes				
HbA1c (%)	7.51 ± 1.35	7.31 ± 1.04	7.56 ± 1.14	0.84
Duration of Diabetes (years)	8.58 ± 7.80	7.56 ± 6.19	8.5 ± 5.06	0.46
Treatment of Diabetes				0.02*
Diet-controlled	14 (23)	22 (116)	16 (21)	
Oral medication	64 (108)	63 (326)	66 (89)	
Insulin injections	22 (38)	14 (73)	19 (25)	
Obesity-related measurements at baseline				
Height (cm)	166.2 ± 8.29	166.62 ± 9.07	164.62 ± 8.89	0.07
Weight (kg)	85.09 ± 16.66	85.65 ± 15.01	89.26 ± 17.41	0.3
Body mass index (kg/m ²)	30.92 ± 6.44	30.88 ± 5.06	32.95 ± 5.98	0.03 *
Waist circumference (cm)	106.1 ± 14.1	105.9 ± 11.8	108.9 ± 12.6	<0.01 **
Hip circumference (cm)	110.5 ± 12.8	109.8 ± 10.8	113.4 ± 13.0	<0.01 **
Waist hip ratio	0.96 ± 0.07	0.97 ± 0.07	0.96 ± 0.08	0.02 *
Other metabolic risk factors				
Systolic blood pressure (mmHg)	134.1 ± 16.9	131.7 ± 15.6	133.5 ± 15.4	0.3
Diastolic blood pressure (mmHg)	69.5 ± 9.1	68.9 ± 8.9	68.4 ± 8.3	0.28

Total cholesterol (mmol/L)	4.41 ± 0.88	4.34 ± 0.92	4.25 ± 0.85	0.43
High density lipoprotein (mmol/L)	1.30 ± 0.34	1.29 ± 0.37	1.30 ± 0.33	0.17
Medical history				
Cardiovascular diseases *				0.05
No	56 (95)	54 (278)	44 (59)	
Yes	43 (73)	46 (235)	56 (76)	
Stroke				0.18
No	96 (163)	94 (484)	97 (131)	
Yes	4 (6)	6 (32)	3 (4)	
Hypoglycemic attack				0.57
No	89 (150)	90 (462)	86 (116)	
Yes	9 (16)	9 (46)	12 (16)	
Hypoglycemic attack (times)				0.57
1-2 times	4 (7)	5 (28)	6 (8)	
3-4 times	3 (5)	2 (10)	4 (6)	
more than 5 times	2 (4)	1 (7)	1 (2)	
Lifestyle factors				
Smoker				0.67
Never	39 (66)	40 (204)	44 (60)	
Former	49 (82)	48 (246)	41 (55)	
Current	12 (21)	13 (66)	15 (20)	
Number of Cigarettes / day	15 (8, 20)	15 (7.14, 20)	20 (13.5, 20)	0.81
Currently Drinking				0.03 *
No	17 (28)	14 (74)	24 (32)	
Yes	83 (140)	85 (441)	76 (103)	
Total Units of Alcohol / week	5.1 (0, 14.77)	6.7 (0, 18)	4.2 (0, 11.85)	0.02*
Genetic factor				
Apolipoprotein E (APOE) genotype				0.71
ε2/ε2 or ε2/ε3 or ε3/ε3	73 (123)	71 (366)	67 (90)	
ε2/ε4 or ε3/ε4	24 (40)	23 (118)	27 (36)	
ε4/ε4	2 (4)	2 (9)	3 (4)	

Values are median and 1st and 3rd quantile for Number of Cigarettes per day and Total Units of Alcohol per week

P-value of total units of alcohol per week is performed by t test of log total units of alcohol per week added 1; P-value of number of cigarettes per day is performed by t test of squared rooted number of cigarettes per day

SIMD: Scottish Index of Multiple Deprivation 2006 (quintile 1 is most deprived)

* Hypertensive status is defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg

* Hyperlipidemia status is defined as total cholesterol ≥ 5 mmol/L

* Cardiovascular disease includes established history of intermittent claudication, myocardial infarction, angina, transient ischaemic attack, coronary or peripheral artery intervention or ankle brachial pressure index below 0.9

Significance note: *, $p < 0.05$, **, $p < 0.01$

Appendix Table 7. Characteristics in People in Different Waist Circumference Change Groups

	WC increase	WC stable	WC decrease	p-value
	mean ± sd, median (Q1, Q3) or %(n)			
Demographics				
Age (years)	67.78 ± 4.15	67.66 ± 4.04	67.58 ± 4.47	0.66
Sex				0.02*
Male	55 (77)	54 (261)	43 (83)	
Female	45 (63)	46 (221)	57 (111)	
highest education attainment				0.93
Primary school	0 (0)	1 (4)	1 (1)	
Secondary school	54 (75)	53 (255)	53 (103)	
Other qualification	29 (40)	28 (133)	31 (60)	
University/college	18 (25)	19 (90)	15 (30)	
SIMD Quintile				0.87
1	11 (16)	12 (59)	10 (20)	
2	15 (21)	17 (82)	20 (38)	
3	20 (28)	17 (80)	16 (31)	
4	20 (28)	16 (79)	18 (35)	
5	34 (47)	38 (182)	36 (70)	
Status of Diabetes				
HbA1c (%)	7.36 ± 1.19	7.43 ± 1.13	7.35 ± 1.12	0.838
Duration of Diabetes (years)	7.81 ± 6.3	8.10 ± 6.67	7.39 ± 5.56	0.461
Treatment of Diabetes				0.1
Diet-controlled	15 (21)	22 (106)	16 (32)	
Oral medication	68 (95)	60 (291)	70 (136)	
Insulin injections	17 (24)	17 (84)	13 (26)	

Obesity-related measurements				
Height (cm)	166.33 ± 8.7	166.83 ± 9.16	164.81 ± 8.37	0.07
Weight (kg)	85.66 ± 14.12	86.02 ± 16.27	87.39 ± 16.7	0.3
Body mass index (kg/m ²)	31.04 ± 5.14	30.93 ± 5.50	32.23 ± 6.09	0.03 *
Waist circumference (cm)	104.1 ± 11.5	106.0 ± 12.5	109.5 ± 13.0	<0.01**
Hip circumference (cm)	109.4 ± 10.2	110.0 ± 11.6	112.9 ± 13.0	<0.01**
Waist hip ratio	0.95 ± 0.08	0.97 ± 0.07	0.97 ± 0.08	0.02*
Other metabolic risk factors				
Systolic blood pressure (mmHg)	134.6 ± 16.5	132.0 ± 15.5	132.5 ± 16.2	0.3
Diastolic blood pressure	69.5 ± 8.7	69.0 ± 9.3	68.4 ± 8.2	0.28
Total cholesterol (mmol/L)	4.39 ± 0.94	4.35 ± 0.89	4.31 ± 0.91	0.43
High density lipoprotein	1.27 ± 0.31	1.29 ± 0.35	1.32 ± 0.40	0.17
Medical history				
Cardiovascular diseases *				0.67
No	56 (78)	53 (255)	51 (98)	
Yes	44 (62)	46 (224)	49 (95)	
Stroke				0.39
No	96 (134)	94 (453)	96 (187)	
Yes	4 (6)	6 (29)	4 (7)	
Hypoglycemic attack				0.71
No	88 (123)	90 (434)	86 (167)	
Yes	11 (15)	9 (43)	10 (20)	
Hypoglycemic attack (times)				0.49
1-2 times	6 (8)	4 (21)	7 (14)	
3-4 times	2 (3)	3 (15)	2 (3)	
more than 5 times	2 (3)	1 (7)	2 (3)	
Lifestyle factors				
Smoker				0.22
Never	33 (46)	41 (197)	44 (86)	
Former	54 (75)	46 (224)	41 (80)	
Current	14 (19)	13 (61)	14 (28)	
Number of Cigarettes / day	20 (9.64, 20)	15 (10, 20)	14.5 (6.86, 20)	0.81
Currently Drinking				0.27
No	14 (20)	16 (75)	20 (39)	
Yes	86 (120)	84 (406)	80 (155)	
Total Units of Alcohol/ week	6.25 (2.08, 17.27)	6.3 (0, 17)	4.2 (0, 14.7)	0.02*

Genetic factor				
Apolipoprotein E (APOE)				0.8
ε2/ε2 or ε2/ε3 or ε3/ε3	71 (100)	72 (349)	68 (131)	
ε2/ε4 or ε3/ε4	24 (34)	22 (106)	25 (49)	
ε4/ε4	1 (2)	2 (10)	3 (5)	

Values are median and 1st and 3rd quantile for Number of Cigarettes per day and Total Units of Alcohol per week

P-values are calculated with: ANOVA in continuous values, chi-squared in categorical values. Fisher's exact test in education, number of hypoglycaemic attacks and APOE-ε4 genes. ANOVA for log total units of alcohol / week and squared root for number of cigarettes / day

SIMD: Scottish Index of Multiple Deprivation 2006

Significance note: *, p<0.05, **, p<0.01

Appendix Table 8. Characteristics in people diagnosed with dementia (n=78) and not diagnosed with dementia (n=743) by year 10 follow up

	No dementia	Dementia (n=78)	
	mean ± sd or %(n)	mean ± sd or %(n)	p-value
Demographics			
Age (years)	67.53 ± 4.16	69.01 ± 3.93	<0.01 **
Sex			0.13
Male	50 (368)	40 (31)	
Female	50 (375)	60 (47)	
highest education attainment			0.09
Primary school	1 (4)	1 (1)	
Secondary school	52 (388)	62 (48)	
Other qualification	30 (221)	18 (14)	
University/college degree	17 (130)	19 (15)	
SIMD Quintile			0.51
1	12 (89)	10 (8)	
2	18 (131)	14 (11)	
3	17 (123)	21 (16)	
4	17 (126)	23 (18)	
5	37 (274)	32 (25)	
Status of Diabetes			
HbA1c	7.37 ± 1.07	7.67 ± 1.64	0.12

Obesity-related physiological measurements			
Baseline			
Weight (kg)	86.55 ± 16.04	83.53 ± 15.81	0.11
Body mass index (kg/m ²)	31.38 ± 5.63	30.22 ± 5.24	0.07
Waist circumference (cm)	106.66 ± 12.54	105.16 ± 12.78	0.32
Waist hip ratio	0.96 ± 0.07	0.98 ± 0.08	0.03
Year 4			
Weight (kg)	86.71 ± 16.42	82.53 ± 16.34	0.03 *
Body mass index (kg/m ²)	31.59 ± 5.76	30.12 ± 5.56	0.03 *
Waist circumference (cm)	105.95 ± 13.14	103.53 ± 13.17	0.13
Waist hip ratio	0.95 ± 0.08	0.97 ± 0.08	0.09
Body weight change (kg)	0.31 ± 5.78	-1 ± 6.16	0.08
Waist circumference change	-0.69 ± 6.56	-1.62 ± 6.86	0.25
Other metabolic risk factors			
Systolic blood pressure (mmHg)	132.5 ± 16.0	132.8 ± 14.2	0.88
Total cholesterol (mmol/L)	4.35 ± 0.90	4.24 ± 0.85	0.30
Medical history			
Cardiovascular diseases *			0.08
No	54 (401)	42 (33)	
Yes	46 (339)	56 (44)	
Stroke			0.79
No	95 (704)	96 (75)	
Yes	5 (39)	4 (3)	
Hypoglycemic attack			0.09
No	90 (666)	83 (65)	
Yes	9 (65)	15 (12)	
Lifestyle factors			
Smoker			0.32
Never	40 (299)	44 (34)	
Former	46 (342)	49 (38)	
Current	14 (102)	8 (6)	
Currently Drinking			0.81
No	16 (120)	18 (14)	
Yes	84 (621)	82 (64)	
Genetic factor			
Apolipoprotein E (APOE)			<0.01 **

€2/€2 or €2/€3 or €3/€3	73 (545)	47 (37)	
€2/€4 or €3/€4	21 (159)	42 (33)	
€4/€4	2 (12)	6 (5)	

Values are median and 1st and 3rd quantile for Number of Cigarettes per day and Total Units of Alcohol per week

SIMD: Scottish Index of Multiple Deprivation 2006 (quintile 1 is most deprived)

* Cardiovascular disease includes established history of intermittent claudication, myocardial infarction, angina, transient ischaemic attack, coronary or peripheral artery intervention or ankle brachial pressure index below 0.9

Significance note: *, p<0.05, **, p<0.01

Appendix Table 9. Skewness values of the Cognitive test data at baseline

Cognitive test	skewness
G	-0.09
Mill Hill Vocabulary Scale (MHVS)	-0.36
Mini Mental State Exam (MMSE)	-1.87
Logical Memory (LM)	-0.22
Trail Making Test B (TMTB)	2.64
Faces	0.02
Matrix Reasoning (MR)	0.03
Digit Symbol Test (DST)	0.24
Borkowski Verbal Fluency Test (BVFT)	0.22
Letter Number Sequencing (LNS)	0.02

Appendix Table 10. Cognitive function in Different Body Weight Change Groups at Baseline and Year 4

	BW gain	BW stable	BW loss	p value
Baseline				
G	0.22 ± 0.89	0.15 ± 0.93	-0.08 ± 0.96	0.009 *
MHVS	31.10 ± 5.12	31.73 ± 4.91	31.09 ± 5.5	0.884
MMSE	28.51 ± 1.93	28.50 ± 1.56	28.39 ± 1.54	0.539
LM	25.55 ± 8.16	26.31 ± 7.81	24.95 ± 8.03	0.618
TMTB	96.5 (77, 124)	100.5 (79.75, 130.25)	109 (84.25, 146)	0.001 **
Faces	66.29 ± 7.38	66.27 ± 7.58	67.08 ± 8.19	0.409
MR	13.43 ± 5.12	13.51 ± 5.25	12.72 ± 5.27	0.289
DST	51.33 ± 13.89	50.74 ± 14.53	48.53 ± 14.12	0.105
BVFT	37.91 ± 12.67	38.02 ± 12.53	36.81 ± 12.56	0.489
LNS	9.96 ± 2.73	10.08 ± 2.59	9.45 ± 2.68	0.128
Year 4				
G	-0.02 ± 0.95	0.05 ± 0.94	-0.11 ± 1.10	0.566
MHVS	30.44 ± 4.82	30.92 ± 4.97	30.42 ± 4.98	0.93
MMSE	28.19 ± 1.94	28.46 ± 1.64	28.15 ± 1.91	0.993
LM	26.56 ± 8.09	27.75 ± 8.40	26.38 ± 7.93	0.973
TMTB	103.62 (82.71, 130.81)	106.68 (82.19, 140.4)	111.83 (84.63, 169.51)	0.002 **
Faces	69.29 ± 8.24	69.33 ± 8.57	68.96 ± 8.35	0.758
MR	11.56 ± 5.24	11.76 ± 5.16	10.97 ± 5.35	0.386
DST	51.59 ± 13.32	50.59 ± 14.17	47.40 ± 13.96	0.014
BVFT	37.12 ± 12.78	37.18 ± 12.77	35.63 ± 12.80	0.352
LNS	9.01 ± 2.94	9.06 ± 2.88	8.39 ± 2.87	0.1
Change				
G	-0.36 ± 1.4	-0.19 ± 1.37	-0.09 ± 1.54	0.106
MHVS	-0.14 ± 0.5	-0.18 ± 0.45	-0.17 ± 0.51	0.577
MMSE	-0.21 ± 1.05	-0.03 ± 1.02	-0.16 ± 1.07	0.556
Memory	0.17 ± 0.91	0.19 ± 0.84	0.18 ± 0.92	0.877
TMTB	-0.25 ± 0.76	-0.2 ± 0.77	-0.21 ± 0.84	0.631
Faces	0.36 ± 0.87	0.39 ± 0.92	0.25 ± 1.03	0.349
MR	-0.37 ± 0.83	-0.33 ± 0.81	-0.34 ± 0.81	0.675
DST	0 ± 0.72	-0.05 ± 0.69	-0.08 ± 0.69	0.279
BVFT	-0.07 ± 0.61	-0.07 ± 0.62	-0.1 ± 0.62	0.736
LNS	-0.39 ± 0.9	-0.4 ± 1.03	-0.46 ± 1.03	0.579

Values are median (Q1, Q3) for trail making test B (TMTB). P-value is for log TMTB.

Change values are standardized results. Zero means the mean at baseline, one means the standard deviation at baseline, positive scores indicates better cognitive performance.

BW, Body weight; MHVS, Mill Hill Vocabulary Scale; MMSE, Mini Mental State Exam; LM, Logical Memory; TMTB, Trail Making Test B; MR, Matrix Reasoning; DST, Digit Symbol Test; BVFT, Borkowski Verbal Fluency Test; LNS, Letter Number Sequencing.

Significance note: *, $p < 0.05$, **, $p < 0.01$

Appendix Table 11. Cognitive function in Different Waist Circumference Change Groups at Baseline and Year 4

	WC increase	WC stable	WC decrease	p value
Baseline				
G	0.12 ± 0.94	0.16 ± 0.94	0.04 ± 0.94	0.378
MHVS	31.5 ± 5.40	31.64 ± 4.83	31.13 ± 5.32	0.440
MMSE	28.41 ± 1.73	28.45 ± 1.69	28.58 ± 1.46	0.328
LM	25.75 ± 8.20	26.06 ± 7.88	25.51 ± 8.03	0.715
TMTB	98.5 (83, 129.5)	100 (78, 131)	106 (81, 134)	0.205
Faces	64.85 ± 7.16	66.76 ± 7.78	66.60 ± 7.62	0.065
MR	13.36 ± 5.50	13.61 ± 5.19	12.88 ± 5.11	0.316
DST	51.57 ± 15.15	50.36 ± 14.11	50.11 ± 14.57	0.389
BVFT	36.12 ± 12.42	38.20 ± 12.46	37.94 ± 12.86	0.248
LNS	10.09 ± 2.69	10.04 ± 2.63	9.62 ± 2.68	0.086
Year 4				
G	0.01 ± 0.97	0.03 ± 0.95	-0.07 ± 1.02	0.433
MHVS	30.70 ± 5.13	30.97 ± 4.92	30.18 ± 4.85	0.259
MMSE	28.27 ± 1.78	28.38 ± 1.78	28.33 ± 1.72	0.824
LM	26.87 ± 7.54	27.77 ± 8.47	26.48 ± 8.31	0.513
TMTB	106.69 (80.48, 135.09)	106.28 (81.86, 140.84)	108.23 (86.39, 146.11)	0.029 *
Faces	68.13 ± 7.75	69.77 ± 8.72	68.89 ± 8.24	0.587
MR	11.27 ± 5.57	11.95 ± 5.25	11.08 ± 4.85	0.558
DST	51.48 ± 14.29	50.28 ± 14.08	49.52 ± 13.67	0.222
BVFT	35.8 ± 12.98	37.25 ± 13.00	36.59 ± 12.20	0.683
LNS	9.01 ± 2.90	9.03 ± 2.85	8.62 ± 3.01	0.198

Change				
G	-0.24 ± 1.4	-0.21 ± 1.39	-0.2 ± 1.46	0.792
MHVS	-0.17 ± 0.49	-0.14 ± 0.45	-0.23 ± 0.49	0.182
MMSE	-0.08 ± 0.97	-0.06 ± 1.08	-0.15 ± 0.96	0.507
Memory	0.16 ± 0.84	0.23 ± 0.89	0.11 ± 0.85	0.494
TMTB	-0.16 ± 0.79	-0.22 ± 0.77	-0.23 ± 0.81	0.46
Faces	0.43 ± 0.89	0.38 ± 0.93	0.3 ± 0.97	0.198
MR	-0.42 ± 0.88	-0.32 ± 0.83	-0.34 ± 0.71	0.486
DST	-0.04 ± 0.69	-0.03 ± 0.72	-0.07 ± 0.66	0.674
BVFT	-0.04 ± 0.65	-0.08 ± 0.61	-0.11 ± 0.6	0.292
LNS	-0.44 ± 1.01	-0.4 ± 0.94	-0.4 ± 1.16	0.701

Values are median (Q1, Q3) for trial making test B (TMTB). P-value is for log TMTB.

BW, Body weight; MHVS, Mill Hill Vocabulary Scale; MMSE, Mini Mental State Exam; LM, Logical

Memory; TMTB, Trail Making Test B; MR, Matrix Reasoning; DST, Digit Symbol Test; BVFT, Borkowski

Verbal Fluency Test; LNS, Letter Number Sequencing.

Change values are standardized results. Zero means the mean at baseline, one means the standard deviation at baseline, positive scores indicates better cognitive performance.

Significance note: *, p<0.05, **, p<0.01

Appendix Table 12. Cognitive tests in People with (n=78) and without (n=743) dementia by year 10

	No dementia (n=743)		Dementia (n=78)		p-value
	Result	standardized	Result	standardized	
Baseline					
G	0.18 ± 0.90	-	-0.39 ± 1.06	-	<0.001 **
MHVS	31.63 ± 4.96	0.03 ± 0.98	30.16 ± 5.6	-0.26 ± 1.11	0.026 *
MMSE	28.59 ± 1.47	0.07 ± 0.90	27.46 ± 2.54	-0.62 ± 1.55	<0.001 **
LM	26.09 ± 7.94	0.02 ± 1.00	24.09 ± 7.90	-0.23 ± 0.99	0.038 *
TMTB	99 (78, 129)	0.06 ± 0.96	120.5 (96.5, 175)	-0.56 ± 1.14	<0.001 **
Faces	66.58 ± 7.61	0.03 ± 0.99	64.36 ± 7.93	-0.26 ± 1.03	0.018 *
MR	13.50 ± 5.17	0.03 ± 0.99	12.16 ± 5.58	-0.23 ± 1.07	0.042 *
DST	51.04 ± 14.34	0.04 ± 1.00	45.16 ± 13.50	-0.37 ± 0.94	<0.001 **
BVFT	38.21 ± 12.39	0.03 ± 0.99	33.87 ± 13.43	-0.31 ± 1.07	0.006 **
LNS	10.11 ± 2.58	0.06 ± 0.98	8.50 ± 2.79	-0.55 ± 1.06	<0.001 **

Year 4					
G	0.07 ± 0.96	-	-0.61 ± 0.96	-	<0.001 **
MHVS	30.87 ± 4.85	-0.12 ± 0.96	29.45 ± 5.57	-0.40 ± 1.10	0.035 *
MMSE	28.5 ± 1.53	0.01 ± 0.93	26.89 ± 2.82	-0.97 ± 1.72	<0.001 **
LM	27.95 ± 7.85	0.26 ± 0.99	21.18 ± 9.64	-0.59 ± 1.21	<0.001 **
TMTB	104.5 (81.6, 136.5)	-0.09 ± 1.01	130 (109.9, 188.7)	-0.94 ± 1.20	<0.001 **
Faces	69.59 ± 8.33	0.42 ± 1.09	66.06 ± 8.96	-0.04 ± 1.17	0.001 **
MR	11.78 ± 5.19	-0.30 ± 0.99	9.89 ± 5.20	-0.66 ± 0.99	0.002 **
DST	51.17 ± 13.71	0.05 ± 0.95	41.88 ± 13.94	-0.60 ± 0.97	<0.001 **
BVFT	37.43 ± 12.61	-0.03 ± 1.00	31.86 ± 13.31	-0.47 ± 1.06	0.001 **
LNS	9.15 ± 2.80	-0.30 ± 1.06	6.80 ± 2.96	-1.19 ± 1.12	<0.001 **
Change					
G		-0.18 ± 1.32		-0.28 ± 1.25	0.540
MHVS		-0.17 ± 0.47		-0.18 ± 0.49	0.786
MMSE		-0.06 ± 1.00		-0.38 ± 1.33	0.038 *
LM		0.23 ± 0.85		-0.21 ± 0.97	<0.001 **
TMTB		-0.18 ± 0.78		-0.48 ± 0.77	0.002 **
Faces		0.38 ± 0.91		0.22 ± 1.11	0.216
MR		-0.33 ± 0.82		-0.43 ± 0.76	0.243
DST		-0.02 ± 0.70		-0.25 ± 0.59	0.002 **
BVFT		-0.07 ± 0.62		-0.17 ± 0.61	0.144
LNS		-0.38 ± 1.0		-0.68 ± 0.94	0.012 *

Values are median (Q1, Q3) for TMTB mean ± standard deviation in original test results. Values are Standardized values of cognitive test results are standardized to the mean and standard deviation at baseline. TMTB are transformed to minus log before standardization. A positive value in rho indicates a positive correlation between both values. (for instance, -0.094 in BMI and MHVS is interpreted as higher BMI is associated with worse performance in MHVS.) G is standardized to all cognitive tests.

Significance note: *, p<0.05, **, p<0.01

MHVS, Mill Hill Vocabulary Scale; MMSE, Mini Mental State Exam; LM, Logical Memory; TMTB, Trail Making Test B; MR, Matrix Reasoning; DST, Digit Symbol Test; BVFT, Borkowski Verbal Fluency Test; LNS, Letter Number Sequencing.