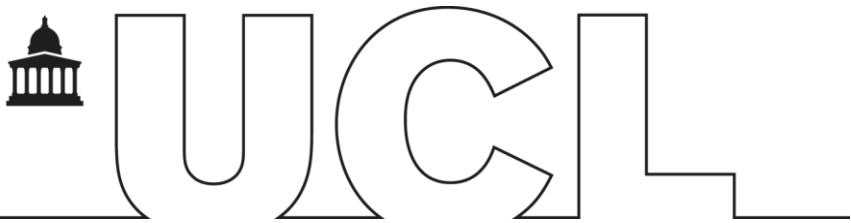

The association of adult lifecourse body mass index, waist circumference and dietary patterns with type 2 diabetes incidence in the MRC National Survey of Health and Development

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Declaration

I, Silvia Pastorino, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

Type 2 diabetes is a major public health problem and its prevalence is increasing worldwide, especially among older people. Overweight and abdominal obesity are known risk factors for the disease, but few studies have analysed their longitudinal pattern. A high glycaemic index (GI), low dietary fibre and high dietary fats have also been linked to type 2 diabetes, but their combined effect has never been studied.

Using data from the MRC National Survey of Health and Development this thesis aimed to examine adult life course (from age 26 to 53 years) body mass index (BMI), waist circumference (WC) and dietary patterns in relation to type 2 diabetes incidence between age 53 and 60-64 years.

At any stage of the adult life course BMI gain was associated with type 2 diabetes incidence. Early (26-36 years) and late (43-53 years) adulthood BMI gains were more important for men whereas late adulthood gains had stronger associations for women. The risk of type 2 diabetes increased with longer durations of overweight or obesity, probably because of the increasing accumulation of weight across the life course. Long-term WC change (36-53 years), independent of concomitant BMI change, was associated with increased risk of diabetes especially among women and people with an initially normal BMI. A high fat, high GI, low fibre dietary pattern was identified that was characterised by a high consumption of refined grains, processed meat, and animal fats, and a low intake of fruits, vegetables, low-fat dairy and wholegrain cereals. Higher scores for this dietary pattern at age 43 (only among women) and 53 were associated with increased type 2 diabetes incidence, predominantly via pathways that were independent of BMI and WC. Long-term score change (36-53 years) was significantly associated with diabetes only among women.

Early interventions to reduce weight and WC gain and improve dietary patterns would be effective public health strategies to prevent type 2 diabetes risk at older ages.

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Abbreviations

AHEI=Alternative Healthy Eating Index
BMI-body mass index
DASH=Adherence to the Dietary Approaches to Stop Hypertension
EPIC=European Prospective Investigation into Cancer and Nutrition
FFA=free fatty acids
FFQ=food-frequency questionnaires
FPG=fasting plasma glucose
GI=glycaemic index
GL=glycaemic load
GP=general practitioner
HbA1c=glycated haemoglobin
HEI=Healthy Eating Index
HOMA-IR=homeostasis model assessment of insulin resistance
IDF=International Diabetes Federation
IFG=impaired fasting glucose
IGT=impaired glucose tolerance
IR=insulin resistance
MDS=Mediterranean Diet Score
MUFA=monounsaturated fatty acids
NSHD=MRC National Survey of Health and Development
OGTT=oral glucose tolerance test
PUFA=polyunsaturated fatty acids
RRR=reduced rank regression
SEP=socioeconomic position
SFA=saturated fatty acids
WC=waist circumference
WHO=World Health Organization
WHR=waist-to-hip ratio
WHtR=waist-to-height ratio

1 Chapter 1: Introduction and literature review

1.1 Prevalence and health burden of diabetes

Diabetes is a major public health problem and its prevalence is rapidly increasing in low, middle and high-income countries. The International Diabetes Federation (IDF) (1) reported that 382 million adult people worldwide had diabetes in 2013, corresponding to a prevalence of 8.3%, and that about 46% of all cases were undiagnosed. By 2035 this number is predicted to increase to an estimated 592 million people (1) The highest increase will be in the over 60 category reflecting the trend towards an ageing society.

According to 2012 Quality and Outcomes Framework reports (2) the number of people aged 17 and over diagnosed with diabetes was 2,544,197 in England, 231,248 in Scotland, 167,537 in Wales and 75,628 in Northern Ireland. This corresponds to an average prevalence of diabetes in the UK of 4.6%. However, if undiagnosed cases of diabetes in the UK were taken into account, it is estimated that the current prevalence might be as high as 6.5% with a projected prevalence of 7.3% by 2035 (1). The prevalence of diabetes is higher among men, Asian and Black ethnic groups and increases with age. Among 55-75 year olds the point prevalence of diabetes in 2010 was estimated to be 14.3% (3).

About 90% of all diabetes cases are type 2 diabetes. People with type 2 diabetes have a higher risk of developing conditions that can lead to increased mortality and reduced quality of life (4). Debilitating long-term complications include increased cardiovascular disease risk, retinopathy, nephropathy and neuropathy (4, 5). The management and treatment of diabetes complications is costly and difficult. Therefore primary prevention of type 2 diabetes is an important public health priority.

1.2 Definition and diagnosis of type 2 diabetes

In contrast to Type 1 diabetes, which is an autoimmune condition, Type 2 diabetes is a multifactorial metabolic disorder characterised by chronically elevated levels of glucose in the blood (hyperglycaemia) and disrupted metabolism of carbohydrate, fat and protein (6). The diagnosis of diabetes is based on blood glucose levels with or without symptoms. The latest criteria for the classification and diagnosis of diabetes have been published in 2006 following a joint consultation of the World Health Organization (WHO) and IDF (7). These criteria have been derived using epidemiological data on the distribution of plasma glucose in the population and on the prevalence of diabetes complications associated with raised glucose levels.

The two methods recommended by WHO for diabetes diagnosis are the determination of fasting plasma glucose (FPG) and the oral glucose tolerance test (OGTT). The latter entails the measurement of plasma glucose two hours after the ingestion of 75g of glucose. A summary of current WHO/IDF criteria for diabetes and intermediate hyperglycaemia are shown in Table 1. In

2011 WHO published an addendum to its 2006 criteria acknowledging the conditional use of glycated haemoglobin (HbA1c) as a diagnostic test for diabetes (8). The recommended cut-point for diabetes diagnosis is 6.5%. Diabetes can also be diagnosed by a random plasma glucose level of ≥11.1mmol/l (200mg/dl), if the patient presents with symptoms of hyperglycaemia, such as polydipsia, polyuria and unexplained weight loss (6).

Table 1. Summary of 2006 WHO diagnostic criteria for diabetes and intermediate hyperglycaemia

Diabetes	
Fasting plasma glucose	≥7.0mmol/l (126mg/dl) or
2–h plasma glucose*	≥11.1mmol/l (200mg/dl)
Impaired Glucose tolerance (IGT)	
Fasting plasma glucose	<7.0mmol/l (126mg/dl) and
2–h plasma glucose**	≥7.8 and <11.1mmol/l (140mg/dl and 200mg/dl)
Impaired fasting Glucose (IFG)	
Fasting plasma glucose	6.1-6.9mmol/l (110mg/dl-125mg/dl) and
2–h plasma glucose**	(if measured) <7.8mmol/l (140mg/dl)

Adapted from WHO, 2006 (7); * Venous plasma glucose 2–h after ingestion of 75g oral glucose load; ** If 2–h plasma glucose is not measured, status is uncertain as diabetes or IGT cannot be excluded

1.3 Aetiology of type 2 diabetes

Insulin is a hormone produced by the islet β-cells in the pancreas. It regulates the metabolism of carbohydrates, fat and protein in target tissues in the body (mainly skeletal muscles, liver and adipose tissue) and is key for maintaining normal levels of glucose in the blood. Insulin is secreted in response to raised blood glucose levels after the ingestion of food. Increased circulating levels of insulin stimulate uptake of glucose by target tissues where it is either stored as glycogen or used for fuel (6). Insulin also stimulates amino acid uptake for protein synthesis in muscles, and free fatty acids (FFA) uptake for triglyceride synthesis in adipose tissue. At the same time it suppresses levels of glucagon and other counter-regulatory hormones, which leads to reduced fat and protein breakdown and endogenous liver glucose production (6). In type 2 diabetes these pathways are disrupted and physiological levels of blood glucose cannot be maintained.

Because of the multifactorial nature of type 2 diabetes, the exact pathophysiology of this condition is still being elucidated. The disorder develops from the interplay of dysfunctions in insulin secretion and action on target tissues (9). A feedback mechanism exists between β-cell insulin secretion and peripheral insulin action that maintains normal glucose tolerance (10). One of the earliest dysfunctions in the development of diabetes is insulin resistance (IR), which arises when the target tissues' responses to physiological levels of insulin are disrupted or

delayed (10). To compensate for IR, β-cells increase insulin secretion (hyperinsulinaemia). In some people the pancreas cannot compensate fully for the protracted decrease in insulin sensitivity and there is a progressive loss of β-cell function, which leads to postprandial hyperglycaemia, impaired glucose tolerance (IGT) and eventually type 2 diabetes (11). Although the relative importance of IR and β-cell dysfunction are unclear, there is evidence that both conditions are present early on in the development of diabetes (12).

1.3.1 Factors affecting insulin resistance and β-cell function

Both genetic and environmental causes are important in the development of insulin resistance and β-cell dysfunction. Type 2 diabetes has a strong hereditability with the risk significantly increased in people with a first-degree relative with diabetes (13, 14).

Multiple environmental factors affect insulin resistance and secretion including age, exercise and fitness levels, smoking, dietary factors, obesity and visceral fat (12). Mounting evidence suggests that one of the primary links between lifestyle factors and diabetes is an imbalance in the delicate interaction between immune and metabolic responses. Inflammation has emerged in the last decade as a key feature of type 2 diabetes and other metabolic diseases (15, 16). The metabolic and immune systems are closely linked and mutually regulated. In normal conditions this interaction has evolutionary advantages, but can have adverse consequences under conditions of metabolic stress, such as over-nutrition and obesity (15). Prospective studies show that high levels of immune mediators and pro-inflammatory molecules are present many years before the development of type 2 diabetes (17, 18).

Insulin exerts its action by binding to specific membrane receptors in target tissues and so activating a signal transduction pathway (8). Modifications or defects in any of the steps involved in this pathway could disrupt normal glucose uptake and lead to decreased tissue sensitivity to insulin (8). Although genetic factors could contribute to some of these defects, it is thought that elevated FFA and inflammatory mediators, mainly caused by environmental factors, such as obesity, visceral fat accumulation and unhealthy diets, are key factors in insulin signal disruption (11, 15, 16, 19).

Individuals with type 2 diabetes have reduced β-cell mass and impaired insulin secretory capacity (9). Factors that have been linked to the slow but constant loss of β-cell function that precedes the development of diabetes include glucose toxicity and lipotoxicity (12, 19-21). Glucose toxicity refers to the metabolic stress caused by chronically elevated blood glucose levels over many years. This stress induces overproduction of reactive oxygen species, which can lead to oxidative damage of β-cells (21). Glucose toxicity affects all body tissues, but can be especially damaging for the pancreatic islet cells because of their limited antioxidant capacity compared to other organs (21). Lipotoxicity refers to the detrimental effects of elevated FFA on the pancreas (20). Excessive levels of FFA can lead to accumulation of fat in the pancreas with consequent disruption of β-cell function (11). It has been hypothesized that an underlying defect

is probably already present in genetically predisposed individuals and that glucose toxicity and lipotoxicity exacerbate β-cell dysfunction (12, 17).

1.4 Type 2 diabetes risk factors

1.4.1 Non-modifiable risk factors

As already mentioned genetic predisposition is a recognised risk factor for type 2 diabetes (13, 14). Age (22) and ethnicity (23, 24) are also established risk factors for the disease. The risk of developing the type 2 (23) diabetes is higher among certain ethnic groups including African Americans (23) and South Asians (24) and increases with age (22).

Social inequalities in health are well known as illustrated by the government-commissioned Marmot Review (25). In fact, the incidence of type 2 diabetes is influenced by socio-economic position (SEP), with persons from a lower SEP having a higher risk of developing the disease compared with persons from higher SEP (26-29). Different explanations might underlie the social gradient in type 2 diabetes. Lower education and income might limit knowledge about risk factors and reduce the material possibilities to act on these (29, 30). People from lower SEP might be more affected by psychosocial stress, which has been linked to diabetes (31).

1.4.2 Modifiable risk factors

Although the contribution of inherited factors is well established, the concomitant rise in obesity, sedentary lifestyle and type 2 diabetes in the last decades suggests a predominant role for environmental factors in the disease aetiology (32). Population studies have shown that the obesity pandemic brought about by a combination of lifestyle factors is a key contributor, particularly in middle and high-income countries, to the recent rise in metabolic disorders, including type 2 diabetes (33).

The widespread adoption of a diet characterized by easily available, abundant and relatively inexpensive energy-dense foods, has led to energy overconsumption. At the same time changes in transport and work patterns have reduced opportunities for physical activity and energy expenditure. These factors are thought to have led to the current global obesity epidemic and a dramatic rise in type 2 diabetes (34). Ecological studies have shown that when people migrate to countries with a more Westernized diet and lifestyle their risk of developing type 2 diabetes increases (35, 36). In middle and high-income countries the prevalence of unhealthy lifestyle risk factors is socio-economically patterned. Obesity, physical inactivity and unhealthy diets are all more common among people with lower SEP and educational attainment (37-42). Furthermore evidence suggests that these risk factors tend to cluster in individuals and that clusters of unhealthy behaviours are more common among lower SEP groups (43, 44). For example, people eating unhealthy diets are also more likely to be inactive (43).

As well as energy imbalance and lack of physical activity, an extensive body of literature reports a dose-response association between cigarette smoking and type 2 diabetes incidence. A

systematic review (45) of 25 studies reported an increased risk of 44% for active smokers compared to non-smokers. Smoking increases insulin resistance (46), inflammation (47) and might have direct toxic effects on pancreatic β-cells (48).

Some of these modifiable factors, namely obesity, abdominal adiposity and unhealthy dietary patterns, will be reviewed in more detail in the following sections.

1.5 Body weight and abdominal obesity

1.5.1 Overweight and obesity

It is well established that being overweight, defined as a Body Mass Index (BMI) of 25-29.9 kg/m^2 or obese (BMI ≥ 30 kg/m^2) increases the risk of developing type 2 diabetes as showed by many prospective studies (49-56). Furthermore, most intervention studies have demonstrated that weight loss decreases the progression to type 2 diabetes, at least in Western countries (57-62). A recent time-trend analysis, based on a sample of 6,460 British men, calculated that among men 26% of the recent rise in type 2 diabetes in the UK could be attributed to BMI changes in the British male population (63). A meta-analysis of 31 follow-up studies on the association between BMI and type 2 diabetes incidence found a pooled relative risk (RR) of type 2 diabetes of 1.19 per unit increase in BMI (64). This association was only slightly affected by adjustments for age, physical activity, smoking and SEP in those studies that included these confounders. A subsequent meta-analysis (65) found a pooled incident rate ratio (IRR) of type 2 diabetes for overweight of 2.40 (95%CI:2.12-2.72) for men and of 3.92 (95%CI:3.10-4.97) for women. Comparing obese people with normal weight subjects the IRR of type 2 diabetes were particularly large: 6.74 (95%CI:5.55-8.19] for men and 12.41 (95%CI:9.03–17.06) for women.

1.5.2 Abdominal obesity

Increasingly there is recognition that central rather than overall obesity might be more important in the pathogenesis of type 2 diabetes. Intra-abdominal visceral fat is more metabolically active than peripheral subcutaneous fat and is closely associated with insulin resistance (66). Although strongly associated with type 2 diabetes, BMI is a measure of overall obesity and gives no information about fat distribution. Measures of central obesity, mainly waist-to-hip ratio (WHR) and waist circumference (WC), have been used to predict metabolic risk related to visceral fat. Several studies have found that both measures are significant risk factors for type 2 diabetes, independently of BMI, in different ethnic groups (67-72). A meta-analysis of 32 studies (73) found similar pooled relative risks for incident diabetes for BMI (RR: 1.87, 95%CI: 1.67, 2.10), WC (1.87, 95% CI: 1.58, 2.20) and WHR (1.88, 95% CI: 1.61, 2.19). However, this analysis did not undertake statistical comparisons of these measures within the same study. When comparing the associations in the subset of studies with both BMI and WC or BMI and WHR, WC was moderately stronger while WHR was moderately weaker than BMI (73) .A subsequent meta-analysis (74) looking at the association between measures of abdominal obesity (WC, WHR, iliac circumference an intra-abdominal fat area) found a pooled odds ratio for type 2

diabetes (for all measures combined) of 2.14 (95%CI: 1.70-2.71) with most studies adjusting for BMI. In statistical comparisons between abdominal obesity measures, WC was slightly more predictive of type 2 diabetes than other measures.

One limitation of these reviews is that they did not consider possible gender differences. Recent findings indicate that the relative importance of abdominal obesity might be greater for women than for men (75-78). Analyses of the Monitoring Trends and Determinants on Cardiovascular Diseases Augsburg cohort study (77) reported a HR for diabetes of 1.48 (95%CI: 0.85, 2.60) for men and 5.60 (95%CI: 1.86, 16.86) for women comparing the highest with the lowest quartile of WC after adjustment for age, education, smoking, BMI, alcohol intake, and physical activity. These strong associations were not observed for WHR in women. For men BMI, WC and WHR had similar HRs for type 2 diabetes. Similar findings and gender differences in risk were recently observed in the large European Prospective Investigation into Cancer and Nutrition (EPIC)-InterAct Case-Cohort Study conducted among 26 countries in Europe (76) and the British Regional Heart Study (78). There might also be an additive effect of BMI and WC with the highest risk observed among men and women with a high WC and a high BMI compared with those having only one of these risk factors (77). However, the measurement of WC might be particularly informative among lower BMI groups (76, 79, 80). In the EPIC-InterAct (76) the risk of diabetes among overweight people with high WC was similar to obese people while the risk in overweight people with normal WC was comparable to people with a normal BMI.

These meta-analyses have shown that WC is as good or a better predictor of type 2 diabetes than WHR (73, 74), therefore WC has been preferred in clinical and epidemiological settings, since WC is simpler to measure and interpret. Recently however, waist-to-height ratio (WHtR) has been proposed as a superior indicator of abdominal obesity and of risk of metabolic disease (81). The argument for adding height to WC is that shorter people have supposedly more abdominal fat than taller ones for the same WC measurement (82). Indeed WHtR has been found to have a stronger correlation with visceral abdominal fat than BMI, WHR or WC, although WC is significantly better than BMI and WHR (83, 84). However, a meta-analysis comparing the association of obesity indices with incident type 2 diabetes confirmed the superiority of WC and WHtR to BMI, but did not find any additional benefit in measuring height as well as WC (80). The pooled relative risks of type 2 diabetes were 1.62 (95%CI: 1.48, 1.78) for WHtR, 1.63 (95%CI: 1.49, 1.79) for WC and 1.55 (95%CI: 1.43, 1.69) for BMI. Therefore, although WHtR might be slightly better than WC in predicting diabetes, its superiority, and therefore clinical utility, has not been completely proved.

1.5.3 Physiological mechanisms

The connection between obesity and type 2 diabetes encompasses a complex interplay of mechanisms, which are still been elucidated. These mechanisms mainly involve pro-inflammatory cytokines, disrupted fatty acid metabolism and cellular processes, such as mitochondrial dysfunction (85).

Increasingly, type 2 diabetes has been viewed as an autoinflammatory disease (86). It is now well-known that obesity is characterised by a state of low-level chronic inflammation, due to the pro-inflammatory molecules produced by adipocytes and immune cells within adipose tissue (15). Over-feeding, particularly excess free fatty acids and glucose, stresses adipose tissue leading to an abnormal production of cytokines and chemokines, such as tumour necrosis factor and interleukin-1β (86). In turn, the release of these inflammatory mediators in the circulation induces inflammation in other tissues, including islet β-cells. Increased tissue inflammation activates intracellular pathways that lead to the development of insulin resistance (87).

Another important mechanism linking obesity to type 2 diabetes is the increase in circulating lipids (hyperlipidemia) typical in obesity. Increased ectopic fat deposition (the storage of triglycerides outside adipose tissue) in the liver and skeletal muscles can induce peripheral IR by interfering with cellular functions (88); while the toxic effect of free fatty acids on the pancreas can contribute to β-cell dysfunction (19). Excess fat storage can also lead to larger adipocytes, which are more resistant to the effect of insulin (14).

It is important to note that not all obese people develop type 2 diabetes. It is probable that an interaction between genetic and environmental cues might cause adipose tissue dysfunction, with associated adipocyte hypertrophy, heightened inflammatory reactions and consequent pathologic ectopic fat accumulation (89).

As noted above, the negative effects of abdominal adiposity are mainly explained by visceral fat rather than subcutaneous fat. Visceral fat is mostly stored around the abdomen while subcutaneous fat is more common in peripheral fat accumulation. Visceral fat tends to increase with age and is more prominent in men and post-menopausal women (90). Compared with subcutaneous fat, visceral fat is more lipolytic, which means that stored lipids are broken down, and FFA are released in the circulation, more easily (91). FFA released by abdominal depots enter the liver directly, and thus are a major contributor to liver IR as well as systemic IR (11). In addition, the overproduction of cytokines and hormones released by adipose tissue is more pronounced in visceral obesity compared to peripheral obesity (90).

The larger effect of abdominal fat on type 2 diabetes risk for women compared to men is not entirely clear. It is thought that hormonal differences affecting fat distribution might play a role in the sex difference of relative risk (92). Women have on average larger hips reflecting higher peripheral subcutaneous fat stores. It is possible that women with a more masculine body shape characterised by higher central adiposity, might have higher metabolic risk because of both the decreased protective effect of peripheral fat and the diabetogenic effect of abdominal fat (75).

1.6 Life course epidemiology of body weight, fat distribution and type 2 diabetes

Life course epidemiology has been defined as the study of the long-term effects of biological or social exposures that act during early life, childhood, adolescence and adulthood on later health

or disease risk (93). Interest in the life course aetiology of chronic diseases has increased in the last decade. A range of models have been proposed to investigate how different factors affect later disease risk by interacting and accumulating over the life course. Three life-course models of growth and weight gain might be of particular relevance for future risk of type 2 diabetes (93). The first is the critical period model, underlying the concept of fetal programming of disease, which argues that impaired fetal growth during a certain window of time can impact irreversibly on birth weight and subsequently on diabetes risk (94). In an accumulation of risk model the duration of overweight or obesity is hypothesised to increase diabetes risk independently of the degree of obesity. The model of sensitive period hypothesises that the risk of diabetes might be higher if weight is rapidly gained during certain periods of the life course compared to others.

1.6.1 Critical period model: birth weight and early growth

The concept of foetal programming of disease refers to a process whereby events affecting the development of the fetus at certain critical periods can have later life repercussions on disease outcome (94). So far, the interest in foetal programming has mainly focused on the effect of malnutrition on birth weight, as a crude marker of foetal growth. It is now well established that low birth weight is associated with increased risk of type 2 diabetes in a wide range of populations (95, 96). In a recent systematic review of 31 studies including a total of 6090 diabetes cases, Whincup et al (96) found a combined OR for type 2 diabetes of 0.80 (CI, 0.72-0.89) per 1-kg increase in birth weight. This association was independent of socio-economic circumstances and adult BMI, both possible confounders. There was a strongly graded inverse relationship between birth weight and diabetes, particularly for birth weights lower than 3kg. For birth weights larger than 4kg there was a modest positive association between birth weight and type 2 diabetes, which might be a consequence of gestational diabetes-related macrosomia (97). This was particularly evident in native North Americans among whom the birth weight-type 2 diabetes relationship was strongly U-shaped. The authors suggested that the high level of maternal diabetes among these populations was associated with high birth weight and subsequently diabetes.

1.6.1.1 Physiological mechanisms

According to the thrifty phenotype hypothesis proposed by Barker and colleagues (98) maternal malnutrition, which diminishes nutrients supply to the foetus, can trigger foetal metabolic adaptations in order to spare vital organs and increase the chances of survival in an environment with limited nutrient supply. These adaptations could lead to reduced β-cell mass growth and permanent changes in the metabolism of glucose (98). The evolutionary advantages of this adaptation have negative consequences when the individual grows up in an environment with abundant nutrient supply (98). As well as growth in utero, weight gain and growth in early life have been linked to diabetes risk (99). The normal body weight curve of infants is characterised by fast growth during the first year of life, followed by a slow-down for a few years and a second phase of rapid weight gain (100). The timing of this second phase, termed adiposity rebound has been linked to type 2 diabetes and adult obesity (100). Children with a

younger age at adiposity rebound, particularly if they were born small, have a higher risk of being glucose intolerant in adulthood (101). Using dual-energy X-ray absorptiometry, Taylor and colleagues showed that early adiposity rebound is characterized by rapid and larger gains in fat tissue compared to late adiposity rebound (102). Therefore this early rapid gain of adiposity might underlie a predisposition to higher glucose intolerance in adulthood.

1.6.2 Accumulation of risk model: duration of obesity

Although there is abundant evidence linking excess weight with type 2 diabetes, most studies have focused on the degree of obesity using only one BMI measurement to assess obesity status. However, the duration of obesity (or overweight) could be an important risk factor for type 2 diabetes independent of the degree of obesity, as it has been suggested by a few prospective studies (103-107). It has been hypothesised that being obese for longer might affect diabetes risk by way of progressively reducing insulin resistance and β-cell function (104). However, the exact mechanism is not clear. In a population of Pima Indians the incidence of diabetes among people who had been obese ≥10 years was twice as high as that in people who had been obese <5 years, independently of current BMI (105). Data from the British Regional Heart Study (107) showed that, compared with normal weight category, men who had been severely overweight (BMI=28-29.9 kg/m^2) for ≥5 years had a higher diabetes risk (4.74, 95%CI: 2.99-7.51) than those who had been severely overweight for <5 years (2.68, 95%CI: 1.50-4.81). The risk associated with ≥5 years of obesity was even higher (8.04, 95%CI: 5.06-12.74 for obesity >5 years and 4.36. 95%CI: 1.33-14.28 for obesity <5 years). In this study however only the initial BMI was based on measured weight and height, while the follow-up values were self-reported. In the Framingham Heart Study (103) the risk of type 2 diabetes for men increased by 11% for each additional 2 years of obesity after adjustment for current BMI. In women the risk increased for duration of 5-14 years compared to less than 5 years but did not change further for longer durations. These studies only looked at adult-onset of obesity. Recent findings from the 1958 birth cohort showed that, compared to never being obese, long-term obesity from childhood was associated with more than 20-fold increased risk of elevated HbA1c at age 45 years (106). Those who became obese in mid-adulthood had a three-fold increased risk. These associations were mostly explained by the higher BMI attained after a longer duration of being obese and were greatly weakened after adjustment for current BMI. Similar trends were found with longer durations of overweight, although the relative risks were smaller than for obesity duration.

Recently two studies have evaluated the combined effect of degree and duration of excess body weight on type 2 diabetes, using a composite measurement in a similar way to how “pack-years” is used to asses the cumulative exposure to cigarette smoking (108, 109). The first study (109) was conducted among adolescents and young adults (at the start of the study) with a mean follow-up of 25 years. Excess BMI-years, an index calculated by summing the differences between the reference BMI (25 for adults or 85th percentile for adolescents) and the observed BMI for each data collection year, was associated with increased type 2 diabetes risk. As an

example the authors reported that the odds of type 2 diabetes for a white 40 years old man with 200 excess BMI-years was 2.94 (95%CI: 2.36-3.67) compared with a similar aged white man with 100 excess BMI-years. Using ROC curves, the model containing excess BMI-years was more predictive of type 2 diabetes risk than baseline BMI. For the same BMI-years the risk was higher for younger adults, which led the authors to suggest that prevention interventions might be more effective at a younger age. The second study (108) analysed a similar index of duration and degree of obesity, which the authors termed Cumulative Excess Weight, in a sample of adult people followed-up from their mid-thirties to mid-fifties. For each standard deviation increase in Cumulative Excess Weight the odds of type 2 diabetes was 1.99 (95%CI: 1.64-2.40) independent of other risk factors for diabetes, age and sex. However, once stratified by baseline BMI, the association was significant only in people with a normal BMI.

Overall the evidence suggests that the duration, as well as the degree of obesity is important in type 2 diabetes risk. However, only a few prospective studies have investigated duration of overweight or obesity longer than 15 years (105, 106, 108, 109) while some used self-reported BMI measures (107, 109). Therefore more studies are needed on the cumulative effect of obesity particularly for longer durations and earlier onsets, given the increasingly younger age of obesity onset.

1.6.3 Sensitive period model

Accelerated gains in weight and BMI during childhood, particularly in children with low birth weight and early adiposity rebound, have been associated with higher glucose intolerance and increased risk of type 2 diabetes in adulthood (99, 101). In a Finnish study people who developed type 2 diabetes in adulthood had faster BMI growths between age 7 and 15 years (99). Bhargava et al (101) found similar results in an Indian population where for 1 standard deviation (SD) increase in BMI between age 2 and 12 years the odds ratio of developing diabetes was 1.26 (95%CI: 1.08-1.48) after adjustment for adult BMI.

Many studies have found that weight gain in adult life (107, 110-115) increases the risk of type 2 diabetes. For example, in the Health Professionals Follow-up study, the risk increased by 7.3% among adult men for each kilogram of weight gained (113). However, it is still not clear whether there are periods over the life-course when weight gain is particularly detrimental for diabetes risk and glucose tolerance. The majority of studies investigated weight gain at different periods over the adult life (110, 113-116); these studies mainly found that weight gain during early adulthood has a stronger impact on later type 2 diabetes risk than weight gain in middle or late adulthood. It has been suggested that people with a higher susceptibility to develop type 2 diabetes, such as those with a specific genotype, might tend to gain weight early in adulthood (116). Alternatively, the stronger association of diabetes with BMI gains in earlier rather than in later adulthood might be explained by the longer exposure to cumulative excessive body weight (115).

A recent analysis of the 1958 birth cohort study (106) extended the investigation of sensitive periods of weight gain to encompass both childhood and adulthood. The authors analysed the association between BMI gain during multiple life-course periods (birth-7 years, 11-16 years 16-23 years, 23-33 years, 33-45 years) and HbA1c levels adjusting for BMI at the beginning of each period. Weight gain at any period was associated with increased risk of hbA1c>7, particularly at age 23-33. When attained BMI was taken into account however, associations between weight gain during adulthood and hbA1c were mainly explained by attained BMI, while associations with weight gain from birth to age 7 were independent of attained BMI.

Thus, although some evidence suggests that both early childhood and early adulthood weight gain might be more detrimental for future diabetes risk, further life course analyses are needed to confirm these findings.

1.6.4 Changes in abdominal obesity

Many studies have reported that abdominal fat is a strong predictor of incident diabetes (67-72). However, changes in WC and other measures of abdominal fat over the life course have not been studied extensively. In the Health Professionals Follow-up Study (113), changes over 9 years of WC and waist to hip ratio were strongly associated with type 2 diabetes among older adult males. However, when controlling for weight change the association was weak (RR: 1.7, 95%CI: 1.0, 2.8 comparing the highest with the lowest quintile) and only significant for substantial WC changes (>14cm). Anthropometric measurements were self-reported, which might have underestimated the results (117). In the Coronary Artery Risk Development in Young Adults Study 15-years changes in WC were associated with increased insulin resistance and diabetes incidence although no adjustment for BMI was attempted (118). The most recent study of WC changes and diabetes was an analysis of more than 35,000 men and women in the Danish Diet, Cancer and Health study (119). Although WC at baseline was a strong predictor of diabetes independently of BMI, 5-years changes in WC were only weakly associated with risk in women (HR: 1.09, 85%CI: 1.04, 1.15, per 5 cm change in WC) after adjustment for body weight and no association was found among men.

The paucity of studies on longitudinal changes in abdominal obesity may reflect the fact that not all studies collected waist measurements until the importance of this risk factor for type 2 diabetes was fully recognized.

1.7 The Diabetes Prevention trials

In the last decade a number of randomised controlled trials (57-62) have demonstrated that lifestyle interventions aimed at reducing weight, improving diet and increasing physical activity, can prevent or delay the development of type 2 diabetes in high risk subjects. Furthermore, 2 trials (57, 60) showed that lifestyle interventions were more effective than the antidiabetic treatment metformin, a glucose-lowering drug, at reducing diabetes risk. There is also evidence

of the lasting benefits of lifestyle interventions even after the intervention has stopped (120-122).

One of the first diabetes prevention trials was the multi-clinic China Da Qing Diabetes Prevention Study (59), which randomised 577 IGT men and women to either a control, diet, exercise, or a diet with exercise group. All interventions were similarly effective with a diabetes risk reduction of up to 46% compared with the control group after 6 years of follow-up. Participants assigned to the diet group were prescribed a balanced macronutrient intake (55-65% carbohydrates and 25-30% fat) and encouraged to consume more vegetables and reduce intake of simple sugar. Those overweight were also recommended to reduce their caloric intake.

A subsequent trial, the Finnish Diabetes Prevention Study (62) randomised 522 high-risk subjects (middle age, overweight and with IGT) to either an intensive diet and exercise intervention or a control group. Participants in the intervention group were advised to lose weight, to limit their intake of total fat to <30% energy intake and saturated fat to <10% energy intake, and to increase their fibre intake to >15g/1,000 kcal. After a mean follow-up of 3.2 years, the intervention group had a reduced diabetes risk of 58% compared to the control group. The same risk reduction of 58% was also achieved in the United States-based Diabetes Prevention Program (57). This study is the largest diabetes prevention trial to date with over 3200 participants randomised to receive a lifestyle intervention, metformin or placebo with an average follow-up of 2.8 years. The dietary intervention of this trial was particularly focused on fat reduction and calorie restriction with emphasis on overall healthy eating.

Three further trials have been conducted among Asian populations. In a Japanese trial of 458 men (58), the diet and exercise intervention was aimed specifically at reducing weight and included advice on fat and portion size reduction and emphasis on vegetables. After 6 years of follow-up the risk reduction for diabetes was 67% compared to the control group. In the Indian Diabetes Prevention Programme (60) the lifestyle intervention group, which received advise on diet and exercise, had a reduced risk of diabetes of 28% compared with the control group. Participants in the intervention group were recommended to balance their energy intake and expenditure, avoid simple sugars and refined carbohydrates, reduce total and saturated fat intake and increase consumption of fibre-rich foods (whole grains, fruits, vegetables and legumes). In a very recent trial (61) of 641 overweight Japanese men, lifestyle modification that included physical activity and dietary advice, reduced type 2 diabetes incidence by 41% in subjects with IGT, although it was not effective among IFG participants. The dietary intervention included recommendations to maintain fat intake at 20-25% of total energy intake and carbohydrate intake at 55-60% of total energy intake as well as increasing fibre intake.

Although most interventions had positive effects on BMI and WC, there were wide variations among studies. In the Finnish Diabetes Prevention Study, the Diabetes Prevention Program and the Japanese trials the authors concluded that weight loss was the main driver of reduced diabetes incidence. However, the Diabetes Prevention Program and the Japanese studies were not designed to assess the independent effect of diet and exercise. Also, subsequent analyses

of the Finnish Diabetes Prevention Study found that composition of the diet was a predictor of lower diabetes incidence independently of BMI changes (123). In the China Da Qing Diabetes Prevention Study and the Indian Diabetes Prevention Programme weight loss was not substantial and not significantly different between control and intervention groups, suggesting that other mechanisms must have been important in reducing diabetes incidence (59, 60). In all Asian trials weight loss was not as high as in Western trials, suggesting that in Asian populations, which have a stronger genetic predisposition to type 2 diabetes, overall weight gain might not be as important as for Western populations. Differences in visceral fat are not properly captured by BMI or body weight. Thus changes in body composition might have been important. However, in the Indian Diabetes Prevention Programme changes in WC were also not significantly different between the control and the intervention groups.

1.8 Dietary factors and type 2 diabetes

Dietary factors are likely to play an important role in the prevention of type 2 diabetes both directly by affecting metabolic pathways and indirectly via body weight modulation. There is agreement that healthy eating advice is a key element of current preventive intervention strategies (124).

One of the main challenges in the study of diet-disease associations is the measurement of habitual food consumption. The major difficulties involved are in the accurate estimation of the quantity of foods habitually consumed by individuals and in the estimation of nutritional and energy intakes based on self-reported food intakes (125). Different methods can be used to assess diet; these are usually categorised into those that record intake as it occurs, such as diet diaries either based on weighted or estimated records, and those based on recall of dietary intake, such as 24-hour recall and food-frequency questionnaires (FFQ). By far the most commonly used methods in nutritional epidemiology are recall methods, particularly FFQs, which are a relatively inexpensive and standardized way to obtain dietary information from a large sample. The disadvantages of FFQs however are the lack of detailed information and the large measurement error (126). In contrast, the dietary record method is more precise and is often considered as the gold standard. However, this method is more costly and therefore is seldom used in large studies; furthermore, it can be burdensome for study members, especially when weighted quantities are used, and therefore can lead to changes in their habitual eating behaviour (127).

Despite the difficulty of assessing diet in the population a growing amount of data suggests a significant protective role for some dietary factors, especially low glycaemic index (GI) foods and dietary fibre and a detrimental role for foods high in total and saturated fat.

1.8.1 Glycaemic index and glycaemic load

The quantity and quality of carbohydrates in food have important metabolic effects. Carbohydrates that more rapidly increase insulin and glucose levels seem to have more

detrimental effects on metabolic health compared to slowly digested ones (128). The GI, introduced by Jenkins et al in 1981 (129), measures the magnitude of change in blood glucose levels (the glycaemic response) after the ingestion of different digestible carbohydrate-containing foods. The GI is calculated by comparing, in the same individual, the post-prandial glycaemic response of a food to the glycaemic response after intake of the same amount of carbohydrate in a reference food, which is either glucose or white bread (129). The type of starch, level of gelatinisation, cooking methods and the amount of fibre, protein and fat affect digestion and the GI of foods (130). The glycaemic load (GL) is the product of the GI of a food and its carbohydrate content (131).

After a high GI meal blood glucose levels increase rapidly and consequently induce a large insulin response. Hyperinsulinaemia triggers faster nutrient absorption, leading to a quicker late-postprandial fall in blood glucose than would be observed with a slower release of insulin (132). The consequent hypoglycemia triggers an elevated counter-regulatory hormone response, which restores blood glucose levels by increasing endogenous glucose production (133). At the same time these hormones induce breakdown of stored fat increasing circulating levels of FFA (133), which as already mentioned can promote insulin resistance and β-cell dysfunction. High GI-induced postprandial hyperglycaemia could also directly affect β-cell functions because of the glucotoxic effect of excess glucose on pancreatic cells (132). Low-GI foods have positive effects on satiety leading to lower energy intake at a subsequent meal (134). A review of randomized trials reported that participants consuming a low GI diet lost an average of 1kg more compared to high GI diets or energy-restricted low-fat diets (134). Finally there is some evidence that high GI foods could lead to preferential visceral fat accumulation (135, 136).

Most studies on GI and type 2 diabetes have shown a protective effect of low GI diets. In the Health Professionals Follow-up Study (137) the relative risk of type 2 diabetes was 1.37 (95%CI: 1.02, 1.83) comparing the highest with lowest quintile of GI. A similar risk estimate for GI (RR: 1.37; 95%CI: 1.09, 1.71) and GL (RR= 1.47; 95%CI: 1.16-1.86) was found among middle-aged women in the Nurses Health Study (131). Similar results were confirmed in other large cohorts, particularly among American, Australian and Asian cohorts (138-144). The evidence is stronger for GI than for GL, with a few studies finding associations with GI but not for GL (141, 142). All these studies adjusted for major confounders, including social confounders, physical activity, smoking and BMI. However, a few studies showed only moderate or no effect for GI or GL and type 2 diabetes (145-147). The discrepancies in findings could be due to the use of different dietary questionnaires, most of which were not designed to capture dietary GI or GL. Other explanations include differences in the range of GI and GL across populations and different genetic responses to GI. Inconsistencies in assignment of GI values to different foods might have also contributed to these contradictions. Most of the data tables used to assign GI values are currently from the United States and Australia, where the interest in GI has been stronger. Few European and country-specific GI tables exist, which might explain the null results in a large European cohort (146).

Two meta-analyses have tried to address these discrepancies. A meta-analysis of nine prospective cohort studies (148) reported that both high GL and high GI diets increase the risk of type 2 diabetes with a relative risk of 1.27 (95 % CI 1.12, 1.45) and 1.40 (95 % CI 1.23, 1.59) respectively when comparing the highest versus the lowest quintiles. The meta-analysis was performed using adjusted models (including adjustment for age, sex, SEP, family history of diabetes, BMI, physical activity and dietary fiber). A subsequent meta-analysis (149) of 13 studies confirmed the protective effect but reported lower risk estimates for GI (RR: 1.16; 95%CI: 1.06, 1.26) or GL (RR:1.20; 95% CI: 1·11, 1·30). Furthermore, a Cochrane review of 11 randomized trials on GI or GL diets among diabetic patients showed a reduction of 0.5% in HbA1c levels in subjects consuming a low GI diet. (150). Thus the evidence points to a role for GI in managing as well as preventing type 2 diabetes, although a few discrepancies remain, mainly due to the methodological challenges of assigning GI values.

1.8.2 Dietary fibre

Dietary fibre is the term for a complex mixture of substances with variable physiological and chemical properties. Generally dietary fibre has been defined as non-digestible carbohydrates, referring to carbohydrates that resist digestion in the small intestine and are partially fermented in the large intestine (151). They consist of non-starch polysaccharides, which are part of the plant cell wall, such as cellulose, hemicellulose and pectin, as well as other polysaccharides, such as gums and oligosaccharides (152). Based on physical and chemical properties, fibre can be subdivided into soluble fibre, which dissolves in water, and insoluble fibre. Some soluble (or viscous) fibres are able to form gels when dissolved in fluid (153). Dietary fibre is fermented by bacteria in the large intestine to a varying degree depending on the type of fibre. These varied characteristics of dietary fibre are involved in different physiological mechanisms, which confer distinctive health benefits. Dietary fibre is abundant in cereals, fruit and vegetables, which contain a mixture of different types of fibre.

Several possible mechanisms have been proposed for the protective effect of dietary fibre. Fibre-rich foods have a lower GI, which results in lower glucose and insulin responses (129). Dietary fibre's low energy density and large volume promote satiation leading to decreased energy intake (154). A review of 38 studies showed that dietary fibre also increased satiety between meals (155). The effect of dietary fibre on satiety is due to its mechanical stimulation of the intestine and its action on appetite-related intestinal hormones (156). Results from the large EPIC study found that fibre intake was associated with higher weight loss and WC changes (135).

The anti-inflammatory properties of fibre have also been shown in molecular and human studies (157-159). Some types of dietary fibre are fermented by bacteria in the gut, resulting in the production of short chain fatty acids (159). These have anti-inflammatory effects that are modulated by a wide range of cellular mechanisms, including reduced expression and proliferation of inflammatory mediators (157). In the Finnish Diabetes Prevention Study dietary fibre intake lowered the levels of C-reactive protein and interleukin 6, two markers of

inflammation linked with type 2 diabetes, independently of changes in BMI (160). Improvement of first-phase insulin secretion in at-risk people has also been reported in a recent trial (161).

High consumption of dietary fibre and whole grain foods, which are a rich source of fibre, has consistently been associated with decreased risk for type 2 diabetes in several prospective epidemiological studies (131, 137, 142, 145, 147, 162). In the Iowa Women's Health Study (145), the risk for type 2 diabetes was reduced by 22% in women consuming an average 26 g/d of dietary fibre. In the Nurses Health Study II (142) the risk reduction was particularly strong for cereal fibre with a RR of 0.64 (95% CI: 0.48, 0.86) comparing the highest with the lowest quintile of intake. Both these large studies reported effects independent of BMI as well as other social and health confounders. Similarly, in a Finnish cohort (163), fibre from cereal, was significantly associated with the risk of type 2 diabetes (RR: 0.36 (95% CI: 0.18, 0.70) independent of BMI, while total dietary fibre had a weaker association. A Cochrane systematic review reported significant risk reductions ranging between 0.37 (95%CI: 0.20-0.77) and 0.79 (95%CI: 0.67-0.93) with high intake of cereal fibre (164). The difference in risk reductions was probably due to the difference range of confounders adjusted for in the various studies; while all studies adjusted for age, sex and BMI not all adjusted for physical activity, SEP and family history of diabetes.

In the diabetes prevention trials increased fibre consumption was part of the dietary intervention that reduced diabetes incidence. Post-hoc analyses in the Finnish Diabetes Prevention Study (123) showed that increased fibre intake was associated with reduced type 2 diabetes risk and waist circumference independently of weight changes.

Although prospective studies show that insoluble fibre, which is mainly found in cereals, are more protective than soluble fibre, found in fruit and vegetable as well as some cereals, intervention trials have mainly focused on the ability of soluble fibre to acutely reduce glycaemia and insulin responses (165). However, long-term beneficial effects on insulin sensitivity of both soluble and insoluble fibre have also been reported (166, 167). It is probable that a mixture of different types of fibre offers the most beneficial effect.

1.8.3 Dietary fat

Dietary fat is an important nutrient in the human diet. Dietary fats comprise triglycerides (fats and oils), phospholipids, and sterols (cholesterol). Triglyceride, which is broken down to fatty acids, is the most abundant type of fat in the diet. Depending on the presence or absence of double bonds on the carbon chain, fatty acids can be classified into saturated (no double bond), monounsaturated (one double bond) and polyunsaturated (two or more double bonds) fatty acids (168). The latter includes the essential fatty acids alpha-linolenic acid and linoleic acid, which cannot be synthesized from the body and are important in many cellular functions and their anti-inflammatory properties. Dietary fat is used as an energy source and storage in the body as well as for insulation and protection from external insults. It also facilitates absorption of

fat-soluble vitamins in the body as well as giving palatability and acting as a flavor carrier in foods (168).

On average, cross-sectional (169-171) and prospective studies (172-174) have found that high fat diets, are associated with impaired glucose tolerance and the onset of type 2 diabetes. In some studies the association between total fat was independent of BMI (172, 173). Some studies however did not find an association between dietary fats and type 2 diabetes (51, 137). These discrepancies could be attributed to the variability of the dietary assessment method as well as the susceptibility of fat and high-energy foods to be underreported from obese people (175). Lately it has been shown that metabolic response to dietary fat intake is highly dependent on genetic susceptibility (176). In a recent analysis of the Data from an Epidemiological Study on the Insulin Resistance Syndrome (177) a high fat diet was a significant predictor of type 2 diabetes, independent of BMI, only among certain genotype carriers. This genetic and nutritional interaction effect for dietary fat might explain why some studies did not find an association in the general population.

Intervention studies aiming at preventing type 2 diabetes in at-risk individuals have demonstrated that a low-fat diet was successful at reducing body weight and type 2 diabetes (59, 121, 122, 178). In the Diabetes Prevention Program the largest dietary association with type 2 diabetes incidence was seen for total fat intake (178). Participants in the lifestyle intervention group of the Diabetes Prevention Program decreased their percent of calories from fat by 6% compared to 0.8% in the control groups. For every 5% reduction of percent calories from fat there was a reduced type 2 diabetes incidence of 25% during the follow-up period. However, the effect of dietary fat was mainly explained by its strong association with weight loss. In post-hoc analyses of the Finnish Diabetes Prevention Study dietary fat was a significant predictor of weight loss and reduced progression to type 2 diabetes (122). Comparing the highest quartile of fat intake with the lowest, the hazard ratio for type 2 diabetes incidence during 4.1 years of follow-up was 2.14 (95% CI: 1.16, 3.92) after adjustment for sex, intervention assignment, weight change and physical activity.

The main link between total dietary fats and type 2 diabetes seems to be the promotion of excess body weight, as suggested by the literature. Fats are high in energy density and very palatable, leading to overconsumption (179). Prospective studies and intervention trials support the connection between lower dietary fat intake and weight loss (180-182). A systematic review of intervention trials confirmed that low-fat diets are associated with significant and sustained weight loss (183). There is also evidence that dietary fats can induce inflammatory cytokine production (184), which promote insulin resistance. It has been shown that following a single high-fat meal concentrations of inflammatory mediators were higher and levels of anti-inflammatory adiponectin were lower (185).

There is increasing evidence that the type of fatty acids consumed, as well as the quantity, might play an important role in β-cell functionality and insulin sensitivity, particularly during the postprandial period (186). Consistently, observational studies have found that saturated fatty

acids (SFA) increase hyperinsulinaemia and risk of developing metabolic diseases, while unsaturated fats, particularly monounsaturated fatty acids (MUFA) and to a lesser extent polyunsaturated fatty acids (PUFA), improve insulin sensitivity and glycaemic control (187, 188). Intervention studies report that decreasing the proportion of SFA in the diet improves insulin sensitivity, glycaemic control, β-cell function and insulin secretion (189-191). A recent systematic review of 9 randomized controlled trials with a duration ranging between 6 and 48 months found that diets high in MUFA and low in SFA were more effective at reducing HbA1c in patients with abnormal glucose metabolism than diets low in MUFA (192).

Different mechanisms can explain the metabolic effects of MUFA and SFA. Compared to MUFA, SFA are known to induce higher insulin secretion in the pancreatic β cells, with consequent postprandial hyperinsulinaemia (189). Evidence from animal studies has shown that SFA have the ability to disrupt insulin signaling pathways in skeletal muscles thus contributing to insulin resistance (193). On the other hand, MUFA do not interfere with signaling pathways. Another potential mechanism is the observation that some SFA preferentially facilitate visceral fat deposition (194). Finally, while SFA have been reported to increase markers of inflammation, MUFA seem to have anti-inflammatory effects (195).

1.8.4 Other dietary factors

Other dietary factors that are purported to reduce type 2 diabetes risk include antioxidants, phenolic compounds, magnesium and moderate alcohol intake (196, 197, 200). However, for any of these factors, more evidence, particularly from controlled trials, is needed to draw valid conclusions. Fruit and vegetables are one of the richest sources of dietary antioxidants. They are also low in energy density and high in insoluble fibre; therefore they may help prevent weight gain as well as reduce inflammatory responses and oxidative stress (196, 197). A recent systematic review of prospective cohort studies reported that green leafy vegetables, but not fruits or vegetables in general, were associated with a modest reduced risk of type 2 diabetes (198). However, the studies included in the review had a high level of heterogeneity, caused by differences in food classification and dietary assessment methods. Thus, the evidence on specific fruits and vegetables from available studies remains inconclusive.

Evidence is emerging that moderate amount of alcohol could lower type 2 diabetes risk (199). Although the mechanisms are not completely understood, alcohol is known to improve insulin sensitivity through different pathways, including elevation of adiponectines and reduction of pro-inflammatory compounds (200).

A recent meta-analysis reported a U-shaped association between alcohol consumption and incidence of the disease (199). Compared to non-drinkers men who consumed moderate amounts of alcohol (22g/day) had a relative type 2 diabetes risk of 0.87 (95%CI: 0.76-1.00); the corresponding RR for women with a moderate alcohol intake (24g/day) was 0.60 (95%CI: 0.52–0.69). Alcohol started to become deleterious at intakes above 60g/day for men and 50g/day for women, although there was more uncertainty regarding the deleterious effect of heavy alcohol

intake. Most of the studies included adjusted only for age and sex. Half of the studies adjusted for BMI and two adjusted for education. Moderate alcohol consumption is more common among people from high SEP (201), thus the lack of adjustment for SEP might have confounded the results.

Phenolic compounds, of which coffee, tea and red wine are rich sources, have been reported to reduce postprandial glycaemia and improve insulin sensitivity (202). A recent systematic review of observational studies reported that high intakes of tea and coffee were associated with decreased type 2 diabetes risk (203). The association was not affected by adjustment for age, family history of diabetes, BMI, SEP, smoking, alcohol and physical activity. However, small-study bias might have overestimated the results. Also, very few studies adjusted for other dietary factors, thus residual confounding by dietary factors associated with tea or coffee consumption might still be possible.

Magnesium deficiency could disrupt insulin-signaling pathways leading to decreased insulin sensitivity (204). A recent meta-analysis of cohort studies reported a modest diabetes risk reduction for high magnesium intakes, but this was significant only among overweight subjects (205). Few studies examining magnesium intake and type 2 diabetes risk adjusted for other dietary factors and specifically for dietary fibre, which is highly correlated with magnesium; thus confounding by other dietary factors is possible.

Although moderate alcohol intake, high coffee and tea intake and magnesium consumption have increasingly been recognised as possible type 2 diabetes protective factors, more studies, especially large cohorts or randomised controlled trials are necessary to draw confident conclusions.

1.8.5 Limitations of studies investigating single dietary factors

The traditional approach to the study of the relation between diet and disease has been to focus on single nutrients and foods. However this approach has several limitations. For example, it does not account for the fact that foods and nutrients are not eaten in isolation, but rather in different combinations that can interact with each other (206). Many nutrients in the diet are strongly correlated, making it difficult to study their separate effects (207). Another limitation is that the effect of single nutrients might not be large enough to be detected, but the cumulative effect of multiple nutrients or foods can be significantly greater (208).

1.9 Dietary patterns and type 2 diabetes

Because of the limitations of a single nutrient approach, dietary pattern analyses have been introduced as an alternative method of studying associations between diet and chronic disease and have acquired increasing popularity in the past two decades. This method approaches diet in a more holistic way; thus it might better reflect the actual dietary habits in free-living people, where foods are consumed together (206). It also overcomes the problem of collinearity and interactions between nutrients since potential dietary confounders are incorporated into the

dietary pattern (209). Furthermore cumulative effects of certain combinations of foods might be stronger than the effects of single foods and nutrients (210).

1.9.1 Methodologies used to derived dietary patterns

Two main approaches have been used for the study of dietary patterns in nutritional epidemiology: theoretically and empirically derived dietary patterns. The first approach defines dietary patterns 'a priori' using current knowledge of nutritional health (211). By contrast, the second approach uses statistical models to derive intake patterns from existing dietary data and involves mainly an 'a posteriori' interpretation. An emerging empirical method, called reduced rank regression, uses a combination of 'a priori' and 'a posteriori' methods (209).

1.9.1.1 Theoretically defined dietary patterns: Diet quality scores

Diet quality scores consist of foods or nutrients that are thought to be healthy and are quantified and grouped into an overall measure of diet quality (212). Dietary recommendations, guidelines and current knowledge of health have been used to create indexes and scores. A critical review identified 20 different scores of diet quality in the published literature, mostly based on variations of four main scores (212). Among these, the Healthy Eating Index (HEI) (213), the Mediterranean Diet Score (MDS) (212) and their variations have been most extensively investigated. The HEI is a score made up of 10 components based on the Dietary Guidelines for Americans. The MDS was created following considerable epidemiological interest in the health-protective benefits of Mediterranean diets. Keys first popularized the term "Mediterranean diet" in the 1960s based on the food habits of some Mediterranean populations (214). The MDS and its variations include plenty of plant foods, such as vegetables, fruits, legumes, nuts and cereals, the use of olive oil (which contains a high proportion of MUFA) as the main source of fat, low intake of red meat and moderate wine consumption, preferably at meals (215).

The strengths of diet quality scores are their simplicity and the good reproducibility (207). This method has also several limitations. For example, investigating the Mediterranean diet in a non-Mediterranean population might not be useful as very few people will adhere to this dietary pattern. The validity and usefulness of dietary scores in predicting disease risk have also been questioned (212). Because they are not created to predict health outcomes but rather adherence to a certain guideline or recommendation, existing dietary scores might not be relevant for certain diseases. Furthermore there are major difficulties in devising diet quality indices. Subjectivity can be a problem, as the investigator has to make several decisions, for example regarding cut-offs of intakes and weighting of different foods included (207).

1.9.1.2 Empirically defined dietary patterns: factor and cluster analyses

Factor analysis is a multivariate statistical technique that identifies common patterns of food consumption from existing dietary data. Principal components analysis is the most common factor analysis method used in nutritional epidemiology. Principal components analysis is a multivariable technique that identifies latent constructs using correlations between data; from a large number of dietary variables a set of a few uncorrelated dietary patterns are created. Food

items, or groups, from questionnaires are aggregated based on the degree to which they correlate with one another. The resulting patterns are linear combinations of foods items that maximally explain the variance in the food intakes. A summary z-score for each pattern is then calculated for each individual calculating the degree to which their dietary intake reflected each dietary pattern. This score is a function of the contribution (loading) of each food to the pattern and the frequency with which is consumed by each individual. Z-scores can be used in regression analyses to investigate associations between dietary patterns and various outcomes, such as disease risk factors (206, 207). Cluster analysis is a multivariate statistical technique that aggregates individuals into mutually exclusive groups (clusters) with similar dietary intakes (206, 208).

One drawback of these methods is that, like a priori methods, they are prone to subjectivity since the investigator has to make many choices during the dietary pattern analysis. For example, the investigator needs to decide whether to collapse and how to group the initial dietary data; how to quantify and treat the input variables; and which dietary pattern to investigate in risk modeling (211). Another limitation is that these methods are purely exploratory and like diet quality scores, not necessarily designed to derive dietary patterns that specifically predict diseases risk and therefore their mechanisms of action may be difficult to elucidate (207).

1.9.1.3 Reduced rank regression (RRR)

RRR is becoming a more frequently applied statistical method in the study of dietary patterns. RRR combines both exploratory and hypothesis-driven elements (210). This statistical method is technically similar to principal components analysis, but it uses two sets of data; one being the predictor variables i.e. food intakes, the second being a small number of response variables. The response variables are chosen on the basis that they are hypothesised to be intermediate variables on the pathway between food intake and the health outcome of interest. RRR-derived dietary patterns are linear functions of food intake that maximally explain the variation in the response variables (210). The response variables may be nutrients or biomarkers for which evidence exists of an association with the outcome of interest. There are some limitations to the use of biomarkers as response variables thus dietary nutrient intermediates might be more desirable. For example, most chronic diseases are caused by a complex interplay of biological pathways, making it difficult to select the most appropriate biomarkers (208). By examining dietary nutrient response variables, which are the product of food intake, there may be more certainty about dietary intakes that are important for the outcome – whereas for biomarkers this may be less clear unless the exact pathways between dietary intake and the biomarkers are known. Also, nutrient based dietary patterns are easier to interpret for giving public health advice compared to biomarkers. Furthermore, some biomarkers, such as blood lipids, may actually be a proxy for the disease of interest and therefore too close to the outcome and not suited as a real ‘intermediate’.

The greatest advantage of RRR is that it is more hypothesis-based than other exploratory empirical methods as it incorporates information on the biological pathways between foods and disease (209, 210). Thus, RRR offers potential to advance the knowledge on dietary patterns predictive of disease outcomes and the pathways through which they might act. A limitation of this method is that the response variables must be chosen carefully, particularly biomarkers, and require a-priori evidence. These variables must also be available for analysis.

1.9.2 Prospective studies of dietary patterns and incident type 2 diabetes

A number of prospective studies have investigated the association between dietary patterns and type 2 diabetes. The majority of these used either diet quality scores (216-224) or empirically derived dietary patterns (216, 223, 225-229) and only a few have adopted RRR (209, 230-232).

1.9.2.1 Studies using diet quality scores

Studies using different diet quality scores have reported protective dietary patterns. In the Nurses Health Study a high score on the Alternative Healthy Eating Index (AHEI), a variation of the original HEI, was associated with a type 2 diabetes relative risk of 0.64 (95%CI: 0.58-0.71) compared to a low score (218). The RR included adjustments for age, BMI, energy intake and physical activity. Further adjustment for WHR changed the RR to 0.76, suggesting a possible mediating role of central obesity. Adherence to the Dietary Approaches to Stop Hypertension (DASH) diet, an overall score that includes fruits, vegetables, low-fat dairy and whole grains, decreased diabetes risk among White adults in the Insulin Resistance Atherosclerosis Study (221). The RR after adjustment for age, sex, BMI, family history of diabetes, education, smoking, energy intake and energy expenditure was 0.31 (95%CI: 0.31-0.77) when comparing extreme tertiles. The DASH diet and the AHEI were also protective in the Health Professionals Follow-up Study (217). The multivariate HR for type 2 diabetes (adjusted for smoking, physical activity, family history of diabetes, BMI, and total energy) comparing quintiles of intake was 0.75 (95%CI: 0.65–0.85) for the DASH diet and 0.77 (95%CI: 0.67–0.88) for the AHEI. However, both the DASH diet and the AHEI were not predictive of diabetes in the large EPIC-InterAct Study (219) although significant protective associations were found before adjustment for BMI and waist circumference, suggesting that these patterns were acting through their associations with body weight and fat.

An increasing number of studies have analysed a Mediterranean dietary pattern as a possible diabetes-protective pattern. The Mediterranean dietary pattern contains a high proportion of MUFA to SFA, is low in energy density and high in fibre, all factors that have been shown to be protective in single nutrients studies. Key food groups which are part of the Mediterranean dietary pattern are fruit and vegetables, olive oil, pasta or bread, fish and beans. Prospective studies investigating this dietary pattern have been mainly conducted among Mediterranean populations. In a large study among Spanish populations higher adherence to the Mediterranean diet reduced diabetes risk by 83% (222). However, although the estimates were adjusted for a range of confounders, including BMI, education, physical activity and energy

intake, the overall number of cases was small (n=33). In the PREDIMED-Reus trial (224), a 4-year randomized trial conducted among 418 Spanish people aged 55-80 years, individuals assigned to a Mediterranean diet with no energy restriction had a reduced incidence of type 2 diabetes of 52% compared with those in the control group (assigned to a low-fat diet). Changes in weight and physical activity did not differ between the control and the intervention groups. Analyses of the large EPIC study reported that among European populations the relative risk of type 2 diabetes for people with high adherence to the Mediterranean diet compared with low adherence groups was 0.88 (95%CI: 0.79-0.97) (219), a smaller RR compared to studies restricted to Mediterranean populations.

1.9.2.2 Studies using factor or cluster analyses

Most studies using either factor or cluster analyses found relatively similar protective or unhealthy dietary patterns. In the Health Professionals Follow-up Study a 'Western' dietary pattern characterized by higher consumption of red and processed meat, French fries, high-fat dairy products, refined grains and sweets significantly increased the risk of type 2 diabetes (228). Similar patterns rich in high-fat dairy, meat or fried foods were predictive of type 2 diabetes risk in a Finnish cohort (226) and in the Melbourne Collaborative Cohort Study (225). A 'healthy' dietary pattern characterized by fruit, vegetables, wholemeal bread, low-fat dairy, and little alcohol significantly lowered the risk of type 2 diabetes in the Whitehall II Study (216). Similar patterns labeled 'prudent', rich in fruit and vegetable and/or whole grains were also protective in the Health Professionals Follow-up Study (228) and Finnish cohort (226). In non-White and multi-ethnic populations results were similar, although the patterns were characterized by somewhat different foods. A pattern made up of fruits, vegetables and soy-rich foods was protective in a Chinese population, while meat, sweetened and fried foods increased risk (229). However, a similarly characterised prudent dietary pattern was not associated with type 2 diabetes in a Japanese population after adjustment for multiple confounders (233). Interestingly, although fruits and vegetables feature in most protective patterns, in single foods analyses neither vegetables nor fruits were particularly protective. This supports the hypothesis that the effect of individual foods might be too small to be detected but their aggregate effect might be large enough to be significant. Indeed the associations between dietary patterns and type 2 diabetes in most studies were stronger than that for individual foods when analysed separately in the same cohort.

The relative risks were comparable across studies in adjusted models (including adjustment for socio-economic class, education, BMI and family history in all models). For healthy and protective dietary patterns, in factor analysis studies the HR ranged between 0.84 and 0.72 when comparing extreme quintiles or quartiles, while in cluster analyses the HRs were 0.77-0.74 when comparing clusters of dietary patterns. Thus, the protective effects of dietary patterns seem relatively modest even when comparing extreme of intakes. This is not surprising, since factor and cluster analyses are purely exploratory methods and are not designed to identify disease-specific dietary patterns.

1.9.2.3 Studies using RRR

One drawback of studies reviewed so far using factor or cluster analysis is that, even if a dietary pattern is identified that associates with disease, an explanation for its biological effect on type 2 diabetes is difficult to find since this exploratory method does not seek to identify etiological pathways of food and disease. Studies using RRR can help overcome this problem as they incorporate a priori knowledge of diet and disease; by choosing hypothesis- based disease-specific nutrient responses, dietary patterns obtained with RRR can better clarify the biological pathways linking foods type 2 diabetes.

To date, few studies have adopted RRR to investigate dietary patterns predictive of incident type 2 diabetes (209, 230-232, 234). Hoffmann et al. (209) were the first investigators to apply RRR in nutritional epidemiology. In their initial model they derived dietary patterns that maximally explained variations in nutrients they presumed to be important for diabetes development using a nested case-control sample within the German EPIC cohort. These nutrients were fibre, alcohol, magnesium and a high ratio of PUFA to SFA. The relative risk reduction for the one protective dietary pattern derived, which was high in fibre but low in magnesium and had a moderate alcohol content was 0.64 (95%CI: 0.54-0.85) comparing extreme quintiles. The authors compared this dietary pattern with one they derived with principal components analysis and noted that the latter was not associated with type 2 diabetes although it explained more variation in the data. This is not surprising since principal components analysis explains variation in food intake while RRR explains variation in the response variables. By choosing different sets of intermediate nutrients and using prospective data, RRR could be used as a tool to investigate the relative importance of different pathways.

A recent cross-sectional analysis of Korean data (235) applied RRR but chose intermediate variables related to the quantity and quality of carbohydrates (total energy intake, total carbohydrate intake, percentage energy from carbohydrate and GI). The authors found that a rice-oriented pattern, characterised by high rice intake and low vegetables, fruit and dairy was associated with hypertriglyceridemia in men and low high-density lipoprotein-cholesterol in both men and women.

To date, four studies have applied RRR using intermediate biomarkers of diabetes to identify dietary patterns associated with type 2 diabetes (230-232, 234). Schulze and colleagues (234) identified a dietary pattern related to inflammatory biomarkers such as IL-6 and CRP, characterized by high intake of sugary soft drinks, processed meat and refined grains and low intake of cruciferous and yellow vegetables, coffee and wine. The relative risk of type 2 diabetes comparing extreme quintiles for this pattern were 2.56 (95%CI: 2.10-3.10) in the Nurses' Health Studies and 2.93 (95%CI: 2.18-3.92) in the Nurses' Health Study II adjusting for age, BMI, physical activity and smoking. In the EPIC Postdam study RRR was used to identify a dietary pattern characterised by low levels of inflammatory biomarkers and HbA1c and high levels of HDL and adiponectin (230); the dietary pattern was high in fruit and low in processed meat, soft drinks, poultry, white bread and beer. The odds ratio for type 2 diabetes, comparing the highest

versus lowest quintile of this pattern, was 0.27 (CI: 0.13-0.64). In the Whitehall II study the homeostasis model assessment of insulin resistance (HOMA-IR), a measure of insulin resistance, was used as the intermediate response variable (232). The derived pattern, which was high in sugary and diet soft drinks, crisps, white bread, sausages and burgers and low in wholemeal bread and high-fibre cereals, was associated with increased risk of type 2 diabetes (HR for extreme quartiles 1.55; 95% CI: 1.13-2.15, adjusted for age, sex, ethnicity, SEP, smoking, alcohol, physical activity and BMI). However, the use of a marker of type 2 diabetes as response variable, such as the HOMA-IR, could be misleading since the derived pattern does not help explain how diet affects intermediate pathways to diabetes, but rather it describes foods associated with diabetes. In the Insulin Resistance Atherosclerosis Study (231) RRR was used to derive a dietary pattern high in red meat, fried potatoes, cheese, eggs and low-fibre cereals and bread and low in wine that maximally explained variations in markers of haemostasis and inflammation (plasminogen activator inhibitor-1 and fibrinogen). The OR for type 2 diabetes comparing extreme quintiles was 4.51 (95% CI: 1.60–12.69) after adjustment for age, sex, ethnicity, family history of diabetes, energy expenditure, smoking, energy intake and BMI. These results suggest that inflammatory responses could play a role in the diet-diabetes association. However, it is not possible in these studies to ascertain whether inflammatory biomarkers are a cause or merely a marker of diabetes. Furthermore most of the studies using biomarkers have used too many response variables resulting in dietary patterns that are difficult to interpret in terms of their pathways.

Recently, two studies have investigated the generalizability of RRR-derived dietary patterns to other populations. Imamura and colleagues (236) have used RRR-derived dietary patterns from the Nurses' Health Study (234), the EPIC-Postdam (230), and the Whitehall II Study (232) to generate three dietary pattern scores in the Framingham Offspring Study. Of these, only the Nurses Health Study-based score was associated with type 2 diabetes. However, a more recent study (219) using the same three RRR-derived scores applied in a case-cohort selected from the multi-centre European EPIC-InterAct study found that all three dietary patterns were significantly associated with type 2 diabetes, even after adjustment for BMI and WC. Conversely in the same study both the AHEI and the DASH were not associated with diabetes after body weight adjustments. These results suggest that, although RRR-derived dietary patterns are generally more strongly predictive of diabetes than diet quality scores, they might not be generalizable to all populations. Reproducibility of pre-defined RRR-scores in other populations is complicated by the use of different dietary intake questionnaires in other cohorts reflecting consumption of different foods specific to certain populations.

In summary, despite the heterogeneity of the methodologies used, the evidence suggests that dietary patterns high in whole grains, fruit and vegetables might decrease diabetes risk while dietary patterns high in red and processed foods, refined grains and sweets might increase the risk. However, so far the majority of dietary patterns studies have not investigated the pathways linking these foods choices with type 2 diabetes. Identifying the specific mechanisms and nutritional pathways that are important for type 2 diabetes is a key step in our understanding of

how diet affects disease risk and in devising specific nutritional recommendations. So far, only two studies have used RRR-derived patterns based on nutrients to examine nutritional pathways associated with type 2 diabetes and one of these was cross-sectional. The studies using biomarkers as response variables are potentially flawed because, as explained earlier, it is not possible to separate the biomarkers from the actual outcome. In particular, HOMA-IR and HbA1c are clinical markers, and therefore proxies for diabetes; thus studies adopting these as response variables do not explore biological pathways linking diet and diabetes.

One limitation of much of the dietary pattern literature is the lack of life course investigations of dietary patterns in relation to type 2 diabetes. Virtually all studies have used only one dietary measurement at baseline and when repeated measurements were available these were not exploited to assess change in diet over time. Individual diet is likely to change with age and as consequence of developing life circumstances with important repercussions for the timing of disease development. Clearly the association between longitudinal changes in diet in relation to diabetes needs to be investigated.

1.10 Literature review summary and conclusions

As demonstrated by a range of epidemiological evidence lifestyle factors are major players in the development of type 2 diabetes. Being overweight or obese at any age increases the risk of type 2 diabetes. As well as overall obesity, the distribution of excess weight is an important risk factor for diabetes, particularly for women. Abdominal obesity measured in different ways has been associated with diabetes, independently of BMI. Among the various abdominal obesity indicators WC has been preferred due to its simplicity and high correlation with visceral intra-abdominal fat. One limitation of much of the research in the field is the paucity of studies using longitudinal data to investigate life-course patterns of body weight or WC and type 2 diabetes. There is evidence that the duration of overweight and obesity, as well as the timing of weight gain, are important life-course risk factors for diabetes. However, most of the prospective studies that have investigated the cumulative effect of obesity and sensitive periods of weight gain had limited data across the life course. Very few studies have investigated changes of WC in relation diabetes and most have looked at only two time points.

Notwithstanding the difficulties of assessing dietary intake, accumulated evidence suggests that certain dietary factors, such as low fibre intake, high GI foods and high total fat and SFA intakes, could increase the risk of type 2 diabetes. Plausible physiological mechanisms support the hypothesis that these factors have protective effects both independently and through their ability to protect from weight gain. However, their synergistic effect, which might be stronger than their individual ones, has not yet been analysed.

In the last decade, dietary patterns have emerged as a method to describe the overall diet in a holistic way, which accounts for the cumulative and synergistic effects of nutrients in the diet. Two approaches have mainly been used. A theoretical approach uses current knowledge to create dietary scores; the empirical approach uses statistical models to derive dietary patterns

from existing dietary data. Dietary patterns high in added sugar, processed meat and refined grains appear to be detrimental for the development of diabetes. On the other hand, healthy and Mediterranean-style dietary patterns appear protective but these are not relevant to all populations, especially those in Northern countries. One limitation of the field is that the majority of dietary patterns used or created have been purely exploratory and as such, may be less disease-specific since they ignore the specific pathways between diet and disease. RRR has the advantage of allowing for the investigation of the biological pathways between foods and disease. However, most studies that have adopted this method to investigate diabetes have mainly examined RRR-derived dietary patterns based on biomarkers of inflammation or proxies for diabetes (HOMA-IR, HbA1c) and therefore do actually explore the pathways linking diet and diabetes. No study has used RRR to investigate dietary patterns characterised by dietary GI, fibre and fat intake, for which there is some evidence of an association with diabetes risk. A further limitation of most dietary patterns studies is the widespread use of FFQs to assess diet. In addition, there is a lack of studies investigating individual changes in diet over time in relation to diabetes incidence.

Because of the gaps in the literature thus highlighted, this thesis proposes to expand the evidence on life-course patterns of obesity, fat distribution and dietary patterns in relation to type 2 diabetes incidence.

1.11 Overall aim and structure of the thesis

The overall aim of this thesis is to examine the life course associations between BMI, WC and dietary patterns in relation to the risk of type 2 diabetes.

- First, it aims to describe the patterns of BMI and WC over the adult life course and their association with an increased risk of type 2 diabetes. Specifically it investigates accumulation models of weight gain and sensitive periods of BMI and WC gain over the adult life course in relation to type 2 diabetes incidence
- Second, this work aims to identify dietary patterns associated with the risk of type 2 diabetes and to investigate whether relationships between these dietary patterns and type 2 diabetes are mediated by body weight and waist circumference. Specifically, this thesis will use RRR to investigate the combined effect of dietary fibre, GI and dietary fat (as a dietary pattern) on type 2 diabetes incidence. Subsequent analyses will investigate changes in the derived dietary pattern over the adult life course in relation to diabetes
- Social class, educational attainment, smoking and physical activity levels will be treated as confounders. BMI and WC will be treated as mediators in the association between diet and diabetes.

The conceptual framework of this thesis is illustrated in Figure 1, with arrows indicating the hypothesised associations between the explanatory variables and type 2 diabetes. The following research questions will be asked:

1.11.1 Research questions:

- Is the duration as well as level of obesity important for type 2 diabetes risk? Are there any periods over the adult life course when gaining weight is particularly detrimental for diabetes (Chapter 3)
- Is waist circumference important independently of BMI or is there an interaction between BMI and WC? Are life-course changes in WC important for type 2 diabetes? Are there any periods over the adult life course when WC gain is particularly detrimental for diabetes (Chapter 4)
- Are dietary fibre, the glycaemic index and dietary fat associated with type 2 diabetes? To what extent is this association mediated by BMI and WC? (Chapter 5)
- Does the consumption throughout adult life of a dietary pattern characterised by high GI, low fibre and high fat predict type 2 diabetes risk in later life? To what extent is the effect of this dietary pattern mediated by BMI and WC? How do changes in this pattern affect diabetes risk independently of BMI and WC? (Chapter 6)

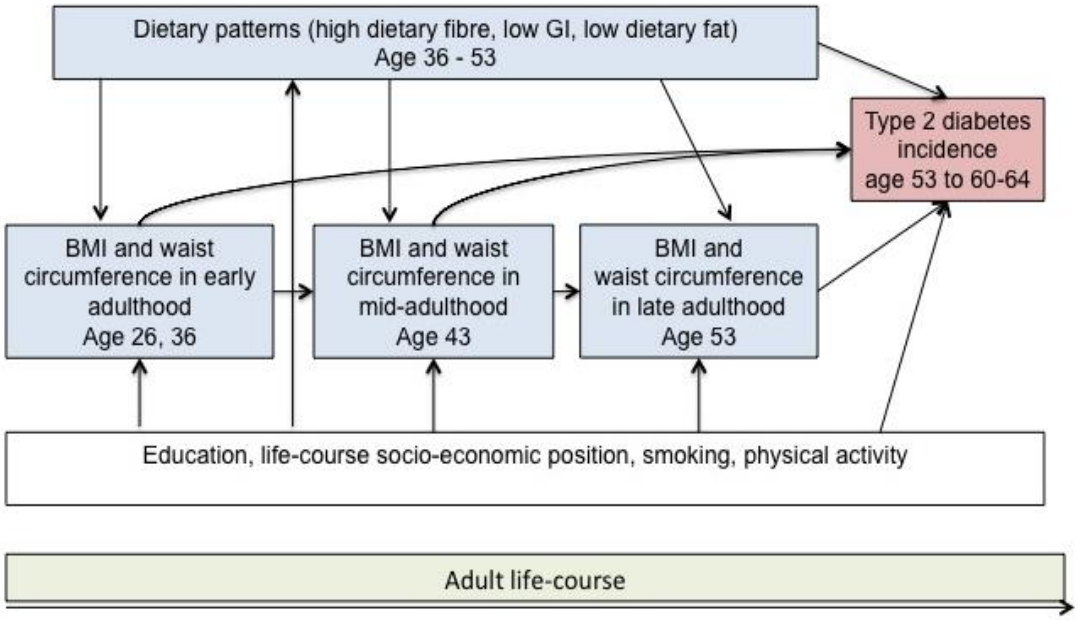


Figure 1. Conceptual framework representing the effect of lifecourse body weight and diet on type 2 diabetes incidence in the NSHD

Main explanatory variables are shown in the blue boxes, confounders in the white box and the outcome in the red box; arrows represent directions of associations.

1.12 Structure of the thesis

Details of the source of data used in this thesis, the MRC National Survey of Health and Development (NSHD) are given in Chapter 2 with detailed description of the outcome used.

This chapter also outlines the analytical strategies used in the thesis. Chapter 3 examines associations between life course patterns of BMI and type 2 diabetes. Chapter 4 expands from chapter 3 by investigating the lifecourse effect of WC (a measure of body fat distribution) and its interaction with BMI. Chapter 5 and 6 investigate the effect of specific dietary factors (dietary fibre, GI and dietary fat) on type 2 diabetes both in isolation (chapter 5) and as a dietary pattern (chapter 6) and whether associations between diet and type 2 diabetes are mediated by the explanatory factors examined in Chapter 3 and 4 (BMI and WC). Chapter 7 draws the main findings of the thesis together and discusses the implications of this work, the overall strengths and weaknesses, and recommendations for future research.

2 Chapter 2. Methods

2.1 Introduction to the NSHD

The NSHD is the oldest birth cohort in Britain. It was initially established as a maternity study in 1946 to investigate the costs of maternity services and the reasons for the falling fertility rate in Britain (237). The initial target sample consisted of all 16,695 births in the first week of March 1946 that occurred in England, Wales and Scotland. Out of this sample, 13,687 mothers were interveiwed for the maternity study. The follow-up study (the NSHD) sample included 5362 births (2,547 women, 2815 men) selected from the maternity survey. This sample comprised all births from non-manual and agricultural workers' wives and 1 in 4 births to wives of manual workers. Births from non-married women and multiple births were excluded. The reason for the sampling strategy was to limit costs and to maintain a socially-representative sample that was easy to track in future years (238).

Between birth and the latest data collection at age 60-64 years, the sample has been followed-up 23 times (Table 2). In the first 16 years data was collected 11 times. Subsequently, contact has been less frequent. Data collections consisted of a mixture of postal questionnaires and interviews administered by health visitors, teachers, school and research nurses. At age 60-64 clinical assessments in a clinical research facility were introduced. The research and policy focus of the study has changed and developed over the years. Initially it was concerned with the impact of social class differences on maternal and child health. In the childhood years the focus shifted to educational attainment and in early adulthood to the occupational results of education. From age 36 onward the focus has been primarily on health and pathways to healthy ageing.

The abundance of detailed data, which in most cases were collected by trained professionals rather than being self-reported, makes this study ideally suited to investigate life course patterns of BMI, weight change, waist circumference and dietary patterns, adjusting for a broad range of confounders.

2.2 Response rate and representativeness of the study

As with all longitudinal studies loss to follow-up due to death, migration and refusal has affected the NSHD sample size. However, the response rate throughout the study has been good (Table 2) (238). Response rate was lowest in early adulthood but it increased in the later years when research was strongly refocused on health and home visits were offered to those unable to travel to a clinical research facility. At the latest data collection in 2006-10, out of the sample available for contact at age 60 years (all those alive, residents in the UK and not permanent refusals) 2,661 (84.1%) provided some information (either a visit or a postal questionnaire). Females, non-smokers and those with higher educational attainment, higher adult social class,

higher childhood and adult cognition and fewer health problems at age 53 were more likely to provide some data at age 60-64 (239).

Despite some differential attrition by social and health characteristics the NSHD at age 60-64 has remained broadly representative of the white British population born in the early post-war years. When compared with age and ethnically relevant data from the 2010 Office for National Statistics Integrated Household Survey and the 2001 England Census, the NSHD had a similar sex and social class profile, and smoking rates were similar (239). However in the NSHD a slightly higher proportion was employed and a lower proportion had limiting illnesses. Similarly, at the previous data collections at age 43 and 53 the NSHD sample was comparable to the 1991 census population, although those from higher social classes and the never married tended to be over-represented (237, 238).

Table 2. Response rate in the MRC NSHD

Year	Age of study member	Respondent	Sample successfully contacted	**% of target sample***
1946	8 weeks	Mother	5,362	(100)
1948	2	Mother	4,698	(94)
1950	4	Mother	4,700	(96)
1952	6	Mother and cohort member	4,603	(95)
1953	7	Mother and cohort member	4,480	(93)
1954	8	Mother and cohort member	4,435	(92)
1955	9	Mother and cohort member	4,181	(87)
1956	10	Cohort member	4,077	(85)
1957	11	Mother and cohort member	4,281	(89)
1959	13	Cohort member	4,127	(86)
1961	15	Mother and cohort member	4,247	(89)
1965	19	Cohort member	3,561	(75)
1966	20	Cohort member	3,899	(83)
1968	22	Cohort member	3,885	(84)
1969	23	Cohort member	3,026	(67)
1971	25	Cohort member	3,307	(74)
1972	26	Cohort member	3,750	(85)
1977	31	Cohort member	3,340	(78)
1982	36	Cohort member	3,322	(86)
1989	43	Cohort member	3,262	(87)
1999	53	Cohort member	3,035	(83)
2006-10	60-64	Cohort member	2,661	(84)

* Target sample excludes deaths, persons living abroad or untraced, and permanent refusals.
Adapted from Wadsworth et al, 2003 (238)

2.3 Main outcome used in this thesis

The main outcome measure used in this thesis was incident type 2 diabetes between 53 and 60-64 years. Diabetes diagnosis was ascertained only by self-reported information at age 53, while at age 60-64 it was ascertained by both self-reported information and by analyses of

fasting blood glucose and HbA1c. One hundred cases of prevalent diabetes at age 53 were excluded from the analyses. Only cases of type 2 diabetes diagnosed between age 53 (1999) and age 60-64 (2006-10) were included, which in total were 257. Of these, 130 were self-reported and a further 127 were identified solely by blood measures at age 60-64.

2.3.1 Self-reported diabetes

Self -reported diabetes was determined in two ways: firstly, in response to a direct question and secondly from all relevant medical information that study members reported (Table 3). Study members were asked whether they had diabetes at ages 36, 43, 53 and between 60 and 64 years. At age 36 study members were asked: “Do you have diabetes all or most of the time?” At age 43, 53 and 60-64 the questionnaire included a question on doctor-diagnosed diabetes since the last contact (“In the last ten years have you had diabetes? Has a doctor said you had this problem?”). Hospital attendances, doctor diagnoses of diabetes, dates of diagnoses, and medications were reported at nurse interviews at 36, 43 and 53 years and on a postal questionnaire at 31 years. Relevant data of those with any report of diabetes or record of anti-diabetic medication was reviewed by a GP with a special interest in diabetes. The validity of self-reported diabetes was assessed using GP records. Results from this validation study are reported below.

Table 3. Questions on diabetes and hospital admission in postal questionnaires and nurse interviews from 1977 to 2006-10

	Questionnaire year				
Questions	1977	1982	1989	1999	2006-10
In-patient hospital admissions	Have you been a hospital inpatient since the last admission you told us about? Reason for admission?	Have you been a patient in hospital for at least one night since the last time you told about being a patient in hospital? Reason for admission	Have you been a patient in hospital for at least one night since the last time you told us about? Reason for admission	Since we last saw you have you been admitted to hospital as an in-patient? Why were you admitted to hospital as an in-patient on this occasion?	Since 1999 have you been admitted to hospital as an in-patient? Why?
Out-patient hospital admissions	Have you attended an outpatient or other clinic since? Reason for attendance		Since you were 36 years old have you been to a hospital outpatient or day care department for consultation or treatment? Reason for consultation or type of treatment	Since we last saw you have you spent a day at a hospital for treatment or surgery and then come home at the end of the day? What was the illness or condition that was being treated?	Since 1999 have you been to hospital for treatment or surgery and then come home again on the same day? Why?
Doctor visits	Have you seen a doctor since this time last year? Why did you go? What did the doctor say was wrong with you?				
Medication	Do you regularly take any medicine, pills or tablets (or have regular injections)? What do you take it for?		Are you regularly taking any medicines or tablets prescribed by a doctor?	Do you now regularly take any prescribed medicines?	Do you regularly take any medicines, tablets, tonics or pills prescribed by a doctor?
Diabetes status		Do you have any of the following all or most of the times? (nurse reads list aloud. List includes diabetes	Have you ever had diabetes? How often have you consulted a doctor or other health professional about this in the last year?	In the last ten years (that is since you were 43 years old,) have you had diabetes? Has a doctor said you had this problem?	Since 1999 have you been told that you have diabetes?
Diabetes type				What kind of diabetes have you had. Was it: o Insulin-dependent o Non-insulin dependent or o High blood sugar or o Some other kind of diabetes?	
Age at diagnosis			How old were you when you had this problem the first time?	How old were you then?	How old were you when you were first told that you had diabetes?
Diabetes treatment			Have you taken any prescribed medicines or tablets for this in the last year?		Is your diabetes controlled by: o Diet alone o Tablets o Insulin injections

2.3.2 Diabetes diagnosed by fasting blood measures

Levels of fasting blood glucose and HbA1c measures were analysed from 50-ml blood samples collected between 2006 and 2011 in 5 clinical research facilities (240). The sample was collected in the morning, mostly between 08.00 and 09.00 hours, by a trained research nurse after the study member had fasted overnight since 22.00. A diagnosis of diabetes was established if fasting plasma glucose was equal or greater than 7mmol/L or HbA1c was equal or greater than 6.5% (48 mmol/mol). This diagnosis was based on the 2006 WHO diagnostic criteria (7) and the updated 2011 WHO guideline for use of HbA1c as a diagnostic tool (8)

2.3.3 Type of diabetes

Individuals only ever treated with diet or oral hypoglycaemic agents, or who had insulin added more than 2 years after diagnosis, were classified as having Type 2 diabetes (n=230). All were aged 30 years or more at diagnosis. Study members who had taken insulin since time of diagnosis were classified as having Type 1 diabetes. All the latter were under 29 years at diagnosis (n=13, of which 8 men and 5 women).

2.3.4 Validation of diabetes

To evaluate the accuracy of self-reported diabetes and age at diagnosis in the NSHD a validation study was conducted at the beginning of the PhD. Details and results of the study have been exhibited at the poster session of the 2011 Diabetes UK Conference in London and recently published in Primary Care Diabetes (241). To validate self-reported diabetes cases these were compared with general practitioners (GP)-confirmed cases. GP are an optimal source of information on disease status in the UK as nearly all British citizens are registered with a GP practice. Moreover, during the last decade diabetes care in the UK has moved into general practice.

The validation study was conducted using all self-reported diabetes cases up to the latest data collection. Of the 230 study members who reported a diagnosis of diabetes 184 (80%) were seen at the latest follow-up, when 172 (75%) gave permission to contact their GP. A validation questionnaire was developed and sent to the GPs, of which 157 returned completed questionnaires (91.2%). The questionnaire consisted of items on diabetes status and type, date of diagnosis, how the diagnosis was established and which type of treatment patients were currently receiving (diet, oral hypoglycaemic agents, insulin or other). Table 4 shows the follow-up process for the validation of self-reported questionnaires and the overall GP response rate. The validity of self-reported diabetes was assessed by calculating the percentage of self-reported diabetes cases that were confirmed to have diabetes by their GP, i.e. the positive predictive value (PPV) with GP confirmation as the gold standard (PPV= b/a x100 where a= number self-reported and b= those confirmed by GP). The difference between self-reported and GP-confirmed age at diagnosis was analysed with a Bland-Altman plot (242); the mean difference, 95% CI and limits of agreements were calculated.

Table 4. Participants available for validation and GP response rate

	No.	%
Total self-reported diabetes 1977-2008	230	
Died	19	
Withdrew	9	
Lost to follow up	15	
Emigrated	2	
Seen at the latest follow-up	184	
Refused consent to contact their GP	7	
Died after follow-up	5	
Available for validation study	172	74.7
1st questionnaire sent to GPs	172	
GPs telephoned	27	
Study members telephoned	11	
Questionnaire resent to GPs	24	
Questionnaire sent to new GPs	11	
Questionnaires returned (GP response rate)	157	91.2

GP= general practitioner

Of the 157 study members who reported a diagnosis of diabetes 149 were confirmed by their GP (PPV=94.9%) (Table 5). Results were very similar when the analyses were performed using only responses to a direct question on diabetes diagnosis (PPV=95.4%). Information on the test used to diagnose diabetes was available for 121 participants. The most common diagnostic tests were FPG (n=68, 56.2%) and OGT (n=15, 12.4%). The date of diagnosis was reported by 148 GPs. The mean age at diagnosis was 55.5 years (±SD 7.3). Information on self-reported age at diagnosis was available for 102 study members. Of these, 37 (36.2%) reported the same age in years at diagnosis as their GP. Figure 2 plots the differences between self-reported and GP-reported age at diagnosis against the average difference. The average difference was 0.6 years (95% CI 0.2-1.1). The 95% limits of agreements were 5.1/-3.7years. Information on treatment was reported by 148 GPs. The combination of diet and oral hypoglycaemic agents was the most common treatment prescribed (37.1%) followed by oral hypoglycaemic agents alone (31%) and diet alone (15.5%). Twenty four (16.2%) study members were treated with insulin.

This study showed that self-reported diabetes in the NSHD was generally confirmed by GP records and could be used as a valid measure of diabetes diagnosis. These results were similar

to previous diabetes validation studies that used family doctors as the gold standard (243-246). However, none of these studies have been conducted among the general British population. It has been suggested that the high agreement of self-reported diabetes might be partly due to the well-defined diagnostic criteria of this disease and to the fact that it often requires treatment once diagnosed (243, 246). This study found that the self-reported age at diagnosis was on average 0.2-1.1 years earlier than the age reported by the GP. This result is similar to previous studies, which indicated that patients tend to overestimate the duration of their condition (247, 248).

Table 5. Proportion of GP-confirmed self-reported diabetes cases

	Total	GP-confirmed (N)	PPV (95% CI)
Self-reported diabetes (from responses to a direct question and from medication information)	157	149	94.9% (90.2-97.7)
Self-reported diabetes (from responses to a direct question only)	153	146	95.4% (90.8-98.1)

PPV= positive predictive value; CI=confidence interval

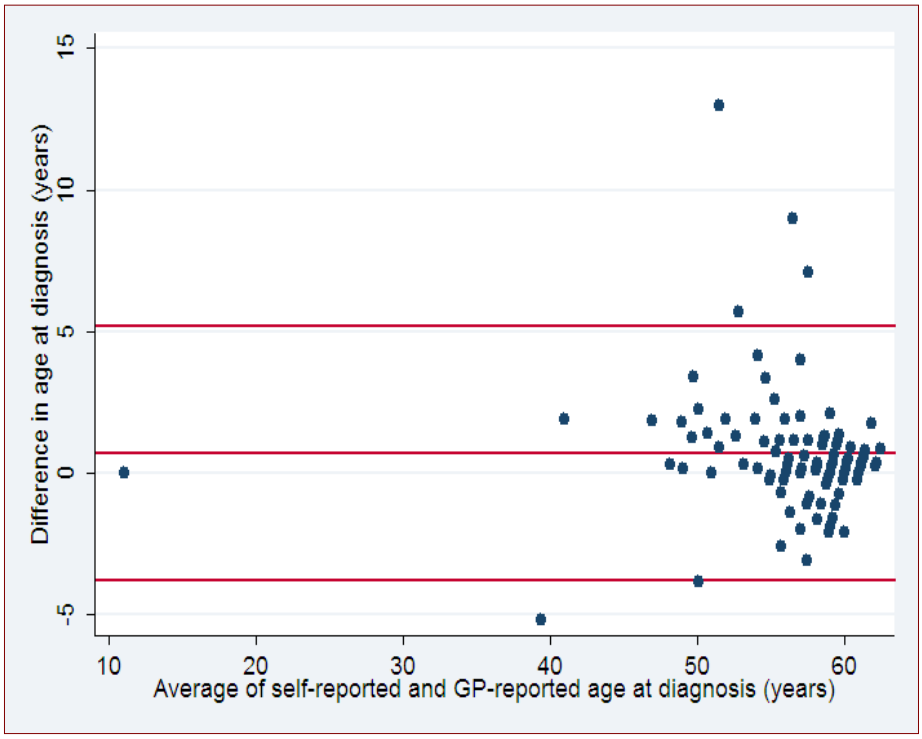


Figure 2. Differences in years between self-reported and GP-confirmed age at diagnosis plotted against the average difference.

Horizontal lines denote the mean difference (0.6 years), and the upper (5.1 years) and lower (-3.7 years) limits of agreement (mean difference ± 1.96 SD of the differences).

2.3.5 Descriptive analyses of the outcome

2.3.5.1 Diabetes prevalence

Table 6 shows the prevalence of diabetes among the NSHD study sample by year, gender and method of diagnosis. The overall prevalence of diabetes (including type 1 and 2, diagnosed and undiagnosed) increased with age, ranging between 0.6% at age 36 to 11.8% at age 64, and tended to be higher for men, although it was statistically higher only at age 60-64. This prevalence is similar to the age-standardized prevalence of total (undiagnosed and diagnosed) diabetes found by other surveys in the UK, which ranged between 3.2% and 7.1% for the European ethnic group and included people aged 20 to 74 years (3, 249-252). As in the NSHD diabetes prevalence was higher for men than women and increased significantly with age. Recent estimates of the Association of Public Health Observatories Diabetes Prevalence Model (3), which used the Health Survey England 2004 and 2006 data applied to people aged 16 years and older in Primary Care Trusts, suggest a point estimate for 2011 of total diabetes prevalence ranging from 5.5 to 10.9%.

In the Health Survey for England 2009 (250) the prevalence of doctor-diagnosed diabetes among the 55-64 years old was 10.5% for men and 6.3% for women. This is comparable to self-reported diabetes between age 53 and 60-64 among the NSHD (8.6% for men and 6.3% for women). The lower proportion of diabetes among men in the NHSD compared to the Health Survey for England might reflect the slightly lower male representativeness in the NSHD, especially from lower-social classes. Also the Health Survey for England includes a sample of the current multi-ethnic English population, which is barely represented in the NSHD, since this study was initiated before the major post-war immigration waves to the UK.

2.3.5.2 Undiagnosed diabetes

Undiagnosed diabetes was defined as a fasting blood glucose level equal or greater than 7 mmol/L or an HbA_{1C} of 6.5% (48 mmol/mol) or greater in the absence of self-reported doctor-diagnosed diabetes. The prevalence of undiagnosed diabetes in the NSHD at age 53 was 2.5%, accounting for 44.6% of all cases of diabetes. Undiagnosed diabetes prevalence was 5.9% in 2006-10 accounting for 40.7% of all diabetes cases. At age 60-64, undiagnosed diabetes was substantially higher in men (7.5%) compared to women (4.4%). These figures are lower than those produced by the IDF (1), which estimates that about 50% of all cases of diabetes worldwide are undiagnosed.

The NSHD estimates of undiagnosed diabetes are also comparable, although higher than those found by other population-based estimates (3, 253). For example, the APHO Diabetes Prevalence Model (3) estimated that undiagnosed diabetes among people aged 16 years and older in England accounted for 30.2% of diabetes cases in 2011 using an HbA_{1c} of 6.5% or greater and 36.5% using fasting plasma glucose of 7 mmol/l or greater. The English Longitudinal Study of Ageing (253), based on an older (55-75 years) White population, reported that 18.5% of cases of diabetes were undiagnosed. Similarly to the NSHD, men in the English

Longitudinal Study of Ageing had a significantly higher prevalence of undiagnosed diabetes than women (2.6% compared to 0.8%). Fasting plasma glucose of 7 mmol/l or greater was used to detect undiagnosed diabetes in the English Longitudinal Study of Ageing. It is probable that the higher estimates in the NSHD are due to the combined use of HbA1c and FBG as diagnostic tools.

Table 6. Prevalence of diabetes by gender and method of diagnosis

	Diabetes prevalence n/N (%)				New cases of diabetes
Age	Total	Males	Females	P*	
36					
(Self-reported)	20/ 3322 (0.6)	13/1656 (0.7)	7/1666 (0.4)	0.17	20
43					
(Self-reported)	36/3254 (1.1)	22/1632 (1.3)	14/1622 (0.8)	0.13	21
53					
Self-reported	83/2987 (2.8)	44/1467 (3)	39/1520 (2.6)	0.23	59
Blood measure (HbA1c >=6.5)	67/2582 (2.5)	29/1293 (2.2)	38/1289 (2.9)	0.26	67
Total	150/2987 (5.0)	73/1467 (4.9)	77/1520 (5.0)	0.68	126
60-64					
Self-reported	185/2439 (7.5)	102/1173 (8.6)	83/1266 (6.5)	0.04	130
Blood measure (HbA1c>=6.5 or FBG>=7mmol/L)	127/2133 (5.9)	78/1033 (7.5)	49/1100 (4.4)	<0.01	127
Total	312/2642 (11.8)	180/1279 (14.0)	132/1363 (9.6)	<0.001	257

FBG= Fasting Blood Glucose; *P value for test of sex difference using Chi-square test

2.4 Exposure variables

2.4.1 BMI and waist circumference

Anthropometric data in the NSHD were collected at different times of the life course. In this thesis BMI at ages 26, 36, 43 and 53 were used. BMI was calculated from weight (in kilograms) divided by height (in meters) squared. Height and weight were measured using standard protocols at all ages except at age 26, when they were self-reported. Overweight was calculated as a BMI $\geq$ 25 - 29.9 kg/m^2 and obesity as a BMI $\geq$ 30 kg/m^2.

WC was measured by a trained research nurse at age 36, 43 and 53 according to a standardised protocol. With the study member standing straight and looking ahead, a nurse applied the measuring tape at the mid-point between the costal margin and the iliac crest and in line with the mid-axilla. WC was measured twice to the nearest 1 mm. In this thesis an average of the two measures will be used. Descriptive statistics for BMI and WC are presented in Appendix 1.

2.4.2 Diet

Dietary data at age 36, 43 and 53 were collected by a research nurse at home visits. The nurse asked study members to complete a 5-day food diary detailing all foods and drinks consumed over the next 5 days and to return it by post (254). Survey members were given guidance on household measures and photographs of portion sizes to aid completion. Nutrient intakes were calculated using in-house programs based on updated versions of the McCance and Widdowson's *The composition of Foods.* Survey members with at least 3-days food records were included, but if food records were provided for more days, these were included in the analyses. The response rate for diet diaries was different than that for the main study. The number of study members completing diet diaries for at least 3 days was 2441 at age 36, 3187 at age 43 and 1776 at age 53, corresponding to a response rate of 63%, 85% and 48% respectively. The response rates for the main study at age 36, 43 and 53 were 86%, 87% and 83%. Descriptive statistics of the key dietary factors used as exposure variables are presented in Appendix 1.

2.5 Confounding and mediating variables

Occupational social class, educational attainment, smoking and physical activity were identified as factors that may confound any associations between the explanatory variables (BMI, WC and diet) and type 2 diabetes. These variables were chosen a-priori on the basis of existing evidence. Specific justification for inclusion of each variable is given in chapters 3 to 6. A confounder is a factor associated with both exposure and outcome, but not on the hypothesised causal pathway (255). Failure to adequately control for the effects of confounders can bias the associations between exposure and outcome. Descriptive statistics of all confounder variables are presented in Appendix 2.

BMI and WC will be treated as mediating variables in the association between dietary factors (chapter 5) or dietary patterns (chapter 6) and type 2 diabetes. A mediator is defined as a variable that is associated with both the exposure and the outcome and is on the causal pathway (255). In this thesis it is hypothesized that BMI and WC partially explain how diet affects type 2 diabetes. The extent to which the relationship between diet and the outcome acts through these mediators is investigated in chapters 5 and 6.

2.5.1 Occupational social class

Lifetime occupational social class was based on the head of the household's occupational social class at age 15-53. Occupational social classes were defined according to the UK Registrar-General's Classification of social classes, which were introduced in 1913 and renamed in 1990 as Social Class based on Occupation (256). The six social classes used in this thesis are: I professional, II managerial and technical, IIINM skilled non-manual, IIIM skilled manual, IV partly-skilled manual, V unskilled manual, the first three being non-manual and the last three manual.

2.5.2 Educational attainment

The highest level of educational qualification achieved by age 26 was grouped into 8 categories (from none attempted to higher degree) using the Burnham scale (Department of Education and Science, 1972) and regrouped into 4 categories for this thesis (none attempted, vocational, advanced secondary and higher education).

2.5.3 Smoking

Information on cigarette smoking was obtained in the NSHD at seven data collections (at ages 20, 25, 31, 36, 43, 53 and 60-64). Up to age 31, information was collected by postal questionnaire; from age 36 onwards a research nurse collected smoking information by interviews at home visits. People who provided an affirmative response to being a current cigarette smoker were classified as 'smokers' regardless of the number of cigarettes smoked. Those who replied negatively were classified as 'non-smokers'. Smoking history variables were created to account for the effect of past smoking habits. A lifetime smoking trajectory up to age 53 variable was created that comprised those who provided data for at least three waves (n = 3387) and for whom missing data are not sequential. Table 7 gives a summary of the smoking variables used in this thesis as confounders.

Table 7. Summary of smoking variables used in this thesis

Variable	Categories
Smoking history up to age 36, 43 and 53	Current smoker Ex-smoker Never smoker
Lifetime smoking trajectory up to age 53	Never smoker Predominantly non-smoker Predominantly smoker Lifelong smoker

2.5.4 Physical activity

Information on physical activity in the NSHD was collected at different times during the life course. In this thesis physical activity at age 36, 43 and 53 were used as confounder variables. At age 36 self-reported physical activity was collected using the Minnesota leisure time physical activity questionnaire, which included a checklist of 25 recreational activities and sports during the previous month. At age 43 an open-ended questionnaire was used to assess sports and vigorous leisure activities. At age 53 years study members were asked one question about whether they had taken part in any sport or vigorous activity or if they had undertaken any physical activity in the previous month.

2.6 Statistical analyses

Different statistical methods will be used in this thesis depending on the specific research questions in each chapter. To avoid repetition the following methods, which are used throughout the thesis are described below. Statistical analyses were conducted using Stata 12 (Statacorp, College Station, TX, USA) and SAS 9.0. Dietary patterns were derived using RRR; details of this methodology are given in chapter 6.

2.6.1 Descriptive analyses

Descriptive analyses of the outcome and the different explanatory variables were conducted prior to multivariable analyses. Descriptive statistics included means and standard deviations for continuous variables and frequencies and percentages for categorical variables. Chi-square test, analysis of variance (for categorical variables) and analysis of variance (for linear variables) were conducted to assess statistical differences according to specific variables or population groups.

2.6.2 Multivariable analyses

The main statistical method used to examine associations between explanatory and outcome variables in this thesis is multiple logistic regression. First the relationship between potential confounding variables and both the exposure and type 2 diabetes will be investigated in each chapter. Then multiple logistic regression models will be constructed to examine associations between the explanatory variables and the outcome, with sequential adjustments made for potential confounders and mediators.

For the analysis of duration of overweight or obesity and type 2 diabetes a Cox proportional hazard model will be employed. This technique was chosen because, unlike logistic regression, survival analyses can handle time to event and duration data. Details of this methodology are given in chapter 3.

3 Chapter 3. BMI across the life course and type 2 diabetes

3.1 Introduction

A substantial body of evidence has highlighted the role of excess body weight as the single most important lifestyle risk factor in the pathogenesis of type 2 diabetes. Several studies have found strong associations between adult BMI measured at one point in time and later risk of type 2 diabetes (49-56, 63). There is a linear increase in risk with higher BMI across the whole range of BMI values, with a suggested pooled RR for type 2 diabetes of 1.19 per unit increase in BMI (64). The degree of overweight is a critical factor for type 2 diabetes risk. Although overweight people (BMI 25-29.9 kg/m^2) are at higher type 2 diabetes risk compared to those in the normal BMI category the risk for the disease is particularly high for obese people (BMI ≥ 30 kg/m^2) (65, 75-77).

Studies suggest that obesity has a greater influence on type 2 diabetes risk in women compared to men. For example, in the Monitoring Trends and Determinants on Cardiovascular Diseases Augsburg survey (77), the adjusted HRs for type 2 diabetes for the 3 highest quartiles of BMI compared to those in the lowest were 1.37, 2.08, 4.15 among men and 3.77, 4.95, 10.58 among women. Similar differences in risk estimates were reported in the Spanish EPIC (75) (adjusted HRs for type 2 diabetes in the highest quartile of BMI compared to the lowest: 2.57 in men and 4.14 in women) and across several European countries in the EPIC-InterAct Study (76), (unadjusted HRs for those obese compared to normal BMI: 7.58 in men and 11.6 in women). The reasons for this sex difference are not completely understood. However, it is likely that endogenous sex hormones, such as testosterone and sex hormone–binding globulin, which are involved in fat accumulation and distribution, have a key role in modulating type 2 diabetes risk differently in men and women (75).

Despite the abundance of evidence on the role of BMI as a risk factor for type 2 diabetes and the increasing interest in life course models of disease, comparatively fewer studies have focused on the longitudinal patterns of excess body weight and their association with type 2 diabetes risk. As outlined in chapter 1, three relevant life course models have been particularly studied in the literature. These are the critical period model, encompassing the foetal programming of disease, the accumulation model and the sensitive period model. Most of the studies have focused on the foetal programming of disease model and it is now recognised that low birth weight, a crude marker of foetal growth, is associated with increased risk of type 2 diabetes in adult life (95, 96). Less is known about the accumulation and sensitive period of weight gain models in relation to type 2 diabetes.

Overall the evidence (103-109) suggests that the duration as well as the degree of overweight or obesity might be an important risk factor for type 2 diabetes. Increasingly, obesity and overweight are becoming more prominent among younger people, underscoring the importance

of elucidating the long-term effects of longer durations of overweight. However, only a handful of prospective studies have investigated duration of overweight or obesity longer than 15 years (105, 106, 108, 109). Furthermore, some studies only used self-reported BMI measures (107, 109), which are known to be inaccurate when compared to objectively measured BMI (257). In particular, height tends to be overestimated in men while body weight tends to be underestimated in women, leading to lower BMI estimates. Furthermore, underreporting of BMI and weight is more common among certain groups, such as women and obese people (258). Therefore, more studies are needed on the cumulative effect of obesity particularly for earlier onsets, given the increasingly younger age of obesity onset.

Faster gains in weight and BMI during childhood, especially in association with low birth weight and early adiposity rebound, have been found to increase type 2 diabetes risk (99, 101). Several studies have also found that weight gain either in early, middle or late adulthood increases the risk of type 2 diabetes (107, 110-115). However, only a few studies have investigated whether weight change during different periods of the life course modulate the risk for diabetes differently (106, 110, 113-116). The studies conducted among adult populations have mainly found that weight gain during early adulthood has a stronger impact on later type 2 diabetes risk than weight gain in middle or late adulthood.

Most of the studies on sensitive periods of BMI gain were limited by a retrospective design (110, 115, 116) or the use of self-reported measures of weight and height (110, 115, 116, 259). Thus, although a few studies suggest that weight gains in early adulthood are particularly detrimental for type 2 diabetes, more high-quality studies, using prospectively measured weight and height during a sufficiently longer period of the adult life course, are needed to confirm these results.

In view of the limited prospective evidence on the accumulation and sensitive period models of body weight and type 2 diabetes, this chapter will investigate longitudinal patterns of weight gain in adult life and their relation with later type 2 diabetes. First, associations will be presented for the effect of BMI on diabetes at different time points from age 26 to age 53 years. Subsequently, the chapter will assess the effect of duration of overweight or obesity and the role of BMI change at different periods of the adult life course on later diabetes risk.

3.1.1 Research question

The main research question of this chapter is how longitudinal patterns of BMI throughout adult life affect type 2 diabetes risk in later life.

3.1.2 Objectives

1. To analyse the association between BMI measured at different time points in the adult life (age 26, 36, 43 and 53 years) and type 2 diabetes incidence
2. To assess the effect of the duration of overweight or obesity on subsequent type 2 diabetes incidence

3. To investigate whether BMI gain at different periods of the adult life (26 to 36, 36 to 43 and 43 to 53 years) has a different impact on later risk of type 2 diabetes incidence

3.1.3 Hypotheses

1. BMI measured at all available time points between age 26 and 53 years is associated with type 2 diabetes diagnosed between age 53 and 64 years and this association is stronger for women than for men
2. Earlier onsets of overweight or obesity are associated with a greater risk of type 2 diabetes compared with later onsets during the adult life course
3. The positive association between weight gain and type 2 diabetes will be stronger in early adulthood (26 to 36 years) than in middle (36 to 43 years) or later adulthood (43 to 53 years)

3.2 Methods

3.2.1 Explanatory variables

The main explanatory variables used in this chapter are BMI measures at age 26, 36, 43 and 53. Overweight was calculated as a BMI $\geq$ 25 - 29.9 kg/m^2 and obesity as a BMI $\geq$ 30 kg/m^2. Height and weight were measured using standard protocols at all ages except at age 26, when they were self-reported.

3.2.1.1 Missing data for BMI

In Appendix 3 and 4 individuals with missing BMI data (those whose anthropometric measurements, i.e. height and weight, were not collected) were compared with those who had BMI information at each age; at all ages those with non-missing data were more likely to be female and to be more educated and less likely to be in manual employment and to be smokers. At age 43 those with non-missing data were also less likely to have a raised WC and to be inactive at the previous data collection (age 36). At all ages there was no difference in BMI category (using data from the previous data collection) and type 2 diabetes diagnosis when comparing missing and non-missing individuals for BMI.

3.2.2 Outcome variable

The outcome used in this chapter is the main outcome of this thesis, type 2 diabetes diagnosed between age 53 and 60-64 years. This was described in more detail in Chapter 2.

3.2.3 Potential confounding variables

Measures of SEP were considered as potential confounders, since both type 2 diabetes (26-29) and excess body weight (34, 38, 42, 260, 261) are more prevalent among people from lower social classes. Two measures of SEP were chosen: lifetime social class based on the head of

the household's occupational social class at age 15-53 years and highest level of educational qualification achieved by age 26 years.

Two lifestyle behaviours were considered potential confounders. Physical inactivity is an established risk factor for type 2 diabetes (262-265). Overweight people are more likely to be physically inactive since these two risk factors are strongly correlated (266, 267). The weight stigma experienced by obese people might decrease their motivation to exercise, resulting in lower levels of physical activity (268).

Smoking has also been recognised as a risk factor for type 2 diabetes (45). On the other hand it is known that on average smokers tend to be leaner than non-smokers (269), although smokers have a more metabolically detrimental fat profile than non-smokers (270). Smoking cessation is also associated with weight gain through increased energy intake, reduced resting metabolic rate and increased lipoprotein lipase activity (271).

Waist circumference was considered a mediator. As detailed in chapter 1, visceral abdominal fat is a strong risk factor for type 2 diabetes; although both BMI and waist circumference independently increase diabetes risk, overall obesity and abdominal obesity are strongly correlated and the effect of BMI on diabetes is, to some extent, explained by excess abdominal fat. Measures of WC were available at age 36, 43 and 53.

For the analyses presented in this chapter, self-reported measures of leisure time physical activity at 36, 43 and 53 years were used as potential confounders. A categorical variable of smoking history was used as a measure of cumulative smoking damage.

More detailed descriptions of the potential confounding measures used in this chapter were given in Chapter 2.

3.3 Statistical analyses

Mean and SD of BMI and percentages of overweight and obesity from age 26 to age 53 were presented by sex. All subsequent analyses were stratified by sex on a priori grounds based on evidence from the literature and to test the hypothesis that the effect of BMI on type 2 diabetes is stronger for women than for men. Associations of potential confounders with BMI at age 26, 36, 43 and 53 and the outcome were examined using linear regression or bivariate analyses.

Multivariable logistic regression was used to examine prospective associations between BMI at 26, 36, 43 and 53 years of age and type 2 diabetes between age 53 and 64 years. These models provide a crude suggestion of the periods during which BMI is more strongly associated with the outcome.

To investigate the cumulative impact of overweight and obesity a variable was derived defining the age at onset of overweight. Using data from 2,277 study members for whom information of BMI was available at 26, 36, 43 and 53 years the variable included five categories: never overweight, onset of overweight at age 26, onset of overweight at age 36, onset of overweight at age 43 and onset of overweight at age 53. This categorisation assumes that those who

became overweight remained overweight. This assumption was justified by the fact that very few people lost weight. Of those first overweight at age 26, 82%, 91%, 95%, were still overweight or obese at age 36, 43 and 53 respectively; of those first overweight at age 36, 86% and 94% were still overweight or obese at age 43 and 53 respectively; of those first overweight at age 43, 89% were still overweight or obese at age 53. Cox's proportional hazards models were used to estimate the association between duration of overweight or obesity until age 53 and incidence of type 2 diabetes diagnosed after age 53. Follow-up was in years from birth until the diabetes diagnosis or the first of the following events: death, emigration or last completed questionnaire. The assumption of proportional hazards was examined using Kaplan-Meier curves and found to be valid.

BMI change per year was calculated by subtracting a later BMI measure by the earlier measure (e.g. BMI at 36 minus BMI at 26) and by dividing this change score by the number of years between measures. These BMI velocities were plotted (272) graphically to allow visual inspection.

A conditional model of change (272) was used to examine whether there are sensitive periods for adult BMI gain. BMI change scores for each period were calculated for each sex conditional on earlier BMI. These change scores were obtained by regressing each BMI measure on the earlier measures and saving the residuals. To allow comparison between the two periods the residuals were standardized (mean=0 and SD=1).

These residuals represent the change in BMI above or below what is expected given an earlier BMI measure and therefore can be interpreted as BMI velocities. Because residuals are uncorrelated with each other all BMI velocity scores for different periods were fitted in the same model with the outcome; the coefficients for each period were then compared using Wald tests.

For all analyses (prospective and longitudinal) associations were first presented unadjusted (Model 1). A series of models were then constructed to sequentially adjust for socio-economic status and educational attainment (Model 2), smoking history and exercise (Model 3) and abdominal circumference (Model 4). In analyses of onset of overweight, a further model adjusting for current BMI (Model 5) was included to determine to what extent the impact of duration of overweight on diabetes is mediated by attained BMI.

3.3.1 Sample

All analyses were restricted to those with data for type 2 diabetes diagnosed between age 53 and 60-64, for BMI at age 26, 36, 43 and 53 and for all confounders (SEP, education, smoking, WC). The final number for prospective analyses of BMI and sensitive periods of BMI gain and type 2 diabetes was 1860. For analyses of duration of overweight and type 2 diabetes the final number was 2130.

3.4 Results

3.4.1 Descriptive analyses of BMI

Descriptive statistics of BMI at age 26, 36, 43 and 53 for those included in the prospective and longitudinal analyses of BMI and type 2 diabetes are shown in Table 8 and Figure 3. BMI increased with age for both men and women. Up to age 43 men had a higher mean BMI than women; however, while overweight was more prevalent among men at all ages, obesity was more common among women from age 36. There was a particularly sharp increase in mean BMI between age 43 and 53, especially for women, for whom obesity prevalence doubled in 10 years. By age 53 more than 70% of males and 60% of women were either overweight or obese.

Table 9 shows correlations between BMI measures from age 26 to age 53. Overall, correlations were similar for men and women. All measures were highly positively correlated with each other. Correlations were stronger for consecutive measures and weaker for those farther apart.

3.4.2 Investigation of potential confounders

Sex, educational attainment by age 26, lifetime smoking trajectory and WC at age 36, 43 and 53, were all associated with type 2 diabetes diagnosed between age 53 and 60-64 (Table 10). However, lifetime social class, based on occupational class of the head of household between age 15-53 was not. People who developed type 2 diabetes between age 53 and 60-64 were more likely to be inactive, but the associations were weak.

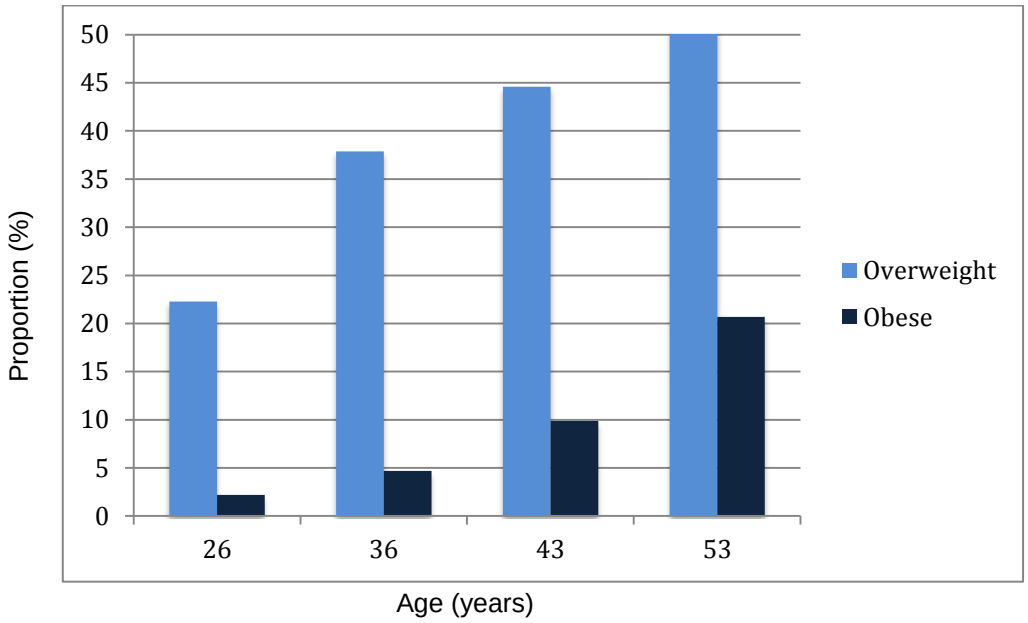
People from a lower SEP, especially those in manual employment, and with lower educational attainments had higher BMI at all ages (Table 11). Waist circumference was significantly associated with BMI. Those in the highest tertile of WC at age 36, 43 and 53 had the highest BMI at all ages. Less active people at age 36, 43 and 53 had significantly higher BMI than more active people. Smoking history was significantly associated with BMI only at age 53, when, compared to never smokers, current smokers had a lower BMI and ex-smokers had a higher BMI.

Table 8. BMI descriptive statistics by sex

	Men N=882		Women N=978		
	n	%	n	%	P value*
BMI at age 26					
BMI (Mean ± SD)	23.2	(2.7)	22.3	(3.1)	<0.001
BMI categories:					
Overweight (BMI ≥25 – 29.9 kg/m^2)	197	22.3	131	13.4	
Obese (BMI ≥30 kg/m^2)	20	2.2	17	1.7	<0.001
BMI at age 36					
BMI (Mean ± SD)	24.6	(3.1)	23.3	(3.6)	<0.001
BMI categories:					
Overweight (BMI ≥25 – 29.9 kg/m^2)	335	37.9	180	18.4	
Obese (BMI ≥30 kg/m^2)	42	4.7	54	5.5	<0.001
BMI at age 43					
BMI (Mean ± SD)	25.6	(3.2)	24.9	(4.4)	<0.001
BMI categories:					
Overweight (BMI ≥25 – 29.9 kg/m^2)	394	44.6	248	25.3	
Obese (BMI ≥30 kg/m^2)	88	9.9	125	12.7	<0.001
BMI at age 53					
BMI (Mean ± SD)	27.3	(3.8)	27.3	(5.2)	0.84
BMI categories:					
Overweight (BMI ≥25 – 29.9 kg/m^2)	447	50.6	359	36.7	
Obese (BMI ≥30 kg/m^2)	183	20.7	248	25.3	<0.001

Note: analyses restricted to those with non-missing data for BMI at age 26, 36, 43 and 53, type 2 diabetes and all covariates; *P value from test of sex difference using t-test for BMI as continuous variable and chi-squared test for categories of BMI. BMI=Body Mass Index

a) Men (N=882)



b) Women (N=978)

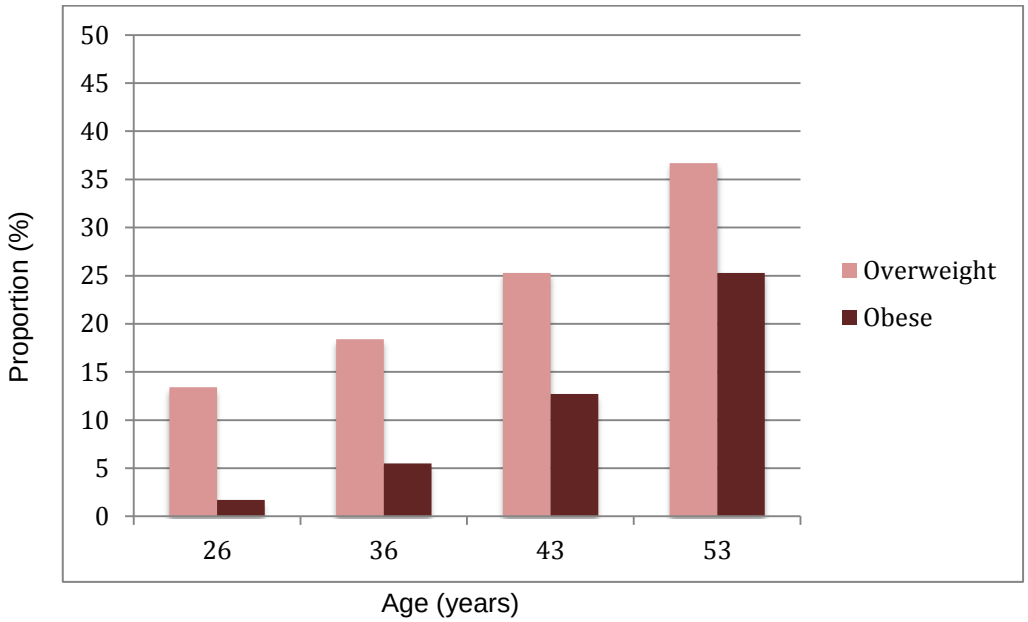


Figure 3. Percentage of people in the overweight and obesity categories* by age among: a) men and b) women.

Note: analyses restricted to those with non-missing data for BMI at age 26, 36, 43 and 53, type 2 diabetes and all covariates. * Overweight = BMI ≥ 25 - 29.9 kg/m2; obesity = BMI ≥ 30 kg/m2.

Table 9. Correlations between BMI measures

a) Males (n=882)

BMI at 36	0.76		
BMI at 43	0.72	0.86	
BMI at 53	0.63	0.76	0.84
	BMI at 26	BMI at 36	BMI at 43

a) Females (n=978)

BMI at 36	0.74		
BMI at 43	0.70	0.86	
BMI at 53	0.61	0.77	0.85
	BMI at 26	BMI at 36	BMI at 43

Note: Analyses restricted to those with non-missing data for BMI at age 26, 36, 43 and 53, type 2 diabetes and all covariates

Table 10. Associations between potential confounders and type 2 diabetes at age 53 to 60-64

	No diabetes		Diabetes	
	n	%	n	%
Male	1127	47.2	152	58.6
P-value (chi-squared test)	*<0.001*			
Lifetime socioeconomic position				
I professional	171	7.2	18	7
II intermediate	894	37.8	95	36.9
III skilled (Non-Manual)	563	23.8	50	19.8
III skilled (Manual)	390	16.5	51	19.8
IV partly skilled	256	10.8	31	12.6
V unskilled	87	3.6	12	4.6
P-value (trend)	*0.22*			
Education attained by age 26				
None attempted	746	33.3	101	40.8
Intermediate	631	28.2	67	27.1
Highest	857	38.3	79	31.9
P-value (trend)	*0.01*			
Waist circumference (WC) (cm)				
WC at age 36 *(Mean ± SD) N=2375*	81.8	(11.7)	88.7	(11.8)
P-value (t-test)	*<0.001*			
WC at age 43 *(Mean ± SD) N=2240*	83.1	(11.9)	92.5	(12.3)
P-value (t-test)	*<0.001*			
WC at age 53 *(Mean ± SD) N=2429*	90.0	(12.5)	101.2	(13)
P-value (t-test)	*<0.001*			
Lifetime smoking trajectory				
Never smoker	688	30.9	59	24.5
Predominantly non-smoker	787	35.4	79	32.9
Predominantly smoker	458	20.6	53	22.0
Lifelong smoker	289	13.0	49	20.4
P-value (trend)	*<0.01*			
Exercise at age 36				
Inactive	746	34.6	95	41.6
Less active	575	26.6	58	25.4
Most active	834	38.7	75	32.8
P-value (trend)	*0.03*			
Exercise at age 43				
Inactive	1107	49.5	124	53.4
Less active	534	23.9	61	26.2
Most active	592	26.5	47	20.2
P-value (trend)	*0.08*			
Exercise at age 53				
Inactive	1000	45.3	121	51.7
Less active	415	18.8	45	19.2
Most active	789	35.8	68	29.0
P-value (trend)	*0.03*			

Note: analyses restricted to those with non-missing data for type 2 diabetes; maximum available sample size used with each indicator. Educational attainment was categorised as none (none attempted), intermediate (GCE 'O' level or Burnam C or lower) or highest (GCE A level or Burnam B or higher); activity at each age was coded as inactive (no participation), moderately active (participated one to four times) and most active (participated five or more times), in the previous month (36 years), per month (43 years) and in the previous 4 weeks (53 years).

Table 11. Associations between potential confounders and BMI at age 26, 36, 43 and 53

	n	26 year	36 year	43 year	53 years
Lifetime socioeconomic position					
I professional	162	22.6 (2.6)	23.8 (2.8)	24.8 (3.2)	26.7 (3.8)
II intermediate	831	22.4 (2.6)	23.6 (3.1)	25.0 (3.5)	27.0 (4.3)
III skilled (Non-Manual)	537	22.3 (2.8)	23.4 (3.6)	24.9 (4.1)	27.3 (5.1)
III skilled (Manual)	392	23.9 (3.0)	25.3 (3.5)	26.3 (3.8)	27.8 (4.3)
IV partly skilled	256	23.3 (4.1)	24.5 (4.6)	26.2 (5.4)	28.2 (6.0)
V unskilled	96	23.7 (3.7)	24.9 (4.3)	26.2 (4.7)	28.2 (5.6)
P-value (trend)		*<0.001*	*<0.001*	*<0.001*	*<0.001*
Education attained by age 26					
None attempted	764	23.4 (3.3)	24.8 (4.0)	26.1 (4.6)	28.1 (4.9)
Intermediate	626	22.8 (3.1)	23.9 (3.6)	25.4 (4.1)	27.5 (5.0)
Highest	814	22.3 (2.6)	23.4 (3.1)	24.7 (3.6)	26.6 (4.3)
P-value (trend)		*<0.001*	*<0.001*	*<0.001*	*<0.001*
Waist circumference age 36					
Lowest tertile	708	21.3 (2.2)	21.7 (2.1)		
Middle tertile	634	22.6 (2.4)	23.7 (2.5)		
Highest tertile	588	24.9 (3.5)	27.2 (3.8)		
P-value (trend)		<0.001	<0.001		
Waist circumference age 43					
Lowest tertile	798	21.2 (2.1)	21.6 (2.2)	22.6 (2.4)	
Middle tertile	743	22.5 (2.3)	23.7 (2.5)	24.9 (2.8)	
Highest tertile	725	25.0 (3.4)	27.1 (3.8)	28.9 (4.3)	
P-value (trend)		<0.001	<0.001	<0.001	
Waist circumference age 53					
Lowest tertile	763	21.2 (2.1)	21.6 (2.1)	22.6 (2.4)	23.8 (2.5)
Middle tertile	764	22.6 (2.4)	23.7 (2.6)	24.9 (2.7)	26.9 (3.0)
Highest tertile	747	24.8 (3.4)	26.9 (3.8)	28.8 (4.3)	31.6 (4.8)
P-value (trend)		<0.001	<0.001	<0.001	<0.001
Smoking history up to 36 years					
Current smoker	676	23.0 (3.1)	24.0 (3.8)		
Ex smoker	901	22.8 (3.0)	24.2 (3.5)		
Never smoker	698	22.7 (2.9)	23.9 (3.5)		
P-value (ANOVA)		*0.27*	*0.10*		
Smoking history up to 43 years					
Current smoker	621			25.2 (3.9)	
Ex smoker	965			25.6 (4.2)	
Never smoker	687			25.3 (4.1)	
P-value (ANOVA)				*0.17*	
Smoking history up to 53 years					

Current smoker	494		26.6 (4.4)
Ex smoker	1103		27.8 (4.8)
Never smoker	680		27.3 (4.7)
P-value (ANOVA)			*<0.001*
Exercise at age 43			
Inactive	987	25.8 (4.6)	27.9 (5.2)
Less active	453	25.2 (3.7)	27.7 (4.5)
Most active	493	24.6 (3.2)	26.5 (3.9)
P-value (trend)		*0.02*	*<0.001*
Exercise at age 53			
Inactive	913		28.0 (5.4)
Less active	359		26.9 (4.1)
Most active	659		26.7 (4.0)
P-value (trend)			*<0.001*

Note: analyses restricted to those with non-missing data for BMI at age 26, 36, 43 and 53; maximum available sample size used with each indicator; educational attainment was categorised as none (none attempted), intermediate (GCE 'O' level or Burnam C or lower) or highest (GCE A level or Burnam B or higher); activity at each age was coded as inactive (no participation), moderately active (participated one to four times) and most active (participated five or more times), in the previous month (36 years), per month (43 years) and in the previous 4 weeks (53 years); p value for trend using Wilcoxon rank-sum test

3.4.3 Adult overweight and obesity and type 2 diabetes

Prospective associations between being overweight or obese at ages 26, 36, 43, 53 and type 2 diabetes diagnosed between 53 and 60-64 years are shown in Table 12 for men and Table 13 for women. For both sexes, overweight people at all ages were about twice more likely to have type 2 diabetes in later adulthood. These associations were not appreciably changed by adjustment for SEP, education, smoking and physical activity (Model 2 and 3). After further adjustment for WC however, the associations were considerably weakened particularly for women, for whom only associations at age 26 remained significant (OR=1.96, 95% CI, 1.07, 3.58, p=0.02) (Model 4).

In men (Table 12) obesity at all ages, except at age 26 (when it was rare), was significantly associated with later type 2 diabetes risk. There was a trend for obesity to become a stronger risk factor for type 2 diabetes with increasing age, with ORs ranging from 1.83 (95% CI, 0.51, 6.53) at age 26 to 9.30 (95% CI, 4.40, 19.63) at age 53. Adjustment for social confounders did not change the risk estimates (Model 2), but after further adjustment for physical activity and smoking the associations were slightly strengthened (Model 3). Further adjustment for WC (Model 4) weakened all associations but these remained significant for age 36 (OR=2.98, 95% CI, 1.01, 8.78), age 43 (OR=3.31, 95% CI, 1.25, 8.79) and particularly for age 53 (OR=7.39, 95% CI 2.70, 20.25).

In women (Table 13) associations between obesity and type 2 diabetes were of similar magnitude than those for men, except for age 26 when it was higher (OR=4.33, 95% CI, 1.36, 13.74). As for men associations were stronger with increasing age, but unlike men adjustment for smoking and physical activity did not strengthen the associations (Model 3). After further adjustment for WC all associations were considerably weakened to a higher degree than for men, and were no longer significant (Model 4). The OR of type 2 diabetes for obese women at age 53 was particularly weakened and changed from 8.61 (95% CI, 4.20, 17.64) in Model 3 to 1.94 (95% CI, 0.73, 5.17) in Model 4.

3.4.4 Duration of overweight and type 2 diabetes

Figure 4 shows mean BMI from age 26 to age 53 in men and women by categories of age at onset of overweight. In summary for all categories mean BMI increased with age in both men and women; those who never became overweight maintained a low BMI ranging from 20.9 kg/m^2 at age 26 to 22.8 kg/m^2 at age 53 in men and from 20.4 kg/m^2 to 22.6 kg/m^2 in women; those who became overweight at a younger age had on average a higher BMI at all ages, with the highest value at age 53; women had sharper increases in BMI in mid to late adulthood and reached highest BMI values at age 53; for example men overweight since age 26 reached an average BMI of 30.9 kg/m^2 by age 53 compared to a BMI of 33.3 kg/m^2 for women overweight since age 26. In short, earlier onset of overweight was associated with higher mean lifetime BMI.

Duration of overweight was associated with incident type 2 diabetes, with longer durations having higher HRs for diabetes, a trend that was particularly evident among women (Table 14). Among men, compared with people who had never been overweight, those overweight since age 26 had a 5-fold increased risk of type 2 diabetes, whereas those with late adulthood onsets were only twice as likely to develop the disease. Women with an early adulthood onset had a 10-fold increased risk of type 2 diabetes versus a 4-fold increased risk for a late adulthood onset. Adjustment for education, socio-economic position, exercise and smoking did not change the associations in men and slightly attenuated the associations among women. Adjustment for average waist circumference between age 36 and 53 (Model 4) attenuated the risk effects and further adjustment for BMI (Model 5) at age 53 substantially reduced all associations.

3.4.5 Sensitive periods of BMI gain and type 2 diabetes

Figure 5 shows the mean BMI gain velocity by sex and type 2 diabetes outcome diagnosed between 53 and 64 years. Men who remained free of diabetes had a slow and constant BMI gain velocity whereas men who developed the disease had higher BMI gain velocities in early and late adulthood. The pattern of BMI gain velocity was similar between women with diabetes and women without the disease: faster in later years, especially between age 43 and 53 compared to early adulthood. However, for diabetic women at all ages BMI velocity was substantially higher.

Among men, conditional on baseline BMI and independent of BMI change on previous periods, for 1 SD BMI gain between 26-36 years there was a 54% increased risk of type 2 diabetes in later years (Table 15). The corresponding risk estimates for the periods 36-43 years and 43-53 years were 13% and 59%. Early and late BMI gains were more strongly associated with diabetes than gains in mid-adulthood (difference in OR between early and mid-adulthood=0.41, p=0.04; difference in OR between late and mid-adulthood=0.46, p=0.03). Among women gains in BMI during each period of the adult life course were associated with diabetes. Gains between age 43 and 53 had the highest OR for diabetes (1.85, 95 % CI: 1.46, 2.34) compared with previous life periods (1.43, 95% CI: 1.14, 1.79 for 26-36 years; 1.36, 95% CI: 1.08, 1.71 for 36-43 years), although there was no statistically significant difference between periods (p>0.05). Adjustments for SEP, education, physical activity and lifetime smoking did not affect the associations considerably for either men or women (Model 2 and 3).

Table 12. Associations at each age between being overweight and obese and type 2 diabetes between age 53 and 60-64 among men

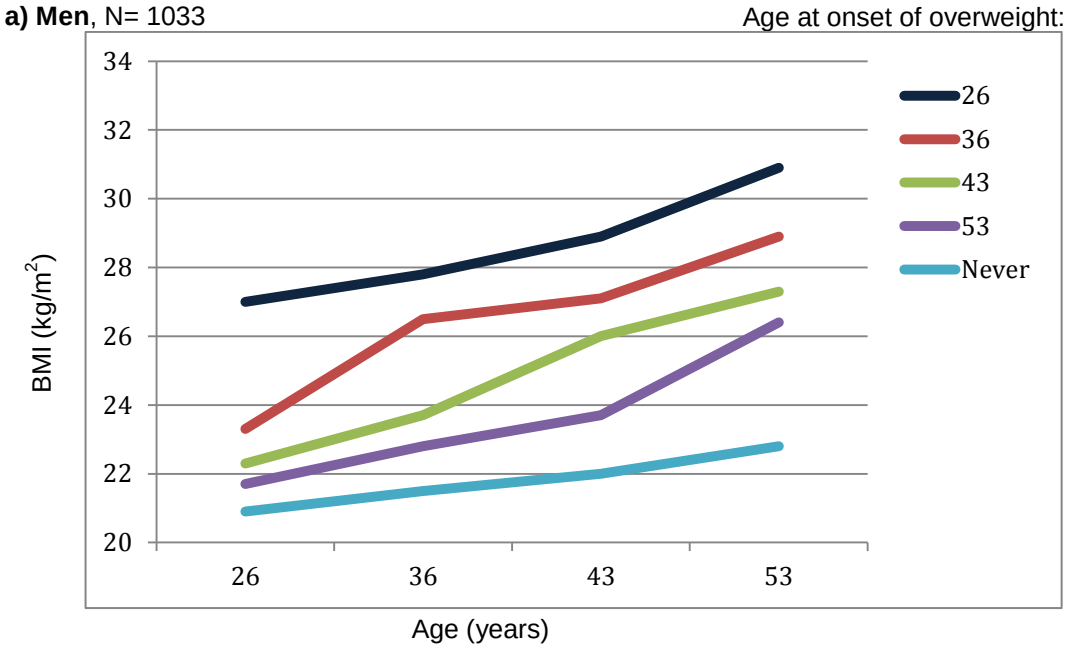
	Model 1 Unadjusted		**Model 2** Adjusted for SEP and education		**Model 3** As Model 2 + physical activity and smoking history,		**Model 4** As Model 3 + WC	
N=882	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
26 years								
Overweight	2.13 (1.36, 3.35)	<0.01	2.18 (1.37, 3.45)	<0.01	2.23 (1.40, 3.56)	<0.01	1.53 (0.91, 2.58)	0.10
Obese	1.74 (0.49, 6.13)	0.38	1.83 (0.51, 6.53)	0.34	1.87 (0.52, 6.73)	0.33	0.84 (0.21, 3.40)	0.81
36 years								
Overweight	2.27 (1.45, 3.55)	<0.001	2.27 (1.44, 3.59)	<0.01	2.29 (1.44, 3.64)	<0.001	1.79 (1.02, 3.13)	0.04
Obese	4.48 (2.08, 9.64)	<0.001	4.61 (2.11, 10.05)	<0.01	5.28 (2.39, 11.67)	<0.001	2.98 (1.01, 8.78)	0.04
43 years								
Overweight	2.32 (1.40, 3.86)	<0.01	2.35 (1.41, 3.92)	<0.01	2.24 (1.34, 3.77)	0.01	1.62 (0.88, 3.00)	0.12
Obese	5.87 (3.14, 10.97)	<0.001	5.97 (3.15, 11.31)	<0.001	6.66 (3.45, 12.86)	<0.001	3.31 (1.25, 8.79)	0.01
53 years								
Overweight	2.87 (1.37, 5.99)	<0.01	2.86 (1.36, 5.93)	<0.01	2.87 (1.36, 6.04)	<0.01	2.46 (1.10, 5.47)	0.02
Obese	9.33 (4.43, 19.62)	<0.001	9.30 (4.40, 19.63)	<0.001	10.46 (4.89, 22.38)	<0.001	7.39 (2.70, 20.25)	<0.001

Note: analyses restricted to those with non-missing data for BMI at age 26, 36, 43 and 53, type 2 diabetes and all covariates; BMI=Body Mass Index; WC=waist circumference; overweight= BMI $\geq$ 25 - 29.9 kg/m^2; obese= BMI $\geq$ 30 kg/m^2; for all associations the reference category was BMI <25 kg/m^2

Table 13. Associations at each age between being overweight and obese and type 2 diabetes between age 53 and 60-64 among women

	Model 1 Unadjusted		**Model 2** Adjusted for SEP and education		**Model 3** As Model 2 + physical activity and smoking history,		**Model 4** As Model 3 + WC	
N=978	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
26 years								
Overweight	3.00 (1.77, 5.08)	<0.001	2.81 (1.64, 4.32)	<0.001	2.77 (1.60, 4.80)	<0.01	1.96 (1.07, 3.58)	0.02
Obese	4.33 (1.36, 13.74)	0.01	3.54 (1.08, 11.57)	0.13	3.45 (1.02, 11.61)	0.04	1.63 (0.43, 6.13)	0.46
36 years								
Overweight	1.77 (1.02, 3.06)	0.04	1.70 (0.98, 2.96)	0.05	1.70 (0.97, 2.97)	0.06	1.23 (0.67, 2.27)	0.49
Obese	4.49 (2.26, 8.94)	<0.001	3.98 (1.96, 8.08)	<0.01	3.63 (1.75, 7.52)	<0.001	1.63 (0.64, 4.15)	0.30
43 years								
Overweight	2.31 (1.31, 4.04)	<0.01	2.22 (1.26, 3.91)	<0.01	2.16 (1.22, 3.82)	0.01	1.32 (0.69, 3.50)	0.38
Obese	6.22 (3.54, 10.92)	<0.001	5.89 (3.29, 10.41)	<0.001	5.72 (3.18, 10.29)	<0.001	1.67 (0.66, 4.24)	0.27
53 years								
Overweight	2.47 (1.15, 5.26)	0.01	2.44 (1.14, 5.23)	0.02	2.51 (1.17, 5.37)	0.01	1.50 (0.67, 3.32)	0.31
Obese	8.88 (4.40, 17.93)	<0.001	8.56 (4.21, 17.39)	<0.001	8.61 (4.20, 17.64)	<0.001	1.94 (0.73, 5.17)	0.18

Note: analyses restricted to those with non-missing data for BMI at age 26, 36, 43 and 53, type 2 diabetes and all covariates; BMI=Body Mass Index; WC=waist circumference; overweight= BMI $\geq$ 25 - 29.9 kg/m^2; obese= BMI $\geq$ 30 kg/m^2; for all associations the reference category was BMI <25 kg/m^2



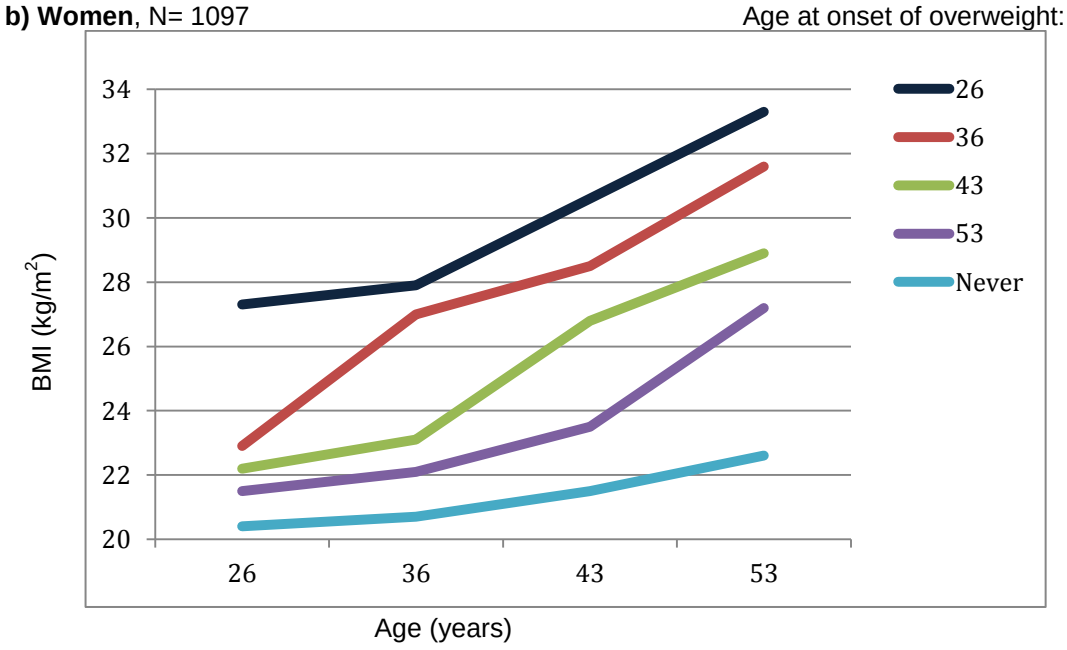


Figure 4. Mean BMI from 26 to 53 years by age at onset of overweight for a) men and b) women.

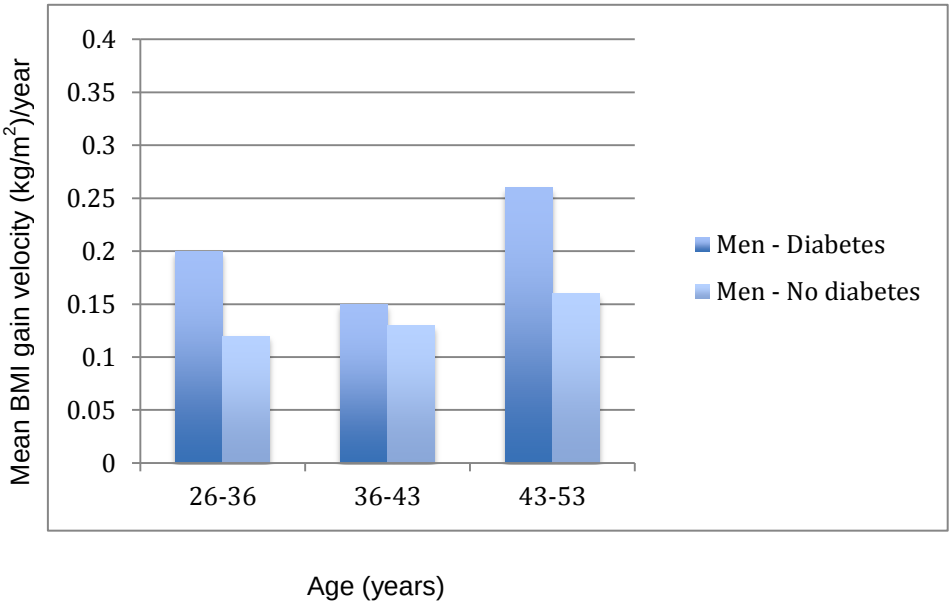
Note: Sample restricted to those included in Cox's proportional hazards models of duration of overweight and type 2 diabetes

Table 14. Associations between duration of overweight or obesity and type 2 diabetes incidence between age 53 and 60-64

		Model 1 Unadjusted		**Model 2** Adjusted for SEP and education		**Model 3** As Model 2 + physical activity and smoking history		**Model 4** As Model 3 + WC*		**Model 5** As Model 4 + adjusted for BMI at age 53	
N=2130		HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age first overweight											
Men	n (%)										
Never	256 (24.8)	Reference		Reference		Reference		Reference		Reference	
26 years	248 (24.0)	4.97 (2.40, 10.29)	<0.001	5.20 (2.37, 11.37)	<0.001	5.18 (2.48, 10.79)	<0.001	3.32 (1.41, 7.77)	<0.01	1.47 (0.58, 3.75)	0.41
36 years	227 (22.0)	3.57 (1.67, 7.62)	<0.01	3.59 (1.59, 8.11)	<0.01	3.54 (1.65, 7.61)	<0.01	2.53 (1.10, 5.78)	0.02	1.44 (0.60, 3.44)	0.40
43 years	144 (13.9)	2.60 (1.11, 6.10)	0.02	2.68 (1.07, 6.70)	0.03	2.71 (1.15, 6.35)	0.02	2.25 (0.94, 5.37)	0.06	1.29 (0.52, 3.18)	0.57
53 years	158 (15.3)	2.15 (0.90, 5.11)	0.08	2.39 (0.96, 5.98)	0.06	2.27 (0.95, 5.42)	0.06	2.01 (0.83, 4.82)	0.1?1	1.36 (0.56, 3.32)	0.475
Women	n (%)										
Never	388 (35.4)	Reference		Reference		Reference		Reference		Reference	
26 years	166 (15.1)	9.61 (4.36, 21.16)	<0.001	8.76 (3.94, 19.49)	<0.001	8.54 (3.81, 19.14)	<0.001	5.80 (2.42, 13.86)	<0.001	2.04 (0.72, 5.74)	0.17
36 years	136 (12.4)	5.07 (2.10, 12.24)	<0.001	4.89 (2.02, 11.85)	<0.001	4.73 (1.95, 11.50)	<0.01	3.57 (1.42, 8.92)	<0.01	1.56 (0.56, 4.27)	0.38
43 years	157 (14.3)	5.03 (2.13, 11.87)	<0.010	4.91 (2.08, 11.59)	<0.001	4.88 (2.05, 11.55)	<0.001	4.48 (1.89, 10.64)	<0.01	2.26 (0.90, 5.68)	0.08
53 years	250 (22.8)	3.76 (1.64, 8.59)	0.01	3.74 (1.63, 8.55)	0.01	3.72 (1.62, 8.55)	<0.01	3.48 (1.51, 8.09)	<0.01	2.21 (0.94, 5.21)	0.06

Note: analyses restricted to those with non-missing data for BMI at age 26, 36, 43 and 53, type 2 diabetes and all covariates; WC=waist circumference Overweight (including obesity) = BMI $\geq$ 25 kg/m^2; * Average waist circumference between age 36-53

Men (n=883)



Women (n=977)

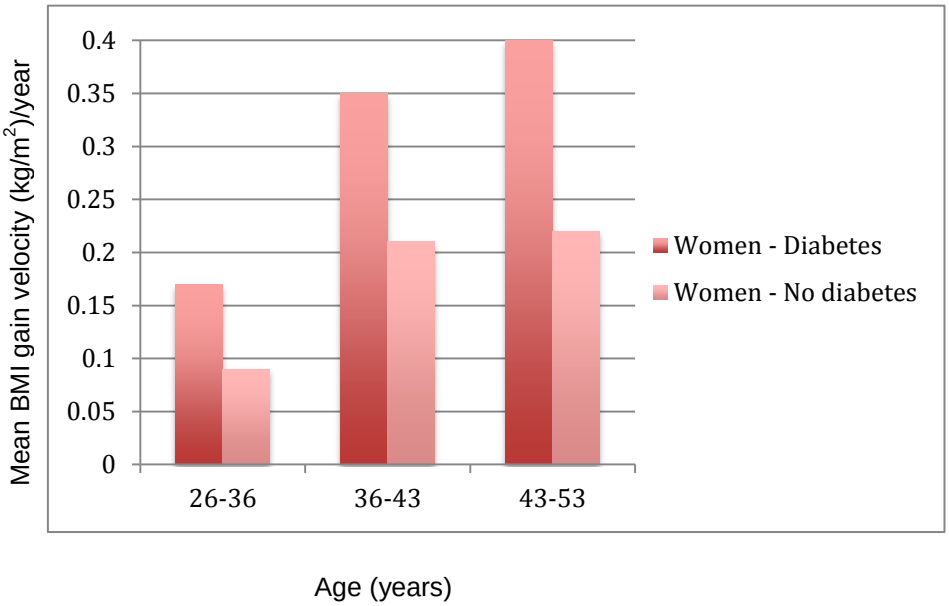


Figure 5. Mean BMI gain velocity per year for different periods of the adult life by sex and diabetes diagnosis at age 53-64

Note: Sample restricted to those included in logistic regression models of sensitive periods of BMI gain and type 2 diabetes

Table 15. Associations between conditional BMI velocity and type 2 diabetes between age 53 and 60-64

	Model 1 Unadjusted		**Model 2** Adjusted for SEP and education		**Model 3** As Model 2 + adjusted for physical activity and smoking history	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Period of change						
Men, n=883						
26-36 years	1.54 (1.24, 1.91)	<0.001	1.52 (1.22, 1.89)	<0.001	1.56 (1.25, 1.95)	<0.001
36-43 years	1.13 (0.91, 1.39)	0.24[a]	1.12 (0.91, 1.39)	0.24	1.15 (0.93, 1.43)	0.24
43-53 years	1.59 (1.28, 1.97)	<0.001[b]	1.58 (1.27, 1.96)	<0.001[b]	1.67 (1.33, 2.08)	<0.001[b]
Women, n= 977						
26-36 years	1.43 (1.14, 1.79)	<0.01	1.41 (1.13, 1.77)	<0.01	1.40 (1.11, 1.76)	<0.01
36-43 years	1.36 (1.08, 1.71)	<0.01	1.36 (1.08, 1.71)	<0.01	1.38 (1.09, 1.74)	<0.01
43-53 years	1.85 (1.46, 2.34)	<0.001	1.85 (1.46, 2.34)	<0.001	1.84 (1.45, 2.35)	<0.001

Note: analyses restricted to those with non-missing data for BMI at age 26, 36, 43 and 53, type 2 diabetes and all covariates. BMI=Body Mass Index; OR of type 2 diabetes for a 1 SD increase in BMI in each interval conditional on previous BMI;
Letter (a): Significantly different from 26-36; Letter (b): Significantly different from 36-43; P for difference between periods estimated with Wald's test

3.5 Discussion

3.5.1 Main findings

The main findings of this chapter are that for both genders, at any stage of the adult life course, overweight and obesity, as well as BMI gains, are associated with later risk of type 2 diabetes. Early and late adulthood BMI gains were more important for men whereas gains in late adulthood had stronger associations for women.

As well as the level of overweight, this chapter found that the duration of overweight or obesity is a significant risk factor for type 2 diabetes incidence, probably because of the increasing accumulation of weight across the life course, with higher attained BMI with longer durations of overweight.

1st objective: To analyse the association between BMI measured at different time points in the adult life (age 26, 36, 43 and 53 years) and type 2 diabetes incidence

It was hypothesised that BMI at any point of the adult lifecourse would be associated with type 2 diabetes and that this association would be stronger for women. In support of the first hypothesis, overweight and especially obese people had higher risks of later type 2 diabetes. This was true for all ages except for obesity at age 26 in men. This might reflect a lack of power because of the few obese men at this age (n=20) or it might be due to misclassification since BMI at age 26 was self-reported. These findings are in agreement with the many studies (49-56, 63) that reported that being overweight, and particularly obese, at any age during adult life is strongly associated with later type 2 diabetes. The associations were not affected by adjustment for SEP and education, suggesting that the effect of overweight and obesity was unlikely to be confounded by these factors. However adjustment for physical activity and smoking slightly strengthened the associations in men but not in women. This is probably due to the BMI-lowering effect of smoking, thus acting as an effect-suppressor. Since there were more smokers among men, the confounding effect of smoking was more evident for men. Adjustment for WC removed most of the associations for women while associations at age 36, 43 and especially 53 remained significant for men. These results suggest that WC is a more important risk for women than for men, a fact that has been acknowledged in other studies (64, 65, 75-77).

In disagreement with the first hypothesis and in contrast with other studies (64, 65, 75-77) that found stronger associations for women, there was no difference in risk estimates between men and women. Specifically in the NSHD cohort the odds of diabetes among obese women were lower than those reported by other studies. Unlike younger samples, the NSHD is a relatively lean cohort with low levels of obesity until middle age particularly among women, whose obesity prevalence had a dramatic increase only between age 43 and 53 (see Figure 3). The difference between men and women might be only evident in this cohort in later adulthood, when women gain most of their weight. Most other studies that showed a differential effect of obesity by sex included a population sample with a range of ages, usually between mid and late adulthood. It is

possible that the different age at BMI calculation might have produced different risk estimates compared with those found in the NSHD, since older women tend to be larger.

The results showed that in both men and women obesity was a more important risk factor for type 2 diabetes at older ages. This might reflect a true differential effect depending on when weight was gained (a sensitive period model) or it might be due to a continuous weight gain over the years leading to a higher BMI at a later age (an accumulation model). To answer this question the sensitive and accumulation models hypotheses were tested in section 3.3.4 and 3.3.5 and findings are explained below.

2nd objective: To assess the effect of the duration of overweight or obesity on subsequent type 2 diabetes incidence.

It was hypothesised that earlier onsets of overweight or obesity would be associated with a greater risk of type 2 diabetes compared with later onsets during the adult life course. The results in this chapter support the second hypothesis and are in agreement with previous studies, which found that duration of overweight is an important risk factor for type 2 diabetes (103-109). This chapter expands on previous studies that investigated shorter durations (105, 106, 108, 109) or only used self-reported measures of BMI (110, 115, 116, 259). Compared with people who had never been overweight, those with the longer duration of overweight (equal or more than 27 years) had the highest diabetes incidence; whereas those with the shorter duration (1-10 years) had the lowest incidence.

The associations were not confounded by SEP, education, physical activity and smoking, since adjusting for these variables had a minimal effect on the HRs. Adjustment for attained BMI at age 53 significantly weakened and removed most associations. This suggests that most of the association between age at onset of overweight and type 2 diabetes could be explained by attained BMI, since those with longer durations reached a higher BMI at age 53, as shown in figure 3. Because in this cohort very few individuals moved from the overweight and obese categories to the normal weight one and many gained weight over the years, it was not possible to single out any additional risk caused by protracted adult exposure to overweight from the association caused by accumulation of BMI. Power and Thomas (106) found that current BMI significantly reduced, but did not completely eliminate, the association between age at onset of obesity and diabetes, suggesting that accumulation of BMI was the predominant explanation, but that a small effect of duration per se was possible. In a study of Pima Native Americans (105) longer duration of obesity remained significantly associated with diabetes even after adjustment for current BMI. However, it is difficult to compare the NSHD sample with this ethnically different population with an extremely high prevalence of obesity and diabetes.

At any age at onset of overweight women had higher HRs for type 2 diabetes compared with men with the same age at onset, particularly for onset at age 26. Although the interaction term for sex and age at onset was not significant, these differences might suggest that duration of overweight could be slightly more important for women. Women with longer durations had a higher BMI at age 53 compared with men with the same duration. Thus the stronger effect of

duration of overweight on type 2 diabetes for women could be explained by their higher BMI reached at age 53.

3rd objective: To investigate whether BMI gain at different periods of the adult life (26 to 36, 36 to 43 and 43 to 53 years) has a different impact on later risk of type 2 diabetes incidence.

It was hypothesised that weight gain at any adult lifecourse period would be associated with type 2 diabetes and that this association between would be stronger in early adulthood (26 to 36 years) than in middle (36 to 43 years) or later adulthood (43 to 53 years). In partial agreement with the third hypothesis, BMI gains at any period of the adult life were significantly correlated with later type 2 diabetes incidence for women, but only BMI gains during early and late adulthood increased diabetes risk for men. The findings in this chapter also partly support the hypothesis that early-adulthood BMI gains are more important for later type 2 diabetes than middle and late adulthood BMI gains. In men, independently of baseline weight and previous periods of BMI change, BMI changes between 26-36 and 43-53 years were significantly more strongly associated with later diabetes risk when compared to changes between 36-43 years. These differences persisted after adjustment for SEP, education, smoking, physical activity for the period 43-53 but not 26-36 years. In women there was no statistical difference between periods of BMI change; however BMI gain in the period 43-53 years had a higher OR for type 2 diabetes compared with the previous periods. Adjustment for SEP, education, smoking and physical activity hardly changed these associations. These findings suggest that, compared to women, early adulthood is a particularly sensitive period for later diabetic risk among men possibly due to the susceptibility of young men to gain weight during these years. However late BMI gains remain a more important period of weight gain, maybe due to the increased susceptibility to develop metabolic complications in later years. Women seem to have a more gradual weight gain during early to mid-adulthood and more substantial BMI gains during late-adulthood; this spike in weight gain could be explained by changes in lifestyle or by the hormonal and physiological changes accompanied by the peri-menopausal years.

These findings are in partial agreement with previous studies, which found that BMI gains during early adulthood were more strongly correlated with later type 2 diabetes than changes in mid-adulthood independently of earlier weight (106, 113-116) but in disagreement with the three studies that included weight change in later adulthood (113-115) and found a more pronounced association with type 2 diabetes for weight gains in early than later life. However, the periods analysed by previous studies are difficult to compare to the present findings. One study compared weight change from age 21 to age 40-75 with 10-years weight change from age 40-75 (113); another study looked at BMI gains from age 25 to 40 versus changes from age 40 to 55 (115); the third study analysed BMI change from 20 years to the baseline examination (average age of 50 years) with change from baseline to 5 years afterwards (114). The results from this chapter add to the previous literature by providing a more detailed characterisation of sensitive periods of adult BMI gain. Whereas previous studies only compared two periods, this chapter compared three periods of change. In an attempt to compare the results in this chapter

with previous studies, the findings from Table 15 were repeated comparing the period 26 to 43 years with 43 to 53 years using the same methodology employed for analyses presented in table 15 (Appendix 5). The results showed that changes in BMI in the later period were slightly more strongly correlated with type 2 diabetes than BMI changes in the earlier period for both men and women, although these differences did not reach statistical significance ($p<0.05$). Thus it seems that the greater effect observed for early compared with later BMI gains in other studies could be mainly driven by changes in the early adulthood years (25 to 36 years) in men.

3.5.2 Strengths

A strength of these analyses is that they used repeated measures of BMI throughout adult life at regular intervals. Most previous studies only used two or three repeated measures to test for sensitive periods of BMI and duration of overweight; in this chapter the richness of the data could be exploited to investigate longer trajectories of overweight and more detailed characterization of BMI history in relation to type 2 diabetes. A further strength is that, unlike other studies, heights and weights were measured using a standardized protocol at 36, 43 and 53. Measures at 26 were self-reported, but were reported at that age rather than being recalled later.

The analytical strategy used had a number of strengths. First models were constructed to account for a range of confounders and mediators that have not always been included in other studies. Second, to enable comparison of BMI gains across intervals of varying length, periods of BMI change were converted into velocities using the residual method, which enabled formal comparison of velocities within the same model.

3.5.3 Limitations

Although BMI was obtained by weight and height measured by a trained professional at ages 36, 43 and 53, BMI at age 26 was derived from self-reported weight and height and this could be a potential source of measurement error. However, self-reported height and weight among younger adults have been found to provide a reliable estimate of measured values, while recall bias could be a problem for older adults (273). Nevertheless, differential misreporting might have introduced some bias in the estimated BMI change between age 26 and 36, since in general weight tends to be underreported particularly from overweight individuals (257).

In this chapter complete case analyses were conducted with only study participants with data for all BMI measures and type 2 diabetes status as well as for all covariates included in the analyses. However, the final sample size in all analyses was large enough to find significant associations and comparable to previous longitudinal studies therefore loss of power was unlikely to be an issue.

In addition to contributing to loss of power, the use of complete case analyses in this chapter might have resulted in bias. However, as shown in Appendix 6 those with non-missing data for all covariates were remarkably similar to those in the maximum sample available for each

covariate and type 2 diabetes. In particular, there was no difference in mean BMI at all ages between the maximum sample available and the sample included in the analyses, suggesting that the use of complete cases was unlikely to have substantially impacted on the results. Similarly, Appendix 3 and 4 show that those with missing data on BMI were not different from those without missing with respect to BMI category and type 2 diabetes status. However, those with non-missing data were healthier (i.e. less likely to smoke and be inactive) and more educated, suggesting results might not be generalizable to all populations.

Another potential source of bias was loss to follow-up in the NSHD sample. Some loss to follow up is inevitable in every longitudinal study and the NSHD has maintained good response rates throughout the study, which are comparable with other cohorts.

A limitation of this chapter is that longitudinal analyses were restricted to adult life. The NSHD sample was a very lean cohort up to age 20-26 compared with younger cohorts thus limiting generalisability. Because there were few overweight and obese children, it was not possible to investigate longer trajectories that encompassed both childhood and later adulthood.

A limitation of the analyses of duration of overweight and type 2 diabetes is the assumption that individuals first overweight at one age remained overweight at the following data collection. Although fluctuation in weight between data collections cannot be ruled out, the assumption was reasonable considering the small number of people who moved from the overweight to the normal weight category.

A possible problem might arise with the use of change measures because of the risk of regression to the mean. However, the effect of regression to the mean is greater with increasing measurement error and when measures used for change scores are poorly correlated (274). BMI values in the NSHD were measured by trained professionals according to standard protocols, and were highly correlated, especially those consecutive in time; thus, the effect of regression to the mean was likely to be small.

3.5.4 Conclusions

This chapter has shown that at any age BMI gains, as well as overweight and obesity per se, are positively associated with later type 2 diabetes. For men, early and late adulthood BMI gains are more strongly associated with the disease than gains in mid adulthood, whereas for women late adulthood BMI gains are more important for type 2 diabetes.

Longer durations of overweight are significantly associated with type 2 diabetes and this associated is mainly explained by attained BMI. These findings suggest that due to accumulation of weight throughout the adult life course, interventions in earlier life to prevent increasing BMI gains with age might be more successful to tackle type 2 diabetes than interventions in mid- to late adulthood. This might be particularly important for men who tend to gain weight earlier in life compared to women.

Although analyses presented in this chapter acknowledge the importance of BMI as a key risk factor for diabetes, BMI cannot measure body fat distribution, which as discussed in chapter 1 might better predict metabolic risk. Chapter 4 builds on the work done in this chapter by investigating associations between WC and type 2 diabetes and its interaction with BMI.

4 Waist circumference across the life course and type 2 diabetes

4.1 Introduction

As illustrated in chapter 3, obesity at any time during the adult life course is a strong predictor of future risk of type 2 diabetes. However, there is growing acknowledgment that central, rather than overall obesity, is particularly detrimental for diabetes. This is because, as outlined in Chapter 1, excess visceral intra-abdominal adipose tissue is a key factor in the pathogenesis of metabolic disorders (66). While BMI is an indicator of generalized obesity, WC has been found to closely associate with localised central fatness and visceral fat (83, 84). WC measures are simple to obtain and interpret and are preferred to other abdominal obesity indicators in clinical and public health settings.

WC is strongly associated with type 2 diabetes risk independently of BMI (67-72); systematic reviews have also found that the relative risk of diabetes is higher with WC than with BMI (80, 275) especially among women (76). However, evidence from large samples suggests that WC is better interpreted in the context of BMI (75, 276, 277); although BMI and WC are highly correlated at the population level, at the individual level, for a given BMI there is a wide variation in WC measures (278). At the same BMI level those with a larger waist have a higher metabolic risk. This was well documented in the International Day for the Evaluation of Abdominal Obesity (276), a 63-country study involving more than 160,000 people: WC had a graded relationship with type 2 diabetes at all levels of BMI and the risk was increased even among those with a normal BMI (<25 kg/m^2) but an elevated WC. Similarly, in the EPIC InterAct study (76), among overweight people, WC identified a sub-group of individuals with a larger waist, whose diabetes risk was similar to that of people in the obese category.

Although the absolute risk of type 2 diabetes is higher for men at any BMI and waist category, it has been reported that the relative effect of WC on diabetes is stronger for women than for men (75-78). This might be particularly evident after adjustment for BMI, suggesting that WC might be a better indicator of excess abdominal fat and metabolic abnormalities among women once the effect of overall obesity is removed.

Although there is strong evidence of an association between WC measured at one point in time and type 2 diabetes, it is less clear whether changes in WC, controlling for initial abdominal fatness, are also important for diabetes risk. This is mainly because few longitudinal studies have repeated WC measures, and most rely on self-reported values.

In the Coronary Artery Risk Development in Young Adults study (118) a steady gain in WC over 15 years was associated with increasing insulin resistance after adjustment for confounders. There was an interaction between initial WC and change in WC, such that the association of WC change with insulin resistance was stronger for those who had a lower initial WC. This study was limited to young people and did not test sex differences. Increases in WC were also

associated with progression to type 2 diabetes in people with IFG in the Data from an Epidemiological Study on the Insulin Resistance Syndrome cohort (79). In this study there was an interaction between WC changes and initial BMI: the effect of WC change was larger for people within the normal BMI category (<25 kg/m^2) than for those with a BMI equal or higher than 25 kg/m^2. Only two studies investigated whether WC changes are predictive of type 2 diabetes independently of changes in total body weight (113, 119). In the Health Professionals Follow UP study (113) the risk of diabetes increased with higher WC changes over 10 years among middle-age and older adults; however, only the highest quintile of WC gain (>14.6 cm) remained significantly associated with diabetes after adjustment for concurrent weight change. Conversely, in a subsequent Danish study (119) 5-year WC changes were not associated with later diabetes risk in men but were weakly associated among women after adjustment for BMI change.

These findings suggest that the effect of WC change on type 2 diabetes might be different according to initial levels of overall and abdominal fatness and that these might be more pronounced among women. There is also some suggestion that WC changes act independently of weight change, but only for substantial increases in WC. However, only two studies (113, 119) included adjustment for weight change and both studies used self-reported anthropometric measures at least at one point. Furthermore only one study investigated men and women separately (119). To the author's knowledge, no study has investigated whether there are sensitive periods when WC gains are more detrimental for future type 2 diabetes risk.

Because of the limited available evidence on life course abdominal obesity in relation to metabolic conditions, this chapter will analyse how change in WC over the adult life course influences type 2 diabetes risk and whether changes are independent of concurrent BMI change. Subgroup analyses will also be performed to confirm any differential effect according to sex and to categories of initial BMI. Finally sensitive periods of WC gain (36-43 years and 43-53 years) will be investigated.

4.1.1 Research question

The main research question of this chapter is how WC throughout the adult life course affects type 2 diabetes risk in later life.

4.1.2 Objectives

1. To analyse the association between WC measured at different time points in the adult life (age 36, 43 and 53 years) and incident type 2 diabetes
2. To assess whether the effect of WC on type 2 diabetes risk is different according to different levels of BMI
3. To investigate whether WC changes during the adult life-course are associated with later risk of type 2 diabetes independently of initial WC and of concurrent BMI changes
4. To assess whether the effect of lifecourse WC change on type 2 diabetes risk is different according to levels of initial BMI

5. To investigate whether WC gain at different periods of the adult life (36 to 43 and 43 to 53 years) has a different impact on later risk of type 2 diabetes

4.1.3 Hypotheses

1. WC at age 36, 43 and 53 years is associated with type 2 diabetes diagnosed between age 53 and 64 years independently of BMI and this association is stronger for women than men
2. The relative risk of type 2 diabetes for a raised WC will differ according to BMI categories. In particular risk will be higher for normal weight people than for overweight and obese individuals
3. Increases in WC over the lifecourse are associated with type 2 diabetes risk independently of BMI changes and this association will be stronger for women
4. The association between WC increases and diabetes will be stronger for people with an initial lower BMI

4.2 Methods

4.2.1 Explanatory variables

The main explanatory variables used in this chapter are WC measures at age 36, 43 and 53. As well as using WC as a continuous variable, in this chapter categories of WC were defined according to the National Institute for Health and Care Excellence (NICE) cut-offs for increased risk of type 2 diabetes (279). A WC of 94-102 cm in men and 80-88 cm in women was defined as high risk WC; a WC of >102 cm for men and >88 cm for women was defined as very high risk WC. These cut-offs are based on the IDF consensus worldwide definition of metabolic syndrome (280).

4.2.2 Outcome variables

The outcome used in this chapter is the main outcome of this thesis, the risk of type 2 diabetes diagnosed between age 53 and 60-64 years. This is described in more detail in Chapter 2.

4.2.3 Potential confounding variables

Level of education and of socio-economic position (SEP) were considered as potential confounders since, as mentioned in previous chapters, type 2 diabetes (31-35) is more prevalent among people from lower social classes and with lower educational attainment. Studies have also reported an inverse relationship between education (281) and WC as well as an association between low socio-economic status (282) and abdominal obesity, in particular among women.

Lifetime social class based on the head of the household's occupational social class at age 15-53 years was used as a measure of SEP and highest level of educational qualification achieved by age 26 years was used to adjust for education.

Lack of physical activity is a risk factor for obesity, both general and abdominal (266, 267). Although smoking cessation is associated with weight gain (267), there is a dose-response relationship between the amount of cigarettes smoked, as well as the length of smoking, and abdominal and visceral fat (270).

BMI was used both as a confounder and as an effect modifier, to test the hypotheses that WC acts independently of BMI and that the effect of WC might be different according to BMI categories.

For the analyses presented in this chapter, self-reported measures of leisure time physical activity at 36, 43 and 53 years were used as potential confounders. Three categorical variables of smoking history up to 36, 43 or 53 were used as measures of cumulative smoking damage. BMI was included at age 36, 43 and 53.

More detailed descriptions of the potential confounding measures used in this chapter were given in Chapter 2.

4.2.4 Statistical analyses

Mean and SD of WC and proportions of people with a large (at increased risk of type 2 diabetes) and very large (at greatly increased risk of type 2 diabetes) waist circumference between age 36 and age 53 are presented by sex. All subsequent analyses were stratified by sex on *a priori* grounds based on evidence from the literature and to test the hypothesis that the effect of WC on type 2 diabetes is stronger for women than for men. Associations of potential confounders with WC at age 36, 43 and 53 and the outcome were examined using linear regression or bivariate analyses.

Multivariable logistic regression was used to examine prospective associations between low risk (<94 cm for men and <80 cm for women), high risk (94-102 cm in men and 80-88 cm in women) and very high risk (>102 cm for men and >88 cm for women) categories of WC at 36, 43 and 53 years of age and type 2 diabetes between age 53 and 64 years. An interaction between WC and BMI categories was formally tested and analyses were subsequently stratified by categories of BMI.

To investigate life-course changes in WC a conditional change approach (277) was adopted. To analyse the effect of long-term WC changes on the outcome, changes in WC (cm) from age 36 to 53 (calculated by subtracting WC at 53 minus WC at 36) were regressed on type 2 diabetes conditional on WC at age 36.

A conditional model of change (272) was used to examine whether there are sensitive periods for adult WC gain in a similar manner as in chapter 3. WC change scores for the periods 36–43 and 43–53 years were calculated for each sex conditional on earlier WC using the residual method, which has been described in chapter 3. As in the previous chapter the residuals were fitted in the same model with the outcome and compared using Wald tests.

For all analyses associations were first presented unadjusted (Model 1). A series of models were then constructed to sequentially adjust for socio-economic status and educational attainment (Model 2), smoking history and exercise (Model 3) and either BMI for prospective models or change in BMI analyses of WC change (Model 4).

4.2.5 Sample

All analyses were restricted to those with data for type 2 diabetes diagnosed between age 53 and 60-64 and all covariates included in fully adjusted models (SEP, education, smoking, physical activity, BMI). For prospective associations of WC at each age the available number differed by year and was 2242 for WC at age 36, 2290 for WC at age 43 and 2269 for WC at age 53. The final number for longitudinal analyses of change in WC and sensitive periods of WC change and type 2 diabetes was 2007.

4.3 Results

4.3.1 Descriptive analyses of WC

Descriptive statistics of WC at age 36, 43 and 53 for those included in the prospective analyses of WC and type 2 diabetes are shown in Table 16 and Figure 6. WC increased with age for both men and women, in particular from age 43 to 53. At any age men were more likely to be in the "high risk" WC category (men ≥94-102cm, women ≥80-88cm), while women were more likely to be in the "very high risk" WC category (men >102cm, women >88cm). Between age 43 and 53 there was a sharp increase in proportion in the "very high risk" WC category especially among women, the prevalence of which more than doubled in 10 years. By age 53 more than 62% of males and 63% of women had a WC that put them at increased risk of type 2 diabetes.

Table 17 shows correlations between WC measures from age 36 to age 53. Correlations between WC at age 36 and 43 and between WC at age 36 and 53 were stronger for men than for women, while correlations between WC at age 43 and 53 were similar for men and women. All measures were positively correlated with each other. Correlations were stronger for consecutive measures and weaker for those farther apart.

At all ages there was a strong positive correlation between WC and BMI among men; for women the correlation was strong at age 43 and 53 and slightly weaker at age 36

4.3.2 Investigation of potential confounders

On average, people in manual employment and with the lowest educational attainment tended to have a larger WC at all ages (Table 18). WC was significantly positively associated with BMI categories, in a clear dose-response way. At age 36 and 43 both current and ex smokers had significantly larger WC than never smokers, while at age 53 ex smokers had the highest WC compared to the other categories. Less active people at all ages had a significantly higher WC than more active people, with a stronger trend at age 43 and 53.

Table 16. Waist circumference descriptive statistics by sex

	Men		**Women**		
	n	%	n	%	P value*
WC at age 36 (N=2242)					
WC (Mean ± SD)	89.1	(8.9)	76.3	(10.8)	<0.001
WC categories:					
Low (Men <94cm, women <80cm)	763	71.3	831	70.7	
High (Men ≥94-102cm, women ≥80-88cm)	231	21.6	176	14.9	<0.001
Very high (Men >102cm, women >88cm)	75	7.0	168	14.3	
WC at age 43 (N=2290)					
WC (Mean ± SD)	91.4	(9.5)	77.2	(10.5)	<0.001
WC categories:					
Low (Men <94cm, women <80 cm)	685	62.6	828	69	
High (Men ≥94-102cm, women ≥80-88cm)	271	24.7	210	17.5	<0.001
Very high (Men >102cm, women >88cm)	138	12.6	162	13.5	
WC at age 53 (N=2269)					
WC (Mean ± SD)	97.4	(10.5)	85.3	(12.4)	<0.001
WC categories:					
Low (Men <94cm, women <80cm)	407	37.2	442	36.9	
High (Men ≥94cm, women ≥80cm)	346	32.0	332	27.7	<0.001
Very high (Men >102cm, women >88cm)	326	30.2	423	35.2	

Note: analyses restricted to those with non-missing data for type 2 diabetes and all covariates; WC=waist circumference; categories of WC were defined according to the National Institute for Health and Care Excellence (NICE) cut-offs for increased risk of type 2 diabetes (279)
*P value from test of sex difference using t-test for WC as continuous variable and chi-squared test for categories of WC.

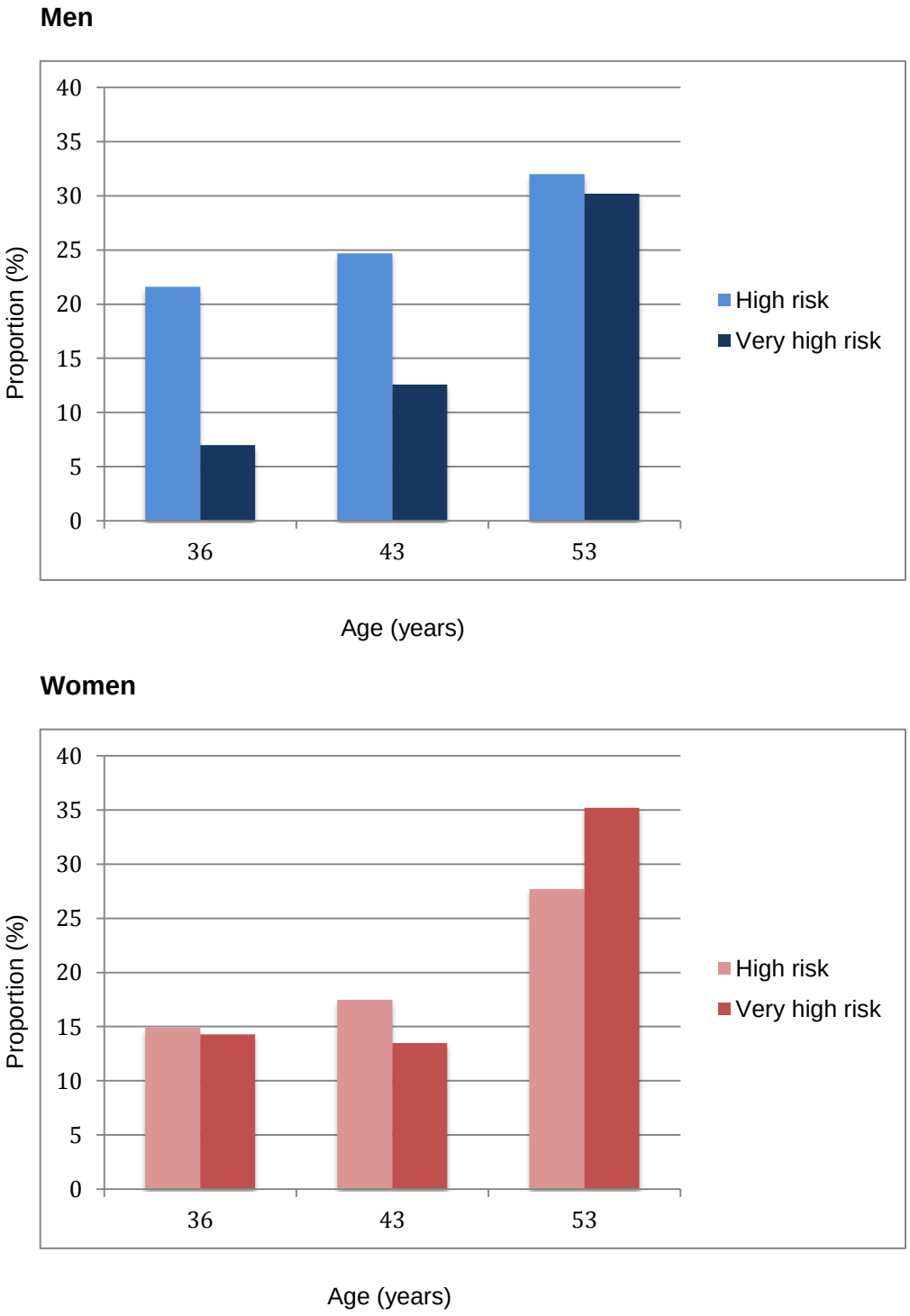


Figure 6. Percentage of people in the high risk and very high risk WC category* by age and gender

Note: analyses restricted to those with non-missing data for WC, type 2 diabetes and all covariates for each age. Men: at age 36 N=1068, at age 43 N=1092, at age 53 N=1075. Women: at age 36 N=1174, at age 43 N=1198, at age 53 N=1194.
* High risk category = Men: WC of 94-102 cm; women: WC of 80-88 cm. Very high risk category = Men: WC >102 cm; women: WC > 88 cm. Categories of WC were defined according to the National Institute for Health and Care Excellence (NICE) cut-offs for increased risk of type 2 diabetes (279).

Table 17. **Correlation between WC and BMI measures**

a) Males (n=947)

WC at 43	0.74				
WC at 53	0.69	0.77			
BMI at 36	0.70	0.70	0.65		
BMI at 43	0.70	0.83	0.72	0.84	
BMI at 53	0.65	0.72	0.86	0.75	0.83
	WC at 36	WC at 43	WC at 53	BMI at 36	BMI at 43

a) Females (n=1060)

WC at 43	0.60				
WC at 43	0.56	0.79			
BMI at 36	0.69	0.76	0.68		
BMI at 43	0.58	0.83	0.75	0.86	
BMI at 53	0.53	0.76	0.88	0.77	0.85
	WC at 36	WC at 43	WC at 53	BMI at 36	BMI at 43

Note: BMI = Body Mass Index. Analyses restricted to those with non-missing data for WC and BMI at age 36, 43 and 53, type 2 diabetes and all covariates

Table 18. **Associations between potential confounders and WC at age 36, 43 and 53**

	WC (cm) at 36 year		WC (cm) at 43 year		WC (cm) at 53 years	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Socioeconomic position						
I professional	218	85.9 (9.5)	223	87.9 (10.3)	207	94.6 (11.0)
II intermediate	1159	82.8 (11.5)	1147	84.2 (12.0)	1067	91.2 (12.7)
III skilled (Non-Manual)	757	78.9 (12.4)	723	80.5 (12.4)	664	88.1 (13.7)
III skilled (Manual)	602	88.2 (11.2)	581	89.9 (11.4)	518	96.0 (12.0)
IV partly skilled	207	83.5 (13.0)	382	84.5 (13.4)	357	91.5 (14.3)
V unskilled	144	82.6 (13.1)	145	85.7 (14.8)	123	91.5 (14.3)
P-value (trend)		*0.01*		*<0.01*		*0.15*
Education attained by age 26						
None attempted	1196	84.5 (12.7)	1128	86.6 (13.2)	1028	93.5 (13.6)
Intermediate	879	81.0 (12.1)	851	82.6 (12.2)	773	89.8 (13.3)
Highest	1061	83.0 (11.5)	1053	84.5 (12.0)	985	91.2 (12.7)
P-value (trend)		*<0.001*		*<0.001*		*<0.001*
BMI category age 36						
Normal (<25 kg/m^2)	2129	77.8 (9.4)				
Overweight (25 -29.9 kg/m^2)	929	90.7 (8.8)				
Obese (≥30 kg/m^2)	215	103.2 (11.4)				
P-value (trend)		<0.001				
BMI category age 43						
Normal (<25 kg/m^2)			1684	77.4 (8.8)		
Overweight (25 -29.9 kg/m^2)			1130	90.1 (9.0)		
Obese (≥30 kg/m^2)			395	101.4 (12.3)		
P-value (trend)				<0.001		
BMI category age 53						
Normal (<25 kg/m^2)					975	80.8 (8.7)
Overweight (25 -29.9 kg/m^2)					1254	92.1 (8.9)
Obese (≥30 kg/m^2)					714	105.7 (11.1)
P-value (trend)						<0.001
Smoking history*						
Never smoker	966	81.8 (12.1)	933	83.3 (12.5)	868	90.2 (13.3)
Ex smoker	1214	84.3 (12.1)	1316	85.6 (12.7)	1403	93.0 (13.4)
Current smoker	1119	83.2 (12.3)	967	85.0 (12.4)	690	90.7 (12.6)
P-value (ANOVA)		*<0.001*		*<0.001*		*<0.001*
Exercise at age 36						
Inactive	1210	84.1 (13.4)	1070	85.4 (13.2)	974	92.5 (14.1)
Less active	832	82.8 (11.9)	747	84.7 (12.8)	679	91.6 (13.0)
Most active	1250	82.6 (11.2)	1136	84.2 (12.0)	1021	90.9 (12.4)

P-value (trend)		<0.01		*0.03*		*<0.01*
Exercise at age 43						
Inactive			1673	85.7 (13.2)	1431	92.7 (13.7)
Less active			749	84.4 (12.1)	646	91.0 (12.5)
Most active			800	83.2 (11.5)	708	89.9 (12.2)
P-value (trend)				*<0.001*		*<0.001*
Exercise at age 53						
Inactive	1456					93.2 (13.8)
Less active	516					90.8 (12.2)
Most active	988					89.8 (12.7)
P-value (trend)						<0.001

Note: maximum available sample size used with each indicator; educational attainment was categorised as none (none attempted), intermediate (GCE 'O' level or Burnam C or lower) or highest (GCE A level or Burnam B or higher); activity at each age was coded as inactive (no participation), moderately active (participated one to four times) and most active (participated five or more times), in the previous month (36 years), per month (43 years) and in the previous 4 weeks (53 years);BMI = Body Mass Index; p value for trend using regression; * Smoking history up to age 36 using for WC at age 36, smoking history up to age 43 using for WC at age 43, smoking history up to age 53 using for WC at age 53.

4.3.3 Prospective associations between adult WC and type 2 diabetes

Prospective associations between categories of WC at ages 36, 43, 53 and type 2 diabetes diagnosed between 53 and 60-64 years are shown in Table 19 for men and Table 20 for women. At all ages, men within the high risk category (WC = 94-102 cm) had more than double the risk of type 2 diabetes compared with those within the normal WC range. Men in the very high risk category (WC> 102 cm) had a five-fold increased risk.

Among women the risk for type 2 diabetes increased with higher WC categories, especially for the highest category, and this trend was stronger at older ages. Women within the very high risk category (WC> 88 cm) had a five-fold increased risk at age 43 and 14 times higher risk at age 53 compared to those in the normal WC.

For both sexes, adjustment for SEP, education, smoking and physical activity (Model 2 and 3) made little difference to risk estimates. After further adjustment for BMI however, the associations were considerably weakened particularly for men, for whom the associations with WC were no longer significant except for the very high risk category at age 43 (Model 4). Among women adjustment for BMI did not eliminate the associations between WC and type 2 diabetes apart from age 36, although the associations for the highest category were greatly weakened (Model 4).

Tests for trend showed that the risk of type 2 diabetes increased linearly across categories of WC, although after adjustment for BMI associations were not linear among men. In men for each 5 cm of WC the odds of type 2 diabetes increased by 28%, 41% and 39% at age 36, 43 and 53 after adjustment for SEP, education, physical activity and smoking (Table 21, Model 3). The corresponding relative increase among women was 24%, 37%, 42% at age 36, 43 and 53.

Inclusion of an interaction term between WC and BMI categories in these models showed a significant interaction ($p<0.05$) at age 36 and 43 for men and a weak interaction ($p>0.05$) at age 53 for women, therefore analyses were stratified by BMI categories. The association between WC and type 2 diabetes was strong for men in the normal BMI category, particularly at age 43; there was also some evidence of an association between WC (at 36 years) and type 2 diabetes among overweight men, whereas among obese men, at all ages there was no evidence of an effect of WC on the odds of diabetes (Table 21). Similarly, obese women had smaller ORs for diabetes for each extra 5cm of WC compared with overweight and, particularly, normal weight women (Table 22). This differential effect increased with age and was higher at age 53 (normal BMI: OR=1.89 (95%CI: 1.26, 2.84); overweight: OR=1.40 (95%CI: 1.04, 1.88); obese: OR=1.29 (95%CI: 1.12, 1.49).

4.3.4 Lifecourse change in WC and type 2 diabetes

Figure 7 shows the mean WC between age 36 and 53 by sex and type 2 diabetes. As before, at all ages those with diabetes diagnosed between age 53 and 60-64 had a higher WC compared to those without diabetes, with the difference being larger among women (Figure 7).

Table 23 shows the association between lifecourse change in WC and type 2 diabetes. For every 5-cm gain in WC between age 36 and 53 the risk of type 2 diabetes increased by 34% among men and 44% among women. Adjustments for SEP, education, physical activity and lifetime smoking did not affect the associations noticeably (Model 2 and 3). After further adjustment for BMI change between age 36 and 53 associations among women were weakened but were not eliminated, while among men the associations were significantly reduced.

In models with categories of WC change (tertiles), the risk of diabetes for the highest tertile of change was considerably larger among women (OR: 6.28, 95%CI: 3.21, 12.27) then men (OR: 2.71, 95%CI: 1.62, 4.53) after adjustment for lifestyle and social covariates (Model 3). After adjustment for BMI change the associations were weakened, but the highest tertile of WC change remained significant for both men (OR: 1.89, 95%CI:1.01, 3.53) and women (OR: 2.73, 95%CI: 1.22, 6.11).

When associations were stratified by baseline BMI categories (Table 24) WC change was associated with later diabetes only for men and women with a BMI <30kg/m^2 (normal or overweight). The size of the association was larger for normal weight women whereas, normal weight and overweight men had similar risk estimates. In fully-adjusted models (Model 4) the associations remained significant only among women with a normal BMI.

4.3.5 Sensitive periods of WC change and type 2 diabetes

Figure 8 shows the mean WC velocity for the periods 36-43 and 43-53 years, by sex and type 2 diabetes. For both men and women at both age intervals those with diabetes had higher WC velocities compared to non-diabetics. The difference in WC velocity between diabetic and non-diabetic was larger among women especially between age 36 and 43. From figure 8 it can be seen that although WC velocity was larger at a later age, the difference between those who remained free of diabetes and those who developed it was slightly larger at 36-43 years (0.21 cm/y for men and 0.44.cm/y for women) than 43-53 years (0.13 cm/y for men and 0.36 cm/y for women).

For each period of the adult life course, conditional on previous WC, an increase in WC was associated with higher odds of type 2 diabetes in later life (Table 25). For both men and women the association between WC gain from 36-43 and type 2 diabetes was slightly larger than the association between 43-53 years however this was not statistically significant. Among men the odds of diabetes in fully-adjusted models (Model 3) were 1.62 (95%CI: 1.23, 2.14) per SD increase in WC velocity between 36-43 years and 1.48 (95%CI: 1.16, 1.88) for the period 43-53 years. The corresponding ORs in women were 1.77 (95%CI: 1.42, 2.21) and 1.66 (95%CI: 1.36, 2.09).

Table 19. **Associations at each age between high risk and very high risk WC categories* and type 2 diabetes between age 53 and 60-64 among men relative to normal WC**

	Model 1 Unadjusted		**Model 2** As Model 1 + SEP and education		**Model 3** As Model 2 + physical activity, smoking history,		**Model 4** As Model 3 + BMI	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
36 years (N=1068)								
High risk WC	1.63 (1.07, 2.60)	0.02	1.63 (1.04, 2.55)	0.03	1.59 (1.01, 2.50)	0.04	0.93 (0.56, 1.55)	0.80
Very high risk WC	3.40 (1.91, 6.06)	<0.001	3.33 (1.86, 5.98)	<0.001	3.20 (1.77, 5.70)	<0.001	0.88 (0.39, 1.99)	0.77
P for linear trend	<0.001		<0.001		<0.001		0.75	
43 years (N=1092)								
High risk WC	2.32 (1.48, 3.65)	<0.001	2.29 (1.45, 3.60)	<0.001	2.33 (1.47, 3.70)	<0.001	1.57 (0.92, 2.67)	0.09
Very high risk WC	5.65 (3.51, 9.08)	<0.001	5.57 (3.45, 9.01)	<0.001	5.81 (3.55, 9.49)	<0.001	2.58 (1.23, 5.43)	0.01
P for linear trend	<0.001		<0.001		<0.001		0.01	
53 years (N=1075)								
High risk WC	2.09 (1.18, 3.70)	0.01	2.05 (1.16, 3.65)	0.01	2.08 (1.16, 3.71)	0.01	1.28 (0.69, 2.36)	0.41
Very high risk WC	5.08 (3.01, 8.57)	<0.001	4.93 (2.91, 8.33)	<0.001	5.15 (3.09, 8.75)	<0.001	1.52 (0.74, 3.14)	0.25
P for linear trend	<0.001		<0.001		<0.001		0.25	

Note: analyses restricted to those with non-missing data for WC, type 2 diabetes and all covariates for each age. BMI=Body Mass Index; SEP=socioeconomic position; WC=waist circumference. * High risk category: WC of 94-102 cm; very high risk category = WC of >102 cm; categories of WC were defined according to the National Institute for Health and Care Excellence (NICE) cut-offs for increased risk of type 2 diabetes (279).

Table 20. Associations at each age between high risk and very high risk WC categories* and type 2 diabetes between age 53 and 60-64 among women relative to normal WC

	Model 1 Unadjusted		**Model 2** As Model 1 + SEP and education		**Model 3** As Model 2 + physical activity, smoking history,		**Model 4** As Model 3 + BMI	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
36 years (N=1174)								
High risk WC	2.27 (1.33, 3.87)	<0.01	2.24 (1.30, 3.85)	<0.01	2.24 (1.29, 3.88)	<0.01	1.62 (0.90, 2.90)	0.10
Very high risk WC	2.65 (1.57, 4.46)	<0.001	2.50 (1.47, 4.26)	<0.01	2.50 (1.46, 4.28)	<0.01	1.17 (0.58, 2.37)	0.64
P for trend	<0.001		<0.001		<0.001		0.50	
43 years (N=1198)								
High risk WC	3.84 (2.25, 6.55)	<0.001	3.73 (2.18, 6.38)	<0.001	3.66 (2.13, 6.31)	<0.001	2.83 (1.56, 5.13)	<0.01
Very high risk WC	6.17 (3.65, 10.42)	<0.001	5.84 (3.42, 9.96)	<0.001	5.77 (3.34, 9.96)	<0.001	3.16 (1.41, 7.05)	<0.01
P for trend	<0.001		<0.001		<0.001		<0.01	
53 years (N=1194)								
High risk WC	5.69 (2.30, 14.10)	<0.001	5.69 (2.29, 14.10)	<0.001	5.70 (2.29, 14.15)	<0.001	4.32 (1.75, 10.84)	<0.01
Very high risk WC	14.20 (6.15, 33.09)	<0.001	13.86 (5.92, 32.42)	<0.001	13.91 (5.92, 32.66)	<0.001	5.54 (2.10, 14.61)	<0.01
P for trend	<0.001		<0.001		<0.001		<0.01	

Note: Analyses restricted to those with non-missing data for WC, type 2 diabetes and all covariates for each age. BMI=Body Mass Index; SEP=socioeconomic position; WC=waist circumference. * High risk category: WC of 80-88 cm; very high risk category = WC of >88 cm; categories of WC were defined according to the National Institute for Health and Care Excellence (NICE) cut-offs for increased risk of type 2 diabetes (279).

Table 21. Associations at each age between WC and type 2 diabetes between age 53 and 60-64 among men by BMI categories

		Model 1		**Model 2**		**Model 3**		**Model 4**	
		Unadjusted		As Model 1 + SEP and education		As Model 2 + physical activity, smoking history,		As Model 3 + BMI	
	N	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
WC at Age 36 (5 cm)									
All men	1068	1.30 (1.17, 1.43)	<0.001	1.29 (1.17, 1.43)	<0.001	1.28 (1.16, 1.42)	<0.001	0.98 (0.82, 1.17)	0.85
By BMI category:									
BMI <25 kg/m^2	607	1.24 (0.98, 1.57)	0.06	1.23 (0.97, 1.56)	0.07	1.23 (0.97, 1.55)	0.06		
BMI ≥25 – 29.9 kg/m^2	411	1.24 (1.00, 1.54)	0.05	1.24 (1.00, 1.54)	0.04	1.24 (0.97, 1.52)	0.05		
BMI ≥30 kg/m^2	50	0.76 (0.52, 1.09)	0.14	0.75 (0.50, 1.11)	0.15	0.66 (0.40, 1.08)	0.10		
WC at Age 43 (5 cm)									
All men	1092	1.41 (1.28, 1.56)	<0.001	1.41 (1.28, 1.56)	<0.001	1.41 (1.28, 1.56)	<0.001	1.16 (0.96, 1.41)	0.10
By BMI category:									
BMI <25 kg/m^2	498	1.50 (1.12, 2.23)	<0.01	1.69 (1.21, 2.37)	<0.01	1.50 (1.12, 2.23)	<0.01		
BMI ≥25 – 29.9 kg/m^2	486	1.19 (0.96, 1.49)	0.10	1.20 (0.96, 1.49)	0.10	1.20 (0.96, 1.51)	0.10		
BMI ≥30 kg/m^2 *	108	0.98 (0.77, 1.25)	0.90	0.95 (0.74, 1.25)	0.72	0.96 (0.73, 1.24)	0.74		
WC at Age 53 (5 cm)									
All men	1075	1.37 (1.26, 1.50)	<0.001	1.37 (1.25, 1.49)	<0.001	1.39 (1.27, 1.52)	<0.001	1.01 (0.83, 1.22)	0.10
By BMI category:									
BMI <25 kg/m^2	170	1.70 (1.05, 2.73)	0.02	1.68 (1.04, 2.73)	0.03	1.52 (0.91, 2.53)	0.10		
BMI ≥25 – 29.9 kg/m^2	544	1.23 (0.97, 1.57)	0.08	1.22 (0.95, 1.56)	0.10	1.22 (0.96, 1.56)	0.10		
BMI ≥30 kg/m^2 *	227	1.06 (0.91, 1.25)	0.40	1.06 (0.91, 1.25)	0.41	1.04 (0.87, 1.23)	0.62		

Note: analyses restricted to those with non-missing data for WC, type 2 diabetes and all covariates for each age; BMI=Body Mass Index; SEP=socioeconomic position; WC=waist circumference. * p for interaction term between BMI category and WC <0.05

Table 22. Associations at each age between WC and type 2 diabetes between age 53 and 60-64 among women by BMI categories

		Model 1 Unadjusted		**Model 2** As Model 1 + SEP and education		**Model 3** As Model 2 + physical activity, smoking history,		**Model 4** As Model 3 + BMI	
	N	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
WC at Age 36 (5 cm)									
All women	1174	1.26 (1.16, 1.36)	<0.001	1.24 (1.14, 1.35)	<0.001	1.24 (1.14, 1.35)	<0.001	1.12 (0.99, 1.27)	0.06
By BMI category:									
BMI <25 kg/m^2	888	1.29 (1.13, 1.48)	<0.001	1.28 (1.11, 1.47)	<0.001	1.27 (1.10, 1.46)	<0.01		
BMI ≥25 – 29.9 kg/m^2	217	1.12 (0.89, 1.43)	0.31	1.15 (0.89, 1.47)	0.26	1.18 (0.91, 1.52)	0.19		
BMI ≥30 kg/m^2	60	1.18 (0.92, 1.50)	0.17	1.20 (0.92, 1.56)	0.16	1.08 (0.81, 1.44)	0.56		
WC at Age 43 (5 cm)									
All women	1092	1.39 (1.27, 1.51)	<0.001	1.37 (1.25, 1.50)	<0.001	1.37 (1.25, 1.50)	<0.001	1.32 (1.12, 1.56)	<0.01
By BMI category:									
BMI <25 kg/m^2	740	1.55 (1.17, 2.06)	<0.01	1.52 (1.14, 2.02)	<0.01	1.54 (1.15, 2.05)	<0.01		
BMI ≥25 – 29.9 kg/m^2	306	1.46 (1.13 1.87)	<0.01	1.44 (1.11, 1.86)	<0.01	1.41 (1.09 1.84)	<0.01		
BMI ≥30 kg/m^2	152	1.17 (0.98, 1.41)	0.08	1.16 (0.96, 1.40)	0.10	1.16 (0.96, 1.41)	0.10		
WC at Age 53 (5 cm)									
All women	1194	1.40 (1.30, 1.52)	<0.001	1.39 (1.29, 1.51)	<0.001	1.42 (1.30, 1.54)	<0.001	1.30 (1.09, 1.55)	<0.01
By BMI category:									
BMI <25 kg/m^2	450	1.84 (1.26, 2.68)	<0.01	1.85 (1.24, 2.76)	<0.01	1.89 (1.26, 2.84)	<0.01		
BMI ≥25 – 29.9 kg/m^2	442	1.41 (1.05, 1.88)	0.01	1.38 (1.03, 1.83)	0.02	1.40 (1.04, 1.88)	0.02		
BMI ≥30 kg/m^2	302	1.28 (1.11, 1.46)	<0.001	1.27 (1.11, 1.46)	<0.001	1.29 (1.12, 1.49)	<0.001		

Note: Analyses restricted to those with non-missing data for WC, type 2 diabetes and all covariates for each age; BMI=Body Mass Index; SEP=socioeconomic position; WC=waist circumference.

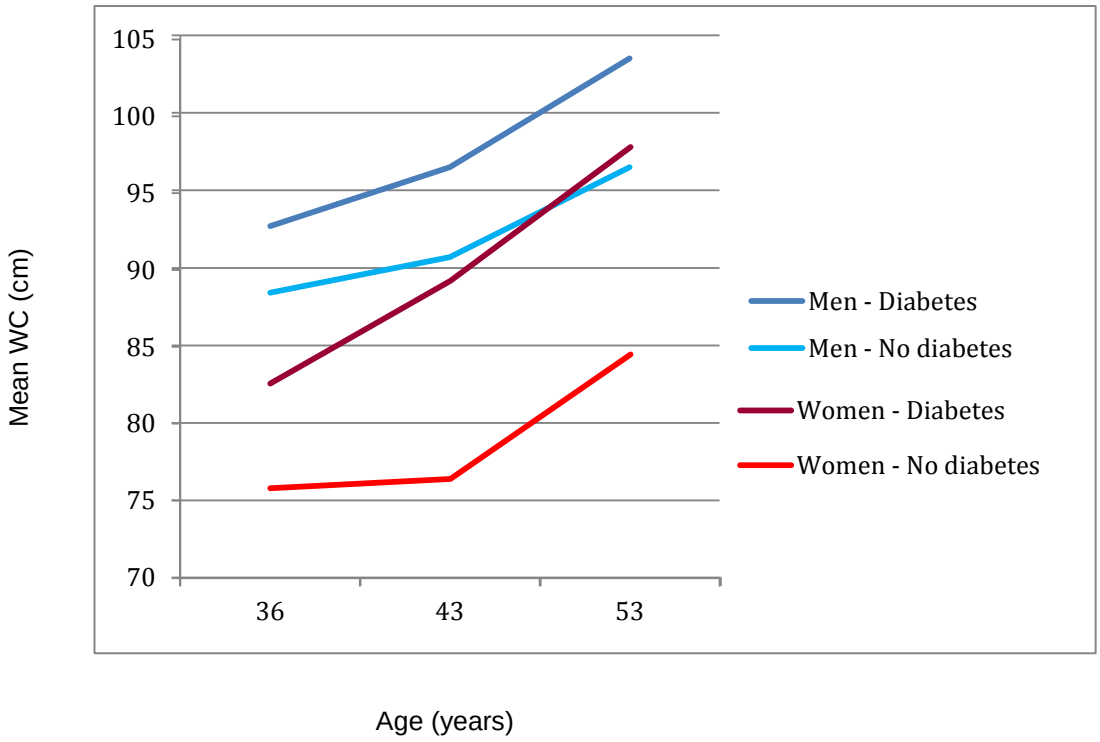


Figure 7. Mean WC at 36, 43 and 53 years by sex and type 2 diabetes diagnosis at age 53 to 60-64

Note: Sample restricted to those with non-missing values for WC, type 2 diabetes and all covariates (N=2007

Table 23. Associations between lifecourse change in WC and type 2 diabetes between age 53 and 60-64

		Model 1		**Model 2**		**Model 3**		**Model 4**	
		Unadjusted		As Model 1 + SEP and education		As Model 2 + physical activity, smoking history,		As Model 3 + BMI change*	
	N	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Men									
WC change age 36-53 (5 cm)	947	1.34 (1.17, 1.53)	<0.001	1.33 (1.16, 1.52)	<0.001	1.36 (1.18, 1.57)	<0.001	1.03 (0.82, 1.30)	0.74
Tertiles of WC change:									
< 5.3 cm	317	1		1		1		1	
5.4 – 11 cm	319	0.79 (0.43, 1.43)	0.44	0.77 (0.42, 1.41)	0.41	0.79 (0.43, 1.44)	0.45	0.68 (0.36, 1.26)	0.22
> 11 cm	311	2.64 (1.60, 4.36)	<0.001	2.55 (1.54, 4.22)	<0.001	2.71 (1.62, 4.53)	<0.001	1.89 (1.01, 3.53)	0.04
P for trend		<0.01		<0.01		<0.01		0.28	
Women									
WC change age 36-53 (5 cm)	1060	1.44 (1.30, 1.61)	<0.001	1.44 (1.29, 1.60)	<0.001	1.44 (1.29, 1.61)	<0.001	1.28 (1.04, 1.57)	0.01
Tertiles of WC change:									
< 5.4 cm	354	1		1		1		1	
5.5 – 14 cm	355	2.87 (1.38, 5.94)	<0.01	2.79 (1.34, 5.79)	<0.01	2.90 (1.39, 6.05)	<0.01	2.01 (0.95, 4.28)	0.06
> 14 cm	351	6.47 (3.34, 12.53)	<0.001	6.18 (3.18, 11.98)	<0.001	6.28 (3.21, 12.27)	<0.001	2.73 (1.22, 6.11)	0.01
P for trend		<0.001		<0.001		<0.001		0.57	

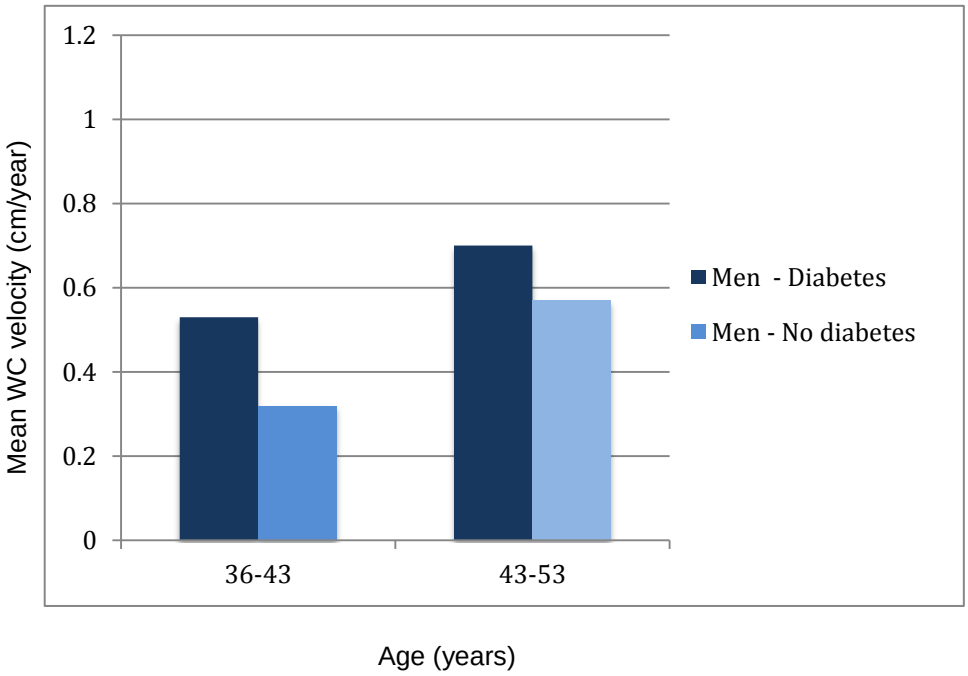
Note: analyses restricted to those with non-missing data for WC, type 2 diabetes and all covariates; all models adjusted for WC at age 36. BMI=Body Mass Index; SEP=socioeconomic position; WC=waist circumference. * BMI change between age 36 and 53

Table 24. Associations between lifecourse change in WC and type 2 diabetes between age 53 and 60-64 by categories of baseline (age 36) BMI

		Model 1		**Model 2**		**Model 3**		**Model 4**	
		Unadjusted		As Model 1 + SEP and education		As Model 2 + physical activity, smoking history,		As Model 3 + BMI change*	
	N	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Change in WC from 36 to 53 (5 cm) by BMI categories									
Men									
BMI <25 kg/m^2	545	1.39 (1.09, 1.78)	<0.01	1.38 (1.08, 1.76)	0.01	1.37 (1.07, 1.75)	0.01	1.18 (0.87, 1.60)	0.27
BMI ≥25 – 29.9 kg/m^2	358	1.37 (1.14, 1.66)	<0.01	1.37 (1.13, 1.65)	<0.01	1.43 (1.17, 1.74)	<0.001	1.06 (0.76, 1.49)	0.79
BMI ≥30 kg/m^2	44	0.95 (0.61, 1.49)	0.83	0.78 (0.46, 1.34)	0.45	0.79 (0.43, 1.45)	0.45	0.93 (0.42, 2.06)	0.87
Women									
BMI <25 kg/m^2	801	1.64 (1.40, 1.93)	<0.001	1.64 (1.39, 1.92)	<0.001	1.64 (1.39, 1.94)	<0.001	1.44 (1.14, 1.82)	0.01
BMI ≥25 – 29.9 kg/m^2	199	1.49 (1.20, 1.85)	<0.01	1.47 (1.17, 1.83)	<0.01	1.48 (1.17, 1.87)	<0.01	1.32 (0.88, 1.99)	0.17
BMI ≥30 kg/m^2	60	1.29 (0.95, 1.75)	0.09	1.25 (0.94, 1.66)	0.11	1.36 (0.96, 1.93)	0.07	1.29 (0.68, 2.44)	0.43

Note: analyses restricted to those with non-missing data for WC, type 2 diabetes and all covariates; all models adjusted for WC at age 36. BMI=Body Mass Index; SEP=socioeconomic position. * BMI change between age 36 and 53

Men (n=947)



Women (n=1060)

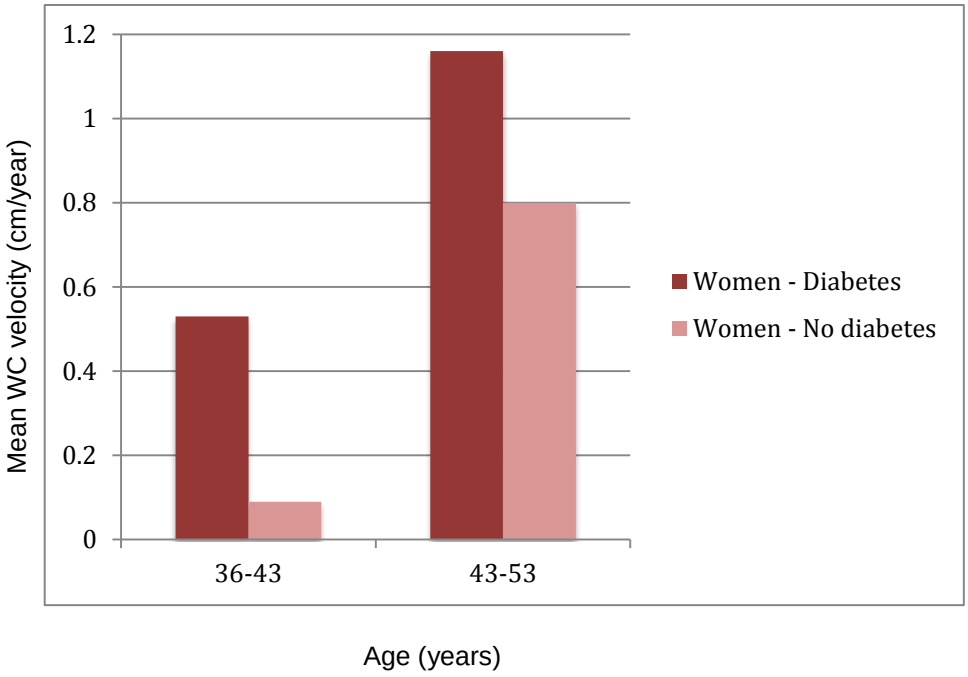


Figure 8. Mean WC velocity (cm per year) at different periods by sex and type 2 diabetes diagnosis between 53 and 60-64 years.

Note: Sample restricted to those with non-missing values for WC, type 2 diabetes and all covariates

Table 25. **Associations between conditional WC velocity at different age intervals and type 2 diabetes between age 53 and 60-64**

	Model 1 Unadjusted		**Model 2** Adjusted for SEP and education		**Model 3** As Model 2 + adjusted for physical activity and smoking history	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Period of change						
Men, n=947						
36-43 years	1.60 (1.22, 2.11)	<0.01	1.59 (1.21, 2.10)	<0.01	1.62 (1.23, 2.14)	<0.01
43-53 years	1.44 (1.14, 1.81)	<0.01	1.42 (1.12, 1.79)	<0.01	1.48 (1.16, 1.88)	<0.01
P for difference between periods*	0.55		0.55		0.61	
Women, n= 1060						
36-43 years	1.82 (1.46, 2.25)	<0.001	1.77 (1.42, 2.20)	<0.001	1.77 (1.42, 2.21)	<0.001
43-53 years	1.68 (1.35, 2.08)	<0.001	1.69 (1.37, 2.09)	<0.001	1.66 (1.36, 2.09)	<0.001
P for difference between periods*	0.69		0.77		0.75	

Note: analyses restricted to those with non-missing data for WC at age 36, 43 and 53, type 2 diabetes and all covariates. SEP=socioeconomic position, WC=waist circumference; OR of type 2 diabetes for a 1 SD increase in WC in each interval conditional on previous WC; P for difference between periods estimated with Wald's test

4.4 Discussion

4.4.1 Main findings

The main findings of this chapter are that for both genders, at any time of the adult life course, having a large WC is associated with a greater risk of type 2 diabetes being diagnosed between age 53 to 60-64 years. The relative risk is especially high among older women with a WC greater than 88 cm (high risk WC category). A high WC is a risk factor for type 2 diabetes in normal weight and overweight, but not obese, men and women.

Long-term WC change, conditional on initial WC, was associated with increased risk of diabetes; the associations were independent of concomitant BMI change only for men and women in the highest tertile of WC change. Also, changes in WC are particularly important for people who have an initially normal BMI. There was no particular period over the adult life course during which WC gains were more detrimental for later diabetes risk.

1st objective: To analyse the association between WC measured at different time points in the adult life (age 36, 43 and 53 years) and type 2 diabetes

It was hypothesised that WC would be independently associated with type 2 diabetes and that this association would be stronger for women. In support of the first hypothesis, at all ages (36, 43 and 53 years) people with a larger WC had higher risks of type 2 diabetes compared with those with a normal WC. The effect of abdominal obesity was only marginally affected by confounding factors. In agreement with other studies (65-77) these findings suggest that having a very large (clinically defined) WC, at any age during the adult life course is strongly associated with later type 2 diabetes. The size of the association was similar between men and women at age 36 but became increasingly larger for women at age 43 and especially at age 53. Adjustment for BMI significantly weakened most of the associations for men while associations remained significant among women, for whom the risk was still strong at the highest category of WC. These results, taken together with those in chapter 3, seem to confirm that the effect of WC is relatively more important for women than for men, as previous studies have suggested (75-78), especially once the effect of overall obesity is removed. However, in two large studies such as the EPIC InterAct (76) and the Spanish Epic (75), WC remained significantly associated with diabetes among men after adjustment for BMI, a discrepancy that could be attributed to differences in power.

2nd objective: To assess whether the effect of WC on type 2 diabetes risk is different according to different levels of BMI

It was hypothesised that the relative risk of type 2 diabetes for a raised WC would differ according to BMI categories. In agreement with the second hypothesis the results showed that in both men and women the association between abdominal obesity and diabetes was relatively more important among people with a lower BMI, particularly those within the normal BMI category. On the contrary for obese people, except obese women at age 53, there was no

relative increase in diabetes risk. The difference among BMI categories was stronger at age 53, particularly for women, although the overlapping confidence intervals suggest a non-significant difference. These results are in agreement with previous studies (75, 276, 277) that found an interaction between WC and BMI, so that the association between WC and diabetes was strongest among individuals with a normal BMI. It has been suggested that in people with a lower BMI, WC could be a better indicator of visceral fat, since these individuals have less total subcutaneous fat compared with those with a higher BMI. Therefore, results suggest that WC is a good discriminator of type 2 diabetes risk in normal BMI individuals because it is a direct measure of visceral fat. Whereas, among obese individuals WC is not an independent risk factor for diabetes because this groups is already at increased risk of diabetes due to the metabolic dysfunction brought about by their large total amount of adipose tissue, which seems to override the association between WC and diabetes. Indeed in this cohort the correlation between WC and BMI was higher among obese people than it was among those with a normal weight, suggesting that the measurement of WC would not add any additional risk information when total body fatness is already very high (Appendix 7). For example, at age 53 the correlation between WC and BMI was 0.78 for obese men and 0.79 for obese women, while the corresponding correlations among individuals with a BMI<25 kg/m^2 were 0.56 for men and 0.53 for women.

3rd objective: To investigate whether WC changes during the adult life-course are associated with later risk of type 2 diabetes independently of initial WC and of concurrent BMI changes

It was hypothesised that increases in WC over the lifecourse would be associated with type 2 diabetes risk independently of BMI changes and that this association would be stronger for women. As hypothesised, long-term WC changes from age 36 to 53 years were associated with type 2 diabetes at age 53 to 60-64 for both genders. The size of the associations was stronger and the trend of increasing risk with larger WC measures was more robust among women. This is in line with analyses of WC and diabetes at one point in time and in accordance with the few studies that analysed WC change over varying lengths of time (79, 113, 117, 119).

Importantly, the associations among the highest tertile of WC change (>11 cm for men and >14 cm for women) were independent of concomitant BMI change. Interestingly even before controlling for BMI change, moderate WC changes (5.4-11 cm for men and 5.5-14 cm for women) were not significantly related to diabetes among men but were strongly related to risk among women. This result is similar to the findings from the Health Professional Follow-up Study (113), which found that among men only very large WC gains (≥14.6 cm) were related to diabetes risk both before and after controlling for weight change. Only one study (119) reported WC change separately for men and women and found that short-term (5 years) WC changes, independent of BMI changes, were not related to diabetes in men and only moderately related to risk among women. However, that study only analysed WC change as a continuous variable, and as this thesis has shown, this would miss important information about a group of people with large WC gains, who are at particular high risk of diabetes. Furthermore 5 years might not

be a long-enough time to assess life-course WC gains, which are likely to accumulate over a long period. This thesis adds to previous evidence the important finding that for women long-term WC change is a key risk factor for metabolic disorders even at moderate levels of change and that large WC gains are particularly detrimental. The fact that the effect of large WC gains on diabetes was independent of BMI change points to the need for monitoring WC regularly to prevent large WC gains in the long-term, even in the absence of weight gain, particularly among women.

4th objective: To assess whether the effect of lifecourse WC change on type 2 diabetes risk is different according to levels of initial BMI

It was hypothesised that associations between WC increases and diabetes would be stronger for people with an initial lower BMI. In agreement with this hypothesis, the association of WC changes between age 36-53 with type 2 diabetes was stronger for individuals who initially (age 36) had a lower BMI independently of initial WC. Only one previous study (79) presented associations between WC and diabetes by BMI level (BMI < or $\geq$25 kg/m^2) and found similarly that the risk of progression to diabetes was higher among those with an initially lower BMI. However, that study did not present results separately for men and women and only included individuals with IFG. Thus this thesis expands on previous evidence by including analyses stratified by sex and BMI categories in the same model. Among obese men and women, waist change did not make a significant difference to the risk of future diabetes. On the contrary, the risk was particularly increased for women with a BMI<25 even after adjustment for BMI change, while for men the risk estimates were of similar size for overweight and normal weight individuals, although these were not independent of BMI change. These findings are in line with those in prospective analyses and suggest that, given a certain WC, change in abdominal fatness is a better indicator of metabolic risk for those who start with a lower total amount of body fatness. Crucially, among women with an initially normal BMI a WC change in the absence of BMI change would still predict diabetes risk suggesting a benefit of measuring abdominal changes among this group.

5th objective: To investigate whether WC gain at different periods of the adult life (36 to 43 and 43 to 53 years) has a different impact on later risk of type 2 diabetes

This chapter also explored sensitive periods of WC gain, which to the author's knowledge, has not been investigated before. At any period of the adult life WC changes were significantly correlated with later diabetes risk for both men and women. There was some suggestion that WC changes at an earlier stage of the adult life (36-43 years) were more detrimental than changes at a later stage (43-53 years) however these differences were not significant. Interestingly, results of analyses of sensitive periods of BMI velocity in chapter 3 showed that BMI gains between 43-53 years were more detrimental for future diabetes risk than BMI changes between 36-43 years. This difference suggests that BMI and WC patterns of change are not parallel.

As it can be observed in figure 8, mean WC velocity difference between those who remained free of diabetes and those who developed diabetes appears to be converging with age. However, the graph also shows that those who developed diabetes had faster WC gains from an early adult age; it is probable that an earlier increase will lead to a larger WC in later life, as is clear from figure 6. Interestingly, while for men WC velocity seems to be fairly constant, women had substantially faster WC gain between 43-53 years irrespectively of their diabetes diagnosis. This fast increase probably coincides with the hormonal changes of the peri-menopausal stage, which facilitates abdominal fat accumulation.

4.4.2 Strengths

One of the main strengths of this chapter is that unlike most studies on abdominal obesity, it used repeated measures of WC at three ages during the adult life course. Only few studies have analysed WC change over time and all used only 2 time points. The availability of repeated WC measures allowed the exploration of sensitive periods of WC gain in relation to type 2 diabetes, which have not been investigated before.

Another strength is that, unlike some studies, which used self-reported measures, anthropometric values were measured by trained nurses using a standardized protocol at 36, 43 and 53. Poor agreement between self-reported and technician-measured WC has been reported, with self-reported measurements underestimating WC in both men and women (283, 284); furthermore underestimation increases with higher BMI and WC (283).

Lifecourse analyses of WC in relation to type 2 diabetes are limited in the literature; only a few of these studies investigated WC changes according to BMI level and assessed men and women separately. The findings from this chapter add to the previous literature by investigating long-term analyses of WC change by sex and initial BMI category in the same model, while also including adjustment for BMI change.

4.4.3 Limitations

As in the previous chapter, complete case analyses were conducted with only study participants having data for all WC measures and type 2 diabetes status as well as for all covariates included in the analyses. However, as already demonstrated in the previous chapter, Appendix 3 shows that those with non-missing data for the outcome and all covariates were very similar to those in the maximum sample available for each covariate and type 2 diabetes. At all ages, there was no difference in mean WC between the maximum sample available and those with missing values. However, as shown in Appendix 3 and 4, those with missing values for anthropometric measurements (WC measures were taken at the same time as height and weight, therefore missing values for BMI and WC are essentially the same number) were less educated and more likely to be men, to be in a lower SEP, and to be smokers.

A possible limitation of this chapter is the sample size used in stratified analyses, which might have resulted in lack of power. This was mainly an issue with analyses stratified by BMI

categories because of the few obese people at age 36. However, results were in agreement to previous large prospective studies, suggesting that if lack of power was an issue, it was probably limited.

4.4.4 Conclusions

This chapter has shown that at any age having a large WC is positively associated with later type 2 diabetes. A large WC is particularly detrimental for women and the relative risk is higher for those with a normal BMI.

Long-term, as well short-term WC change is associated with increased diabetes risk but among men only large WC gains are independent of concurrent BMI changes. Women in the normal BMI category have the greatest relative risk of diabetes with increasing WC changes.

5 Chapter 5. Dietary fibre, dietary GI, dietary fat, SFA and type 2 diabetes

5.1 Introduction

Although age and obesity are considered the most important risk factors for type 2 diabetes, an increasing amount of evidence points to the role of diet as a key player in metabolic abnormalities, not only as a major contributor to body weight but also as a direct risk factor. Among the various dietary factors investigated, the evidence is strong for dietary fibre, the GI of foods, and dietary fats, particularly SFA.

5.1.1 Dietary fibre

Dietary fibre, for which wholegrain cereals, legumes, fruit and vegetables are rich sources, have been extensively studied in recent years; evidence supports their beneficial role in reducing post-prandial glycaemic response and improving insulin resistance (152, 156, 165, 166). A large number of prospective studies report a protective role for total dietary fibre against type 2 diabetes (131, 137, 142, 145, 147, 162). The latest meta-analysis (285) including 12 prospective studies up to 2013 reported a RR of 0.81 (95%CI: 0.73-0.90) for high versus low intake of fibre. This meta-analysis also included a dose-response analysis based on 5 studies showing a nonlinear association between total dietary fibre intake and type 2 diabetes; there was a threshold effect for fibre with the risk for the disease significantly decreased only when total fibre intake reached at least 25g/day (285). A number of large prospective studies that analysed the source of fibre in the diet showed that the strongest risk reduction for type 2 diabetes is obtained by consumption of cereal fibre rather than fruit or vegetable fibre. A recent systematic review (286) including 11 reports from 9 mostly large prospective cohort studies showed a risk reduction of 18-40% when high intake of cereal fibre was compared to the lowest intake. Nearly all studies reported a linear trend of reduced risk with increasing cereal fibre intake. A meta-analysis (285) reported a pooled RR for type 2 diabetes for high versus low cereal fibre of 0.77 (95%CI: 0.69-0.85). This risk reduction was significantly greater than that associated with fruit fibre (0.94, 95%CI: 0.88-0.99) and vegetable fibre (0.95, 95%CI: 0.84-1.07). As opposed to total dietary fibre, a linear relationship between cereal fibre and diabetes was found; the risk decreased by 6% for each 2g/day increase in cereal fibre (285). Although these meta-analyses are in agreement regarding the apparent protective role of fibre, particularly from cereal sources, reviews cannot eliminate the bias inherent in each study. For example, although most of the studies included were large and adjusted for major confounders, not all adjusted for either education or social class, which are known to be associated with diabetes incidence.

5.1.2 Glycemic Index

A growing body of evidence indicates that diets with a high GI are associated with increasing risk of type 2 diabetes (131, 137-142, 144, 146). However, as outlined in chapter 1, there are some discrepancies in results, with a few studies not showing significant associations (145-147) Explanations for these divergent results include the use of different dietary assessment tools, some of which were not designed to assess GI, differences in the populations studied and the varying range of GI values (143, 287). Discrepancies in the assignment of GI values can also impact on the ranking of participants (287). A 2011 meta-analysis, which included 13 prospective studies reported a 16% increased risk of diabetes for the highest dietary GI category compared with the lowest (140). Most major confounders were accounted for in the studies, however there was some unexplained heterogeneity among studies included. A more recent meta-analysis that included additional large cohorts (288-290) (291), also assessed the dose-response relationship between dietary GI and type 2 diabetes (291). Based on 15 included studies, the authors reported an adjusted RR for a linear dose-response of 1.08 (95% CI: 1.02, 1.15) per 5 GI units (291). There was some heterogeneity between studies, some of which was explained by length of follow-up and adjustment for covariates, especially family history of diabetes.

It has been reported that the detrimental effect of dietary GI might be more pronounced among overweight and obese people, who are often more insulin resistant than normal weight individuals (292). This has been confirmed in a few prospective studies (139, 142, 144) but not in others (140, 141). An interaction between GI and dietary fibre has also been observed in cohort studies with those individuals consuming a diet with the highest GI and the lowest fibre density having the highest risk of diabetes (131, 137, 145).

5.1.3 Total and saturated fats

Epidemiological evidence from prospective cohort studies support the view that both total dietary fats and SFA may contribute to type 2 diabetes development (165-170). Furthermore, intervention trials to prevent type 2 diabetes conducted among at-risk individuals have demonstrated that a low-fat diet was an important determinant of reduced type 2 diabetes incidence (59, 121, 122, 178). For example, in the Finnish Diabetes Prevention Study those with the highest total fat intake had a two-fold increased risk of diabetes compared with participants with the lowest intake, even after adjustment for weight change (122). However, some studies that did not find an association between dietary fats and type 2 diabetes (51, 137). One reason for these discrepancies might be measurement error; fat intake is especially prone to underreporting given the negative image of high-fat diets portrayed by media and nutritional guidelines in the last decades (293).

Despite the growing number of studies investigating the association between dietary factors and type 2 diabetes, only a few British studies have analysed GI, which has been primarily investigated in United States and Australian cohorts.

5.1.4 Mechanisms of action: direct and indirect pathways

There are different plausible physiological mechanisms through which dietary fibre, GI and dietary fats can affect type 2 diabetes risk either independently or through the mediating effects of BMI and WC, most of which have explained in detail in chapter 1.

High GI foods induce postprandial hyperglycaemia, which may have cumulative glucotoxic effects on pancreatic β-cells, thus affecting insulin secretion (132). Postprandial hyperglycaemia also leads to a quicker fall in blood glucose levels, which in turn triggers a counter-regulatory hormonal response with consequent raised circulating FFA levels (132, 133); these have been linked to insulin resistance and β-cells dysfunction.

Dietary fibre has a lowering effect on the postprandial glycaemic response, thus leading to improved insulin sensitivity (165); dietary fibre, especially fibre that undergoes extensive fermentation in the gut, have strong anti-inflammatory properties (157-159, 286), helping to counteract the pro-inflammatory action of environmental stressors, such as obesity and over nutrition (15).

Evidence shows that increased fat intake can promote insulin resistance and inflammatory responses (182, 183) while SFA can disrupt insulin signal pathways and promote postprandial hyperinsulinaemia (189, 191). SFA in particular can disrupt β-cells functionality and worsen insulin resistance (187-189).

Although the above-mentioned pathways are mostly independent of body weight, one of the key mechanisms by which these nutritional factors could be linked to diabetes is their involvement in energy regulation, caloric intake and abdominal fat storage. For example, the GI of a meal can affect food intake at the subsequent meal by modulating satiety signals; thus a low-GI diet can indirectly promote weight loss or maintenance (134). Dietary fibre has a similar satiety regulating action by affecting intestinal hormones and by directly stimulating the digestive tract (156); the bulk action and low energy-density of dietary fibre also promote satiation at meals (154). Dietary fats, on the other hand, have high energy density and a low satiating effect promoting overconsumption (179). Furthermore, there is some evidence that a high GI diet might promote preferential abdominal fat storage (135, 136) while a diet high in dietary fibre might reduce this (294-297). It has been suggested that the effects of GI and fibre on WC might be due to the higher susceptibility of visceral fat to the detrimental effects of strong insulin responses (135).

Therefore, BMI and WC are important potential mediators in the association between GI, dietary fiber and dietary fats and type 2 diabetes.

5.1.5 Previous findings from the MRC NSHD

Prynne et al (298) previously investigated changes in nutrient intake over 17 years using data from age 36, 43 and 53 years. The percentage of energy from fat fell while that from carbohydrates increased by age 53. They reported that the fall in fat intake might be a

consequence of the shift in consumption from whole milk to semi-skimmed or skimmed milk, and from butter to vegetable spreads. The type of meat also changed with a shift from red meat to poultry. The consumption of fruit and vegetables rose while that of potatoes and bread decreased, substituted by other types of carbohydrates, such as pasta, rice and pizza.

Prynne et al (299) investigated nutrient intake at age 36, 43 and 53 in relation to HbA1c at age 53. They found that lower intakes of iron, folate and fibre at age 36 and lower consumption of protein and carbohydrates and a higher energy from fat at age 43 were significantly associated with higher HbA1c at age 53. At age 53, none of the nutrients investigated was cross-sectionally associated with high HbA1c.

This chapter will build on the earlier analyses conducted in the NSHD by investigating associations between dietary fibre, GI (not previously derived in the NSHD) and dietary fats (both total and SFA) in adult life in relation to type 2 diabetes diagnosed between age 53 and age 60-64.

5.1.6 Research question

The main research question of this chapter is how dietary fibre, GI and dietary fats intake throughout adult life affect type 2 diabetes risk in later life.

5.1.7 Objectives

1. To analyse the association between dietary fibre, GI and dietary fats intake at age 36, 43 and 53 years and type 2 diabetes diagnosed between age 53 and 64 years
2. To assess whether the association between fibre, GI and fat is mediated by BMI and WC
3. To investigate whether associations between dietary factors and type 2 diabetes are stringer among those with higher BMI or WC

5.1.8 Hypotheses

1. Low fibre intake, high GI and high fat intake are prospectively and positively associated with increased risk of type 2 diabetes
2. The association between these dietary factors and type 2 diabetes will be mediated in part by BMI and WC, however direct associations between the above dietary factors and type 2 diabetes will remain
3. A positive association between dietary GI and type 2 diabetes will be stronger among overweight and obese people than those with a normal BMI

5.2 Methods

5.2.1 Explanatory variables

The main explanatory variables used in this chapter are dietary fibre density (g/1000kcal), GI (units), total dietary fat density (g/1000kcal) and SFA density (g/1000kcal) at age 36, 43 and 53. The nutrient density method was adopted to account for confounding by total energy intake. Dietary fibre density was calculated as total daily g fibre (non starch polysaccharide) divided by total daily energy intake (kcal) multiplied by 1000. Fat density and SFA density (g/1000kcal) were calculated as total daily g fat or SFA divided by total daily energy intake (kcal) multiplied by 1000. This method was chosen because it can be calculated directly and it has been used in national dietary guidelines (300). Dietary intake was assessed using 5-day food diaries, details of which have been described in chapter 2.

5.2.2 Assignment of GI values

During the second year of this PhD the author, in collaboration with two members of the MRC HNR Emily Fitt and Nida Ziauddeen, undertook a project to assign GI values to the DINO food codes, as GI values were previously not available in the NSHD data base. Glycemic index values were assigned to each food using the methodology described in detail by Aston et al (301), which was developed to calculate the GI of diets reported in food diaries in the pan-European Diogenes intervention study (302). Briefly, all food codes with total carbohydrate >0.1g per 100g were assigned a GI value, based on five levels of data confidence relating to source of the data used, with levels 1 being the highest. The five decreasing levels of confidence were: 1) Measured values; 2) Published values; 3) Equivalent values; 4) Estimated values; 5) Nominal values. Details of each level of confidence are given in Table 26.

Although a few researchers have expressed some concerns regarding the use of GI in mixed meals (303, 304), many studies have demonstrated that GI of mixed diets can be sufficiently reliably calculated as the weighted mean of the GI of each food item within the meal (305-308). Thus, the average GI of the daily diet was calculated by assigning a GL value for each food item, then summing the GL values for the day and dividing this by the total daily carbohydrates. This method was initially proposed by Wolever et al (307) and was subsequently endorsed by the Food and Agriculture Organization (309).

5.2.2.1 Missing data for dietary intake

In Appendix 8 individuals who completed diet diaries were compared with those who did not provide dietary information at each age; at all ages completers were more likely to be female and to be more educated and less likely to be in manual employment and to be smokers. At age 36 and 53 completers were also less likely to be obese, have a raised WC and, at age 53, to be inactive.

Table 26. **Levels of confidence* used for the assignment of GI values in the NSHD dataset**

Levels 1: Measured values	Where the GI of a specific food had been measured at one of the research centres taking part in the Diogenes study or by the product manufacturer following the published standardized protocol (310)
Levels 2: Published values	When the GI of a specific food was not measured directly but a published value (311-313), of the same item existed
Levels 3: Equivalent values	When there was no exact published value match but the value for a similar food had been published (311-313)
Levels 4: Estimated values	When no published value existed of a similar item an estimate was made to one of three values representing low (45), medium (63) and high GI (85) based on the mid-point of each category (314)
Levels 5: Nominal values	Assigned as 70, when no similar value existed and there was not enough information to assign an estimated value; this methodology had previously been used with the purpose of avoiding biasing the total dietary GI towards the null when zero is assigned to missing values (315)

*Adapted from Aston et al (301)

5.2.3 Outcome variable

The outcome used in this chapter is the main outcome of this thesis, type 2 diabetes diagnosed between age 53 and 60-64 years. This is described in more detail in Chapter 2.

5.2.4 Potential confounding variables

As outlined in chapter 1 and 2, SEP, both as occupational class and as educational attainment, is an acknowledged risk factor for type 2 diabetes. It is well established that diet quality follows a socioeconomic gradient with healthier diets being associated with higher diet quality (316). People in higher SEP groups tend to consume more whole grains, fresh vegetables and fruit, fish and low-fat dairy products, while those in lower SEP groups are more likely to consume refined grains, potatoes, fried foods, fatty meats and added fats (317-320). These associations might be mediated by diet cost, social network, knowledge and attitude towards food (321-323).

Physical inactivity and smoking were considered potential confounders as these may be related to both diet and type 2 diabetes risk. People who consume unhealthy diets are also more likely to be inactive and to smoke, since unhealthy lifestyle choices tend to correlate with each other (41, 44). On the other hand smoking cessation is also associated with increased energy intake (271).

BMI and WC were considered mediators since one of the mechanisms though which fibre, GI and fats affect diabetes risk is their role in body weight and abdominal fat accumulation.

SEP was based on lifetime socio-economic position based on the head of the household's occupational social class at age 15-53 years and highest level of educational qualification achieved by age 26 years. Self-reported measures of leisure time physical activity at 36, 43 and 53 years were used as potential confounders. Three categorical variables of smoking history up to 36, 43 or 53 were used as measures of cumulative smoking damage.

More detailed descriptions of the potential confounding measures used in this chapter are given in Chapter 2.

5.2.5 Statistical analyses

Descriptive analyses compared the proportions of mean and women and those with type 2 diabetes (diagnosed between age 53 and 60-64), mean of intakes of energy, macronutrients (carbohydrates, protein, fat and alcohol) and of the exposure variables according to quintile of intake of fibre density, GI, fat density and SFA density. Mean or median (when the distribution was skewed) of fibre density, GI, fat density and SFA density were graphed by survey year and sex. Food groups with highest correlations with fibre density, GI, fat density and SFA density are presented. Associations of potential confounders with fibre density, GI and fat density at age 36, 43 and 53 and the outcome were examined using linear regression or bivariate analyses.

Multivariable logistic regression was used to examine, in separate models for each dietary exposure, prospective associations between fibre density, GI, total fat density and SFA density at 36, 43 and 53 years of age and incident type 2 diabetes between age 53 and 60-64 years.

For all analyses associations were first presented unadjusted (Model 1). A series of models were then constructed to sequentially adjust for socio-economic status and educational attainment (Model 2), smoking history and exercise (Model 3), BMI (Model 4) and abdominal circumference (Model 5).

Interactions between dietary factors and sex, BMI or WC were tested by inclusion of interaction terms in the model with both main effects and p values were reported.

5.2.6 Sample

All analyses were restricted to those participants who provided data on type 2 diabetes diagnosed between age 53 and 60-64, diet and for all confounders (SEP, education, smoking history, BMI, WC). The final number was different depending on the year of the dietary assessment (N=1804 for age 36; N=2267 for age 43; N=1477 for age 53).

5.3 Results

5.3.1 Descriptive analyses

Nutritional characteristics and type 2 diabetes diagnosis (age 53 to 60-64) by quintile of intake of fibre density, average daily GI, fat density and SFA density at age 36, 43 and 53 for participants included in prospective analyses are shown in Tables 27-29. At all ages the percentage of male participants was significantly lower in the highest quintiles of fibre intake and higher in the highest quintiles of average GI. At all ages, the proportion of people diagnosed with type 2 diabetes between age 53 and 60-64 decreased with increasing quintiles of fibre intake and increased with higher GI quintiles, in a clear dose-response manner. The relationship between fat, SFA and diabetes was less straightforward; there was no apparent pattern at age 36, and a non-significant tendency for the proportion of diabetes to increase with higher fat quintiles, and to a lesser extent SFA quintiles, at age 43 and 53. At age 36 women were more likely to be in the highest quintiles of fat and saturated fat intake, while the opposite was true at age 53. At all ages high fibre density intake was associated with a lower GI and lower energy, total fat, SFA, and alcohol intakes and with higher carbohydrates and protein intakes (p for trend <0.01). Average daily GI was positively associated with energy intake and alcohol and negatively associated with protein and fibre (p for trend <0.001). At age 36 fat and SFA tended to decrease with increasing quintiles of GI, while the opposite was true at age 43 and 53. At all ages, those in the highest quintiles of fat and SFA intake consumed less carbohydrates, fibre and alcohol.

Figure 9. Mean or median intakes by age and sex for a) fibre density b) GI c) fat density and d) Saturated fat density shows the mean (or median when distribution was found to be skewed) intakes of the explanatory variables by age and sex. The median fibre density intake was similar at age 36 and 43 but considerably higher at age 53 for both genders, although women had higher intakes at all ages. Mean GI decreased with age and was lower for women at all ages. Median fat density and SFA density was similar at age 36 and 43 and substantially lower at age 53. Figure 10 shows the mean or median intakes of dietary factors by age and diabetes incidence between age 53 and 60-64. At all ages those who developed diabetes had a diet with higher GI and lower fibre density compared to those who did not develop the disease, while there was little difference in fat and SFA intakes.

Table 30 shows food groups correlated with fibre, GI and dietary fats. Foods positively correlated with fibre density were similar at all ages and included fruit, which had the strongest correlation, vegetables, high-fibre breads and cereals and low-fat dairy products. White bread, table sugar (sucrose), butter/animal fat, red or processed meat and potatoes had the strongest negative correlations with fibre. Alcohol was negatively correlated with fibre intake at age 43 and age 53. White bread, table sugar and potatoes (either fried or not) were the foods with the highest positive correlation with GI, while fruit, yogurt and low-fat milk had the highest negative correlations. At all ages butter and animal fat had the strongest correlation with fat and

particularly with SFA density. Full-fat dairy products and biscuits, pastry and cakes were positively correlated with fat and SFA at all ages while processed meat was correlated at age 43 and 53. Low-fat dairy products as well as low-fat plant fat were negatively correlated with fat and SFA at all ages. At age 43 and 53 fruit and alcohol had strong negative correlations with fat and SFA.

5.3.2 Investigation of potential confounders

People from a lower socio-economic class, especially those in manual employment, and with lower educational attainment consumed less fibre and had a diet with a higher GI at all ages (Table 31-33). Fat intake was associated with education only at age 43. There was a tendency for people with higher BMI and WC to consume less fibre (except for BMI at age 36) and have a higher GI compared to those with a lower BMI and WC with associations being stronger for WC. Fat was inversely associated with BMI and WC at age 36 but positively associated with WC at age 53. Never smokers had higher fibre and lower fat (except at age 36) intake and lower GI. More active people had significantly higher fibre and lower fat intake and lower GI.

Table 27. Nutrient intakes and diabetes status (age 53 to 60-64) by quintiles of fibre density, GI, fat density and SFA density at age 36

N=1804	Quintile of daily intake of fibre density*						Quintile of daily GI					
	Q1	Q2	Q3	Q4	Q5	P value	Q1	Q2	Q3	Q4	Q5	P value
Range	<4.5	4.5-5.1	5.2-5.9	6.0-7.2	7.3-27.6		<61.3	61.3-63.6	63.7-65.6	65.7-67.8	67.9-76.8	
Median	4.1	4.8	5.6	6.5	8.6		59.2	62.6	64.7	66.8	69.4	
Male (%)	62.6	54.2	51.5	38.5	30.2	<0.001	22.8	41.1	50.1	61.3	70.1	<0.001
Diabetes (%)	11.3	11.3	9.1	7.4	7.5	0.01	7.2	8.5	8.4	11.1	12.1	0.01
Energy, kcal	2286 ± 605	2164 ± 591	2044 ± 572	1935 ± 614	1737 ± 556	<0.001	1735 ± 571	1970 ± 571	2064 ± 595	2193 ± 650	2182 ± 686	<0.001
CHO density*	106.4 ± 17.5	110.4 ± 14.9	108.7 ± 14.8	110.4 ± 13.4	111.5 ± 15.3	<0.01	105.8 ± 16.8	109.3 ± 15.5	111.2 ± 14.9	110.3 ± 16.2	109.4 ± 15.4	<0.01
Protein density*	34.0 ± 5.8	34.9 ± 5.3	36.5 ± 5.9	37.5 ± 6.5	41.6 ± 9.8	<0.001	41.0 ± 10.4	37.0 ± 6.9	36.7 ± 5.8	35.3 ± 5.5	35.9 ± 6.0	<0.001
Alcohol, g	25.0 ± 29.4	14.1 ± 17.0	12.1 ± 15.2	9.3 ± 14.6	8.2 ± 12.5	<0.001	8.9 ± 14.1	11.0 ± 15.2	12.9 ± 16.2	18.2 ± 27.3	22.3 ± 27.2	<0.001
Fat density*	43.4 ± 6.2	44.4 ± 5.0	44.8 ± 4.9	44.5 ± 4.5	42.2 ± 5.7	0.03	44.6 ± 6.0	44.6 ± 5.1	43.9 ± 4.9	43.2 ± 5.2	42.0 ± 5.7	<0.001
SFA density*	18.2 ± 3.3	18.3 ± 2.8	18.6 ± 2.8	18.3 ± 2.7	17.0 ± 3.1	<0.001	18.4 ± 3.3	18.5 ± 2.9	18.2 ± 2.9	18.0 ± 3.0	17.3 ± 3.1	<0.001
Fibre density*	-	-	-	-	-		7.4 ± 3.1	6.4 ± 2.1	5.7 ± 1.7	5.2 ± 1.3	5.1 ± 1.2	<0.001
Average GI	65.5 ± 3.7	65.4 ± 3.4	64.8 ± 3.7	63.5 ± 3.7	61.5 ± 4.1	<0.001	-	-	-	-	-	-
N=1804	Quintile of daily intake of fat density*						Quintile of daily intake of SFA density*					
	Q1	Q2	Q3	Q4	Q5	P value	Q1	Q2	Q3	Q4	Q5	P value
Range	<39.8	39.8-42.9	43.0-45.3	45.4-48.1	48.2-62.3		<15.6	15.6-17.4	17.5-18.8	18.9-20.6	20.7-28.9	
Median	37.2	41.5	44.2	46.5	50.4		16.5	18.1	19.7	22.0	18.0	
Male (%)	60.1	55.6	46.5	43.7	31.3	<0.001	59.2	55.1	47.3	43.2	32.4	<0.001
Diabetes (%)	9.7	9.7	10.2	8.3	8.8	0.53	10.2	10.2	6.9	10.2	9.1	0.65
Energy, kcal	1979. ± 704	2086 ± 593	2058 ± 613	2067 ± 578	1976 ± 661	0.83	1994 ± 702	2051 ± 596	2066 ± 620	2067 ± 570	1988 ± 586	0.95
CHO density*	113.9 ± 19.8	114.6 ± 15.2	112.3 ± 11.9	108.1 ± 10.2	98.5 ± 11.9	<0.001	111.0 ± 19.4	113.9 ± 14.6	111.0 ± 14.0	109.5 ± 11.9	102.0 ± 13.3	<0.001
Protein density*	38.7 ± 10.1	36.3 ± 6.9	36.1 ± 5.4	35.3 ± 6.0	37.2 ± 7.0	0.53	38.9 ± 10.7	36.3 ± 6.0	36.0 ± 5.9	36.1 ± 5.4	37.3 ± 6.8	0.74
Alcohol, g	28.4 ± 31.4	15.3 ± 16.7	10.7 ± 13.0	8.5 ± 11.2	5.9 ± 7.6	<0.001	27.7 ± 30.9	14.5 ± 16.6	11.6 ± 14.0	8.9 ± 12.1	6.2 ± 9.0	<0.001
Fat density*	-	-	-	-	-		37.4 ± 5.0	42.1 ± 2.9	44.3 ± 3.1	46.1 ± 2.9	49.4 ± 3.4	<0.001
SFA density*	14.6 ± 2.2	16.9 ± 1.7	18.3 ± 1.8	19.3 ± 1.9	21.4 ± 1.7	<0.001	-	-	-	-	-	
Fibre density*	6.6 ± 3.2	6.1 ± 2.0	5.9 ± 1.9	5.9 ± 1.7	5.6 ± 1.5	0.01	6.8 ± 3.2	6.1 ± 2.0	5.9 ± 1.8	5.8 ± 1.7	5.6 ± 1.6	<0.001
Average GI	64.7 ± 4.7	64.5 ± 3.5	64.2 ± 3.7	64.0 ± 3.7	63.4 ± 4.1	<0.001	64.4 ± 4.7	64.6 ± 3.8	64.1 ± 3.5	63.9 ± 3.8	63.7 ± 4.0	0.02

Note: analyses restricted to those with non-missing values for dietary intake, diabetes and all covariates; * = g/1000kcal; GI= Glycaemic Index; SFA= Saturated fatty acids; CHO=carbohydrates

Table 28. Nutrient intakes and diabetes status (age 53 to 60-64) by quintiles of fibre density, GI, fat density and SFA at age 43

N=2271	Quintile of daily intake of fibre density*						Quintile of daily GI					
	Q1	Q2	Q3	Q4	Q5	P value	Q1	Q2	Q3	Q4	Q5	P value
Range	<4.3	4.3-5.3	5.4-6.3	6.4-7.8	7.9-31.3		<59.8	59.8-62.7	62.8-65.2	65.3-68.0	68.1-82.0	
Median	3.6	4.8	5.7	6.9	9.2		57.8	61.4	64.0	66.7	69.9	
Male (%)	67.4	57.0	46.2	37.6	29.7	<0.001	28.3	42.9	48.2	53.5	65.2	<0.001
Diabetes (%)	13.6	10.1	11.0	7.0	5.5	<0.001	5.2	7.7	9.4	11.0	13.9	<0.001
Energy, kcal	2347 ± 758	2227 ± 574	2105 ± 539	2012 ± 559	1708 ± 507	<0.001	1827 ± 561	2086 ± 594	2114 ± 606	2170 ± 623	2203 ± 701	<0.001
CHO density*	102.8 ± 17.7	106.2 ± 14.4	110.6 ± 14.4	112.0 ± 14.9	121.5 ± 17.1	<0.001	113.3 ± 18.6	112.8 ± 16.9	111.9 ± 16.9	110.4 ± 14.8	104.7 ± 15.9	<0.01
Protein density*	35.2 ± 6.6	36.0 ± 5.2	36.8 ± 6.1	38.2 ± 6.4	42.0 ± 9.8	<0.001	40.0 ± 9.3	37.6 ± 6.4	37.2 ± 6.6	36.3 ± 6.4	37.0 ± 7.3	<0.001
Alcohol, g	26.9 ± 36.1	15.0 ± 17.4	11.1 ± 14.3	9.8 ± 12.6	7.4 ± 10.4	<0.001	9.6 ± 12.9	11.9 ± 16.2	11.8 ± 15.7	14.4 ± 20.8	22.4 ± 33.3	<0.001
Fat density*	43.9 ± 7.0	45.3 ± 5.6	44.3 ± 5.0	43.8 ± 5.2	38.2 ± 6.9	<0.001	41.7 ± 7.3	42.9 ± 6.1	43.4 ± 6.1	43.7 ± 5.6	43.4 ± 7.0	<0.001
SFA density*	19.1 ± 4.0	19.3 ± 3.4	18.6 ± 3.1	17.9 ± 3.2	15.2 ± 3.5	<0.001	17.0 ± 3.8	17.8 ± 3.6	18.2 ± 3.5	18.6 ± 3.6	18.6 ± 4.1	<0.001
Fibre density*	-	-	-	-	-		7.8 ± 3.3	6.7 ± 2.3	6.2 ± 2.1	5.5 ± 1.8	4.9 ± 1.7	<0.001
Average GI	66.6 ± 4.0	65.1 ± 4.3	63.9 ± 4.7	62.8 ± 4.5	60.7 ± 4.7	<0.001	-	-	-	-	-	-
N=2267	Quintile of daily intake of fat density*						Quintile of daily intake of SFA density*					
	Q1	Q2	Q3	Q4	Q5	P value	Q1	Q2	Q3	Q4	Q5	P value
Range	<38.2	38.2-42.0	42.1-45.0	45.1-48.1	48.2-68.0		<15.0	15.0-17.1	17.2-18.9	19.0-21.1	21.2-31.4	
Median	34.8	40.3	43.6	46.5	50.5		13.3	16.1	18.0	19.9	22.8	
Male (%)	60.1	55.6	46.5	43.7	31.3	<0.001	48.4	47.6	48.6	47.9	45.4	0.88
Diabetes (%)	7.7	9.7	8.3	9.9	11.7	0.06	8.8	8.6	8.8	10.3	10.8	0.18
Energy, kcal	1839 ± 679	2082 ± 627	2115 ± 536	2180 ± 601	2184 ± 643	<0.001	1828 ± 668	2041 ± 600	2129 ± 586	2200 ± 586	2200 ± 639	<0.001
CHO density*	121.1 ± 21.8	115.0 ± 15.3	111.9 ± 12.4	106.7 ± 11.8	97.9 ± 11.5	<0.001	119.1 ± 22.6	113.2 ± 15	110.7 ± 14.1	107.8 ± 12.6	102.3 ± 13.7	<0.001
Protein density*	40.7 ± 10.2	37.7 ± 6.9	36.8 ± 6.0	36 ± 6.6	36.4 ± 5.5	<0.001	40.7 ± 10.5	38.5 ± 6.8	37.0 ± 6.0	36.3 ± 5.9	35.7 ± 5.4	<0.001
Alcohol, g	24.6 ± 36.1	17.0 ± 19.9	11.8 ± 13.4	10.0 ± 12.3	7.6 ± 10.5	<0.001	22.7 ± 34.9	15.9 ± 19.2	12.8 ± 16.3	10.5 ± 13.9	8.3 ± 12.1	<0.001
Fat density*	-	-	-	-	-		34.7 ± 6.0	40.8 ± 3.2	43.8 ± 3.4	46.2 ± 3.4	49.5 ± 4.0	<0.001
SFA density*	13.4 ± 2.6	16.7 ± 1.9	18.2 ± 2.2	19.6 ± 2.3	22.2 ± 2.8	<0.001	-	-	-	-	-	
Fibre density*	7.8 ± 3.9	6.4 ± 2.2	5.9 ± 1.7	5.7 ± 1.7	5.2 ± 1.5	<0.001	7.9 ± 3.8	6.5 ± 2.2	6.0 ± 1.8	5.6 ± 1.7	5.2 ± 1.6	<0.001
Average GI	63.1 ± 5.8	63.8 ± 4.7	63.7 ± 4.6	63.7 ± 4.7	64.7 ± 4.7	<0.001	63.0 ± 5.5	63.3 ± 4.7	63.5 ± 4.6	64.3 ± 4.7	65.0 ± 4.6	<0.001

Note: analyses restricted to those with non-missing values for dietary intake, diabetes and all covariates; * = g/1000kcal; GI= Glycaemic Index; SFA= Saturated fatty acids; CHO=carbohydrates

Table 29. Nutrient intakes and diabetes status (age 53 to 60-64) by quintiles of fibre density, GI, fat density and SFA at age 53

N=1480	Quintile of daily intake of fibre density*						Quintile of daily GI					
	Q1	Q2	Q3	Q4	Q5	P value	Q1	Q2	Q3	Q4	Q5	P value
Range	<5.6	5.6-6.5	6.6-7.7	7.8-9.2	9.3-25.9		<58.4	58.4-60.9	61-63.0	63.1-65.4	65.5-74.4	
Median	4.9	6.1	7.2	8.5	10.7		56.7	59.7	62.0	64.1	67.0	
Male (%)	71.2	51.0	40.8	36.8	26.0	<0.001	29.3	40.2	40.5	51.3	64.5	<0.001
Diabetes (%)	12.8	8.4	11.1	8.1	4.7	<0.01	4.7	4.4	10.5	14.8	10.8	<0.001
Energy, kcal	2243 ± 530	2082 ± 456	1965 ± 470	1905 ± 427	1725 ± 414	<0.001	1862.3 ± 489	1982 ± 439	1961 ± 448	2020 ± 504	2095 ± 546	<0.001
CHO density*	105.0 ± 19.2	114.2 ± 15.6	119.8 ± 15.1	124.4 ± 16.2	133.2 ± 17.3	<0.001	124.1 ± 20.7	121.8 ± 16.6	121.3 ± 16.1	117.7 ± 19.8	111.7 ± 20.0	<0.01
Protein density*	37.5 ± 6.8	38.3.9 ± 5.9	39.5 ± 5.8	41.2 ± 6.2	43.1 ± 7.8	<0.001	41.3 ± 8.1	39.7 ± 6.4	40.0 ± 6.4	39.5 ± 6.5	39.1 ± 6.5	<0.001
Alcohol, g	29.4 ± 33.6	17.1 ± 18.0	12.1 ± 14.2	11.7 ± 14.0	8.7 ± 12.1	<0.001	12.4 ± 15.3	13.7 ± 14.8	12.8 ± 14.9	17.1 ± 23.0	23.0 ± 31.2	<0.001
Fat density*	40.9 ± 6.8	40.2 ± 5.4	39.0 ± 5.4	36.4 ± 6.0	32.7 ± 6.5	<0.001	36.0 ± 7.2	37.3 ± 6.4	38.0 ± 6.4	38.4 ± 6.1	39.4 ± 6.6	<0.001
SFA density*	17.9 ± 4.0	16.3 ± 3.4	15.4 ± 3.2	13.8 ± 3.1	11.9 ± 3.2	<0.001	14.1 ± 3.8	14.4 ± 3.7	14.9 ± 3.7	15.0 ± 3.7	15.8 ± 3.9	<0.001
Fibre density*	-	-	-	-	-	-	8.9 ± 3.0	8.3 ± 2.3	7.6 ± 2.0	6.8 ± 1.9	6.2 ± 1.8	<0.001
Average GI	64.2 ± 3.7	62.8 ± 3.6	61.8 ± 3.8	61.0 ± 3.4	59.4 ± 3.9	<0.001	-	-	-	-	-	-
N=1480	Quintile of daily intake of fat density*						Quintile of daily intake of SFA density*					
	Q1	Q2	Q3	Q4	Q5	P value	Q1	Q2	Q3	Q4	Q5	P value
Range	<32.3	32.4-36.4	36.5-39.7	39.8-43.5	43.6-59.5		<15.6	15.6-17.4	17.5-18.8	18.9-20.6	20.7-28.9	
Median	29.0	34.5	38.2	41.5	46.3		16.5	18.1	19.7	22.0	18.0	
Male (%)	38.1	46.9	49.3	48.3	43.4	0.04	40.2	47.9	42.3	43.5	52.0	0.03
Diabetes (%)	6.4	7.7	9.4	12.8	8.8	0.06	6.7	8.1	13.2	5.4	11.8	0.15
Energy, kcal	1756 ± 513	1938 ± 454	2032 ± 444	2100 ± 504	2094 ± 460	0.83	1994 ± 702	2051 ± 596	2066 ± 620	2067 ± 570	1988 ± 586	0.95
CHO density*	134.2 ± 21.9	123.9 ± 17.1	118.9 ± 15.3	115.5 ± 13.4	104.2 ± 13.4	<0.001	111.0 ± 19.4	113.9 ± 14.6	111.0 ± 14.0	109.5 ± 11.9	102.0 ± 13.3	<0.001
Protein density*	43.3 ± 8.3	40.3 ± 6.8	39.5 ± 5.7	38.3 ± 5.9	38.2 ± 6.1	<0.001	38.9 ± 10.7	36.3 ± 6.0	36.0 ± 5.9	36.1 ± 5.4	37.3 ± 6.8	0.74
Alcohol, g	20.7 ± 31.5	19.4 ± 22.2	16.0 ± 18.6	12.3 ± 14.4	10.5 ± 12.7	<0.001	27.7 ± 30.9	14.5 ± 16.6	11.6 ± 14.0	8.9 ± 12.1	6.2 ± 9.0	<0.001
Fat density*	-	-	-	-	-	-	37.4 ± 5.0	42.1 ± 2.9	44.3 ± 3.1	46.1 ± 2.9	49.4 ± 3.4	<0.001
SFA density*	10.2 ± 2.1	13.0 ± 1.6	14.9 ± 1.9	16.4 ± 2.1	19.5 ± 3.0	<0.001	18.4 ± 3.3	18.5 ± 2.9	18.2 ± 2.9	18.0 ± 3.0	17.3 ± 3.1	<0.001
Fibre density*	9.6 ± 3.2	7.9 ± 2.2	7.1 ± 1.8	7.0 ± 1.7	6.3 ± 1.5	<0.001	6.8 ± 3.2	6.1 ± 2.0	5.9 ± 1.8	5.8 ± 1.7	5.6 ± 1.6	<0.001
Average GI	60.4 ± 4.0	61.7 ± 4.0	62.2 ± 3.8	62.2 ± 4.0	62.6 ± 3.9	<0.001	64.4 ± 4.7	64.6 ± 3.8	64.1 ± 3.5	63.9 ± 3.8	63.7 ± 4.0	0.02

Note: analyses restricted to those with non-missing values for dietary intake, diabetes and all covariates; * = g/1000kcal; GI= Glycaemic Index; SFA= Saturated fatty acids; CHO=carbohydrates

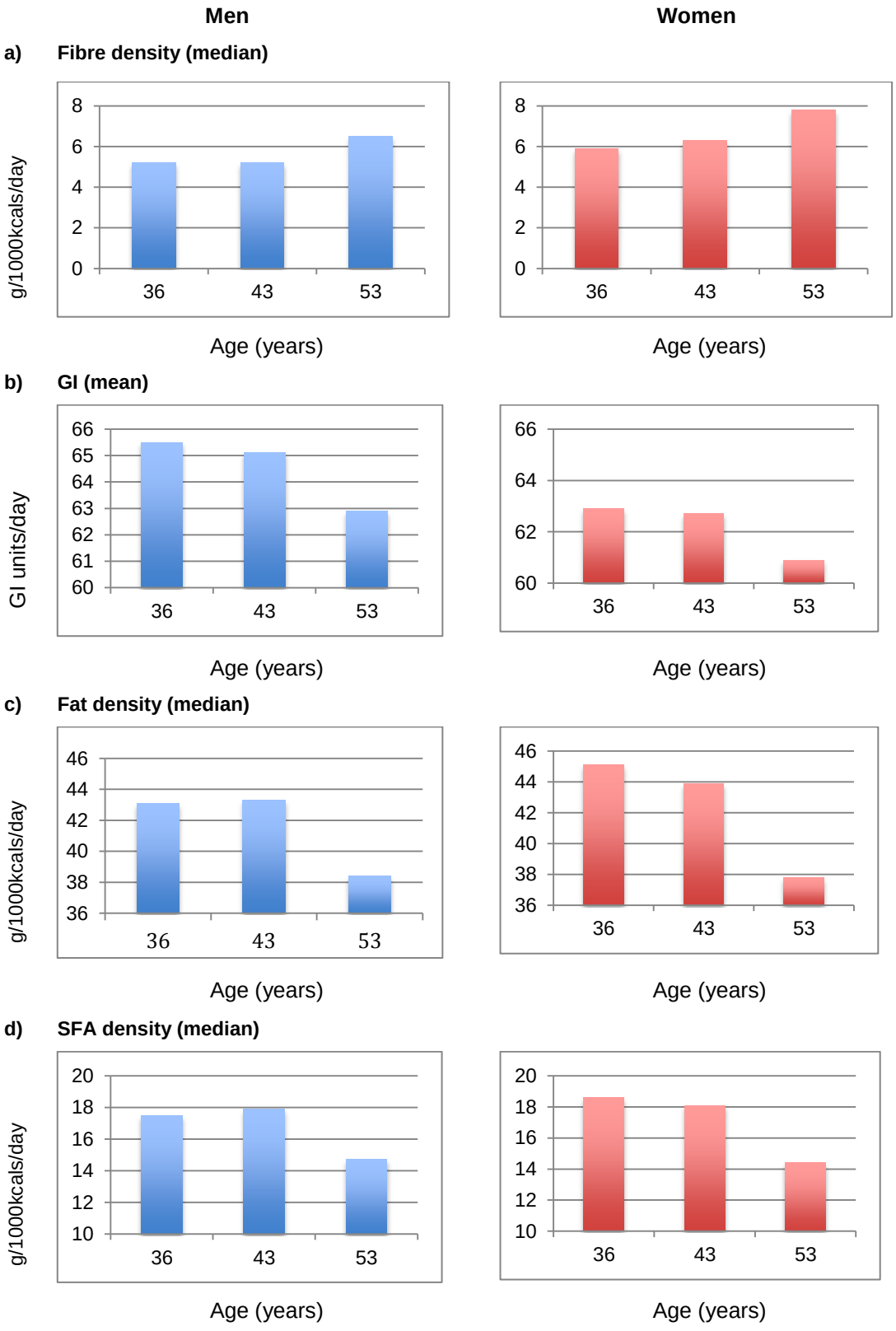


Figure 9. Mean or median intakes by age and sex for a) fibre density b) GI c) fat density and d) Saturated fat density

Note: analyses restricted to those with non-missing data for dietary intake, type 2 diabetes and all covariates at each age; at age 36 N=1804; at age 43 N=2267, at age 53 N= 1477
* Overweight = BMI ≥ 25 - 29.9 kg/m^2; obesity = BMI ≥ 30 kg/m^2.

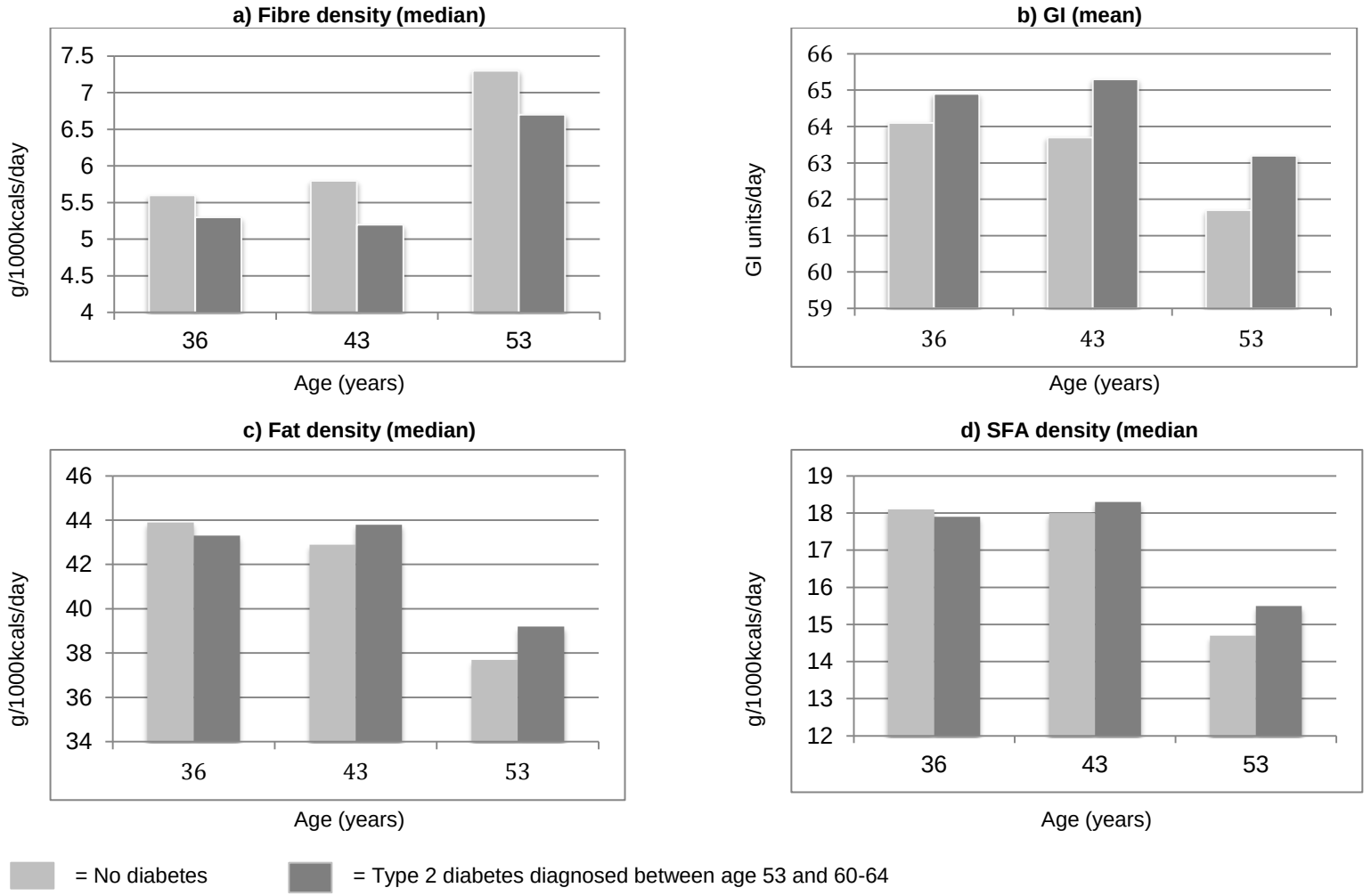


Figure 10. Mean or median intakes by age and type 2 diabetes diagnosis (age 53 to 60-64) for a) fibre density b) GI c) fat density and d) SFA density

Note: analyses restricted to those with non-missing data for dietary intake, diabetes and all covariates at each age; at age 36 N=1804; at age 43 N=2267, at age 53 N= 1477; SFA=saturated fatty acids

Table 30. **Food groups correlated with fibre density, GI, fat density and SFA density**

Age 36		Age 43		Age 53	
Food group	Correlation	Food group	Correlation	Food group	Correlation
Fibre density					
Fruit	0.32	Fruit	0.45	Fruit	0.53
Skimmed milk	0.24	High-fibre cereals	0.28	Vegetables	0.38
Vegetables	0.20	Vegetables	0.28	Low-fat yogurt	0.25
High-fibre cereals	0.16	Wholemeal bread	0.26	Wholemeal bread	0.24
White bread	-0.36	White bread	-0.33	White bread	-0.32
Table sugar	-0.30	Fried potatoes	-0.32	Alcohol	-0.30
Butter/animal fat	-0.26	Table sugar	-0.31	Table sugar	-0.29
Potatoes	-0.23	Processed meat	-0.29	Processed meat	-0.28
GI					
Potatoes	0.49	White bread	0.32	White bread	0.36
White bread	0.39	Fried potatoes	0.32	Fried potatoes	0.32
Table sugar	0.31	Potatoes	0.26	Table sugar	0.25
Butter/animal fat	0.29	Table sugar	0.23	Processed meat	0.23
Fruit	-0.36	Fruit	-0.36	Fruit	-0.45
Yogurt	-0.31	Low-fat yogurt	-0.31	Low-fat yogurt	-0.30
Skimmed milk	-0.26	Skimmed milk	-0.26	Pasta	-0.21
Fruit juice	-0.18	High-fibre cereals	-0.18	Wholemeal bread	-0.19
Dietary fat density					
Butter/animal fat	0.19	Butter/animal fat	0.29	Butter/animal fat	0.35
Biscuits/pastry/cakes	0.15	Processed meat	0.22	Processed meat	0.20
Cream	0.13	Whole milk	0.20	Biscuits/pastry/cakes	0.19
Whole milk	0.10	Red meat	0.18	Whole milk	0.18
Skimmed milk	-0.23	Alcohol	-0.23	Fruit	-0.25
Table sugar	-0.20	Skimmed milk	-0.21	Low-fat yogurt	-0.22
Soup	-0.11	Fruit	-0.14	Low-fat plant fat	-0.15
Low-fat plant fat	-0.10	Low-fat plant fat	-0.13	Skimmed milk	-0.14
Saturated fat density					
Butter/animal fat	0.37	Butter/animal fat	0.50	Butter/animal fat	0.56
Whole milk	0.21	Whole milk	0.31	Whole milk	0.23
Cream	0.17	Cheese	0.20	Cheese	0.20
Cheese	0.13	Processed meat	0.17	Processed meat	0.20
Skimmed milk	-0.22	Skimmed milk	-0.24	Fruit	-0.24
Low-fat plant fat	-0.14	Alcohol	-0.19	Low-fat plant fat	-0.20
Plant fat	-0.13	Low-fat plant fat	-0.15	Low-fat yogurt	-0.18
Oils	-0.11	Fruit	-0.14	Vegetables	-0.15

Note: analyses restricted to those with non-missing values for dietary intake, diabetes status and all covariates at each age; SFA=saturated fatty acids

Table 31. Associations between potential confounders and mediators and selected dietary factors at age 36

		Dietary factors		
		Fibre density	GI	Fat density
	n	Median (IQR)	Mean (SD)	Mean (SD)
Socioeconomic position				
I professional	146	5.7 (2.4)	63.7 (3.5)	43.3 (4.2)
II intermediate	697	5.7 (2.3)	63.5 (4.1)	43.9 (5.3)
III skilled (Non-Manual)	490	5.6 (2.3)	63.9 (3.9)	43.4 (5.3)
III skilled (Manual)	297	5.1 (1.6)	66.0 (3.8)	43.1 (5.8)
IV partly skilled	202	5.5 (2.0)	64.6 (4.3)	43.9 (5.6)
V unskilled	68	5.4 (1.8)	65.8 (3.7)	43.3 (5.8)
P-value (trend)		<0.001	<0.001	0.57
Education attained by age 26				
None attempted	574	5.3 (1.6)	65.5 (3.9)	43.9 (5.7)
Intermediate	528	5.6 (2.2)	64.3 (4.0)	43.6 (5.2)
Highest	716	5.8 (2.4)	63.1 (3.9)	43.9 (5.2)
P-value (trend)		<0.001	<0.001	0.80
BMI category at age 36				
Normal (<25 kg/m^2)	1283	5.6 (2.2)	64.2 (3.9)	44.2 (5.1)
Overweight (25 -29.9 kg/m^2)	510	5.4 (2.1)	65.0 (3.9)	43.2 (5.6)
Obese (≥30 kg/m^2)	92	5.7 (2.1)	64.5 (4.9)	42.7 (6.7)
P-value (trend)		0.29	<0.001	<0.01
Waist circumference at age 36				
Lowest tertile	635	5.9 (2.5)	62.9 (4.1)	44.7 (5.1)
Middle tertile	629	5.4 (2.1)	65.8 (3.8)	43.8 (5.5)
Highest tertile	629	5.3 (1.8)	65.0 (4.0)	43.1 (5.4)
P-value (trend)		<0.001	<0.001	<0.001
Smoking history up to age 36				
Current smoker	502	5.1 (1.6)	65.6 (3.7)	43.2 (5.5)
Ex smoker	783	5.6 (2.3)	64.0 (4.1)	43.8 (5.4)
Never smoker	614	5.8 (2.2)	63.3 (4.1)	44.5 (5.1)
P-value (ANOVA)		<0.001	<0.001	<0.001
Exercise at age 36				
Inactive	659	5.5 (1.9)	64.6 (4.0)	44.4 (5.5)
Less active	519	5.5 (2.1)	64.4 (3.9)	44.0 (4.9)
Most active	721	5.7 (2.5)	63.7 (4.2)	43.2 (5.5)
P-value (trend)		<0.001	<0.001	<0.001

Note: analyses restricted to those with non-missing data for type 2 diabetes diagnosis; maximum available sample size used with each indicator; educational attainment was categorised as none (none attempted), intermediate (GCE 'O' level or Burnam C or lower) or highest (GCE A level or Burnam B or higher); activity at 36 years was coded as inactive (no participation), moderately active (participated one to four times) and most active (participated five or more times) in the previous month. IQR=Interquartile range

Table 32. Associations between potential confounders and mediators and selected dietary factors at age 43

		Dietary factors		
		Fibre density	GI	Fat density
	n	Median (IQR)	Mean (SD)	Mean (SD)
Socioeconomic position				
I professional	182	5.8 (2.6)	63.4 (4.3)	42.3 (5.5)
II intermediate	913	6.0 (2.6)	63.1 (4.9)	42.7 (6.4)
III skilled (Non-Manual)	569	5.9 (2.7)	63.4 (4.9)	43.4 (6.1)
III skilled (Manual)	399	4.9 (2.3)	65.5 (4.9)	43.2 (6.9)
IV partly skilled	266	5.6 (2.6)	64.5 (4.9)	43.3 (7.1)
V unskilled	93	5.1 (2.2)	64.7 (5.5)	42.6 (7.3)
P-value (trend)		<0.001	<0.001	0.25
Education attained by age 26				
None attempted	772	5.3 (2.5)	65.3 (5.0)	43.6 (7.0)
Intermediate	648	5.8 (2.5)	63.7 (4.8)	42.9 (6.5)
Highest	874	6.2 (2.9)	62.7 (4.7)	42.5 (6.00)
P-value (trend)		<0.001	<0.001	<0.001
BMI category at age 43				
Normal (<25 kg/m^2)	1314	5.9 (2.7)	63.2 (5.0)	43.1 (6.3)
Overweight (25 -29.9 kg/m^2)	834	5.5 (2.6)	64.4 (4.8)	43.8 (6.4)
Obese (≥30 kg/m^2)	268	5.6 (2.7)	64.6 (4.9)	43.0 (7.4)
P-value (trend)		0.01	<0.001	0.84
Waist circumference at age 43				
Lowest tertile	815	6.3 (2.8)	62.4 (5.0)	43.3 (6.3)
Middle tertile	796	5.9 (2.8)	63.8 (4.8)	42.8 (6.4)
Highest tertile	800	5.2 (2.2)	65.2 (4.6)	42.9 (6.8)
P-value (trend)		<0.001	<0.001	0.13
Smoking history up to age 43				
Current smoker	617	4.9 (2.3)	65.5 (4.9)	43.5 (7.1)
Ex smoker	1050	5.9 (2.8)	63.2 (4.8)	42.7 (6.5)
Never smoker	756	6.1 (2.8)	63.2 (4.9)	42.9 (6.0)
P-value (ANOVA)		<0.001	<0.001	0.04
Exercise at age 43				
Inactive	1214	5.6 (2.5)	64.3 (4.9)	43.4 (6.6)
Less active	589	5.7 (2.5)	63.6 (5.1)	42.8 (6.2)
Most active	625	6.2 (3.1)	63.0 (4.8)	42.3 (6.3)
P-value (trend)		<0.001	<0.001	<0.001

Note: analyses restricted to those with non-missing data for type 2 diabetes diagnosis; maximum available sample size used with each indicator; educational attainment was categorised as none (none attempted), intermediate (GCE 'O' level or Burnam C or lower) or highest (GCE A level or Burnam B or higher); exercise at age 43 was coded as inactive (no participation), moderately active (participated one to four times) and most active (participated five or more times) per month. IQR=Interquartile range

Table 33. Associations between potential confounders and mediators and selected dietary factors at age 53

		Dietary factors		
		Fibre density	GI	Fat density
	n	Median (IQR)	Mean (SD)	Mean (SD)
Socioeconomic position				
I professional	128	7.4 (2.6)	61.0 (3.2)	38.2 (5.6)
II intermediate	585	7.2 (3.2)	61.3 (4.0)	37.7 (6.5)
III skilled (Non-Manual)	388	7.6 (3.0)	61.6 (3.8)	37.9 (6.4)
III skilled (Manual)	243	6.5 (3.0)	63.4 (4.4)	38.0 (7.5)
IV partly skilled	175	7.2 (3.1)	62.5 (4.3)	38.5 (7.4)
V unskilled	61	7.1 (2.9)	63.0 (3.8)	36.4 (6.9)
P-value (trend)		*0.04*	*<0.001*	*0.53*
Education attained by age 26				
None attempted	435	7.0 (2.7)	63.2 (3.9)	38.3 (6.9)
Intermediate	440	7.3 (3.0)	61.9 (3.9)	37.6 (7.3)
Highest	616	7.4 (3.1)	60.9 (3.9)	37.7 (6.2)
P-value (trend)		*<0.01*	*<0.001*	*0.13*
BMI category at age 53				
Normal (<25 kg/m^2)	576	7.5 (3.2)	61.3 (4.1)	38.1 (7.0)
Overweight (25 -29.9 kg/m^2)	673	7.0 (3.0)	62.1 (4.2)	37.5 (6.3)
Obese (≥30 kg/m^2)	323	7.0 (2.8)	62.4 (3.8)	37.1 (6.9)
P-value (trend)		*0.01*	*<0.001*	*0.71*
Waist circumference at age 53				
Lowest tertile	531	7.9 (3.0)	60.8 (4.0)	37.3 (6.9)
Middle tertile	521	7.1 (3.1)	62.0 (4.2)	38.0 (6.8)
Highest tertile	526	6.6 (2.7)	62.9 (3.8)	38.3 (6.4)
P-value (trend)		<0.001	*<0.001*	*0.01*
Smoking history up to age 53				
Current smoker	265	6.1 (2.5)	63.7 (3.9)	39.4 (6.9)
Ex smoker	813	7.3 (3.0)	61.7 (4.0)	37.6 (6.7)
Never smoker	505	7.5 (3.1)	61.2 (4.0)	37.7 (6.5)
P-value (ANOVA)		<0.001	*<0.001*	*<0.01*
Exercise at age 53				
Inactive	710	7.0 (2.9)	62.5 (4.1)	38.2 (6.8)
Less active	315	7.0 (3.0)	61.9 (3.9)	38.7 (6.2)
Most active	557	7.6 (3.1)	61.1 (3.9)	37.1 (6.8)
P-value (trend)		<0.001	*<0.001*	*<0.01*

Note: analyses restricted to those with non-missing data for type 2 diabetes diagnosis; maximum available sample size used with each indicator; educational attainment was categorised as none (none attempted), intermediate (GCE 'O' level or Burnam C or lower) or highest (GCE A level or Burnam B or higher); exercise at age 53 was coded as inactive (no participation), moderately active (participated one to four times) and most active (participated five or more times) in the previous 4 weeks. IQR=Interquartile range

5.3.3 Prospective associations between fibre, GI, dietary fats and type 2 diabetes

Prospective associations between dietary fibre density, GI, total fat density and SFA density at age 36, 43, 53 and type 2 diabetes are shown in Tables 34-37.

5.3.3.1 Fibre density

At all ages there was a significant negative dose-response relationship across quintiles of dietary fibre density and type 2 diabetes in later adulthood (Table 34, Model 1-2, p for trend <0.05). Those in the highest quintile of intake had significantly lower type 2 diabetes incidence than people in the lowest (at age 36 associations were borderline significant). After adjustment for social and lifestyle confounders associations at age 36 were eliminated. After further adjustment for BMI and WC, the associations at age 53 were weakened and were borderline significant when comparing extreme quintiles of intake; at age 43 the associations remained strong (OR for the highest versus the lowest quintile of fibre density: 0.50, 95%CI: 0.29, 0.88).

5.3.3.2 Dietary Glycaemic Index

the risk of type 2 diabetes increased with increasing quintiles of dietary GI at age 43 and 53 years (Table 35) with significant linear trends in all models; participants in the highest quintile of GI had a more than two-fold increased risk of diabetes compared to those in the lowest quintile. These associations were not considerably changed by adjustment for SEP, education, smoking and physical activity (Model 2 and 3). After further adjustment for BMI and WC the associations were attenuated, but remained significant at age 43 (highest compared to lowest quintile: OR=1.90, 95% CI, 1.11, 3.25) and 53 (fourth compared to lowest quintile: OR=2.65, 95% CI, 1.36, 5.17). Although in the same direction as for age 43 and 53, the associations at age 36 years were not statistically significant.

5.3.3.3 Fat density

Unlike dietary fibre density and GI, significant interactions were observed between total fat and sex; therefore analyses were subsequently presented by sex (Table 36). While there was no association between fat density and type 2 diabetes among men, total fat density significantly increased the risk of diabetes among women in a dose-response manner (p for trend <0.05) except at age 36. After adjustment for SEP, education, smoking and exercise the risk was increased three-fold for the highest compared to the lowest quintile of intake; further adjustment for BMI and WC did not appreciably affect the associations (age 43 OR: 2.96, 95%CI: 1.27, 6.87; age 53 OR: 3.35, 95%CI: 1.05, 10.68). There was a similar interaction between SFA intake and sex (although only significant at age 53), therefore results were presented by sex (Table 37). As with total fat, no association was found for men but there was a significant positive association among women, although only at age 53, which remained significant after adjustment for all considered confounders. Those in the highest quintile of intake had a 4-time increased risk of type 2 diabetes, although there was no linear trend across quintiles of SFA intake.

5.3.4 Investigation of interactions between dietary factors and BMI and WC

Associations between dietary factors and type 2 diabetes risk were further analysed according to BMI and WC categories (Tables 38-39) to test the hypothesis that these dietary factors might be more important for those at higher risk of type 2 diabetes. This was confirmed for fibre density and BMI at 36 and 53 years (p value for interaction = 0.02) and dietary GI and BMI at 36 years (p value for interaction = 0.02). In models adjusted for all social and lifestyle confounders, the protective association with dietary fibre was more pronounced among the overweight and obese than among people with a BMI<25 (Table 38).

Although interactions between categories of WC and fibre density were non-significant, consumption of high dietary fibre (highest tertile) was significantly associated with lower diabetes risk only among participants in the very high risk WC category (Table 38). Similarly, no significant interaction between categories of WC and GI was found; however dietary GI was positively associated with diabetes only among the very high risk WC category at age 43 and 53 (Table 39).

At all ages, the association with fibre was stronger in participants with a larger WC, whereas associations among those with a normal WC tended to be weak and not significant

Similarly, there were significant interactions between GI and BMI (at age 36 $p<0.05$). While weak associations were found among those with a BMI<25, GI was significantly associated with type 2 diabetes among overweight and obese people (Table 39). A similar pattern was observed for WC with the effect of GI being stronger for participants with a higher WC.

Table 34. Associations at each age between dietary fibre density intake and type 2 diabetes between age 53 and 60-64

	Model 1		**Model 2**		**Model 3**		**Model 4**		**Model 5**	
	Adjusted for kcal intake and sex		Adjusted for SEP and education		As Model 2 + physical activity, smoking history		As Model 3 + BMI		As Model 4 + WC	
Quintiles of fibre density intake	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age 36 (N=1804)										
Q2	1.00 (0.63, 1.53)	0.99	1.00 (0.63, 1.60)	0.97	1.03 (0.64, 1.63)	0.90	1.06 (0.66, 1.70)	0.79	1.06 (0.66, 1.70)	0.79
Q3	0.76 (0.47, 1.25)	0.28	0.76 (0.47, 1.25)	0.29	0.79 (0.48, 1.30)	0.36	0.82 (0.50, 1.36)	0.46	0.82 (0.49, 1.35)	0.44
Q4	0.63 (0.37, 1.07)	0.09	0.64 (0.38, 1.09)	0.10	0.66 (0.39, 1.13)	0.13	0.64 (0.37, 1.10)	0.01	0.64 (0.37, 1.10)	0.11
Q5	0.62 (0.36, 1.00)	0.05	0.64 (0.36, 1.10)	0.10	0.70 (0.40, 1.21)	0.20	0.71 (0.40, 1.24)	0.23	0.73 (0.42, 1.29)	0.28
P for trend	0.02		0.03		0.06		0.06		0.07	
Age 43 (N=2267)										
Q2	0.72 (0.48, 1.08)	0.12	0.73 (0.48, 1.10)	0.14	0.80 (0.52, 1.21)	0.29	0.76 (0.49, 1.17)	0.20	0.76 (0.49, 1.18)	0.23
Q3	0.80 (0.53, 1.20)	0.29	0.83 (0.55, 1.24)	0.37	0.92 (0.61, 1.40)	0.72	0.97 (0.63, 1.49)	0.91	0.98 (0.64, 1.51)	0.94
Q4	0.50 (0.31, 0.79)	<0.01	0.52 (0.32, 0.83)	<0.01	0.58 (0.36, 0.94)	0.02	0.63 (0.38, 1.02)	0.06	0.64 (0.39, 1.05)	0.08
Q5	0.36 (0.22, 0.61)	<0.001	0.38 (0.22, 0.64)	<0.001	0.45 (0.26, 0.78)	<0.01	0.47 (0.27, 0.82)	<0.01	0.50 (0.29, 0.88)	0.01
P for trend	<0.001		<0.001		<0.01		0.01		0.02	
Age 53 (N=1477)										
Q2	0.67 (0.39, 1.15)	0.15	0.67 (0.39, 1.63)	0.15	0.68 (0.39, 1.18)	0.17	0.77 (0.44, 1.36)	0.37	0.74 (0.42, 1.30)	0.30
Q3	0.95 (0.57, 1.60)	0.87	0.96 (0.57, 1.62)	0.90	0.97 (0.57, 1.64)	0.92	1.12 (0.65, 1.93)	0.67	1.09 (0.65, 1.89)	0.73
Q4	0.68 (0.39, 1.20)	0.19	0.71 (0.40, 1.25)	0.24	0.71 (0.40, 1.27)	0.25	0.79 (0.44, 1.44)	0.46	0.78 (0.43, 1.43)	0.43
Q5	0.41 (0.21, 0.80)	0.01	0.42 (0.21, 0.84)	0.01	0.44 (0.22, 0.88)	0.02	0.49 (0.24, 1.02)	0.05	0.48 (0.23, 1.00)	0.05
P for trend	0.02		0.04		0.05		0.13		0.13	

Note: analyses restricted to those with non-missing data for dietary intake at each age, type 2 diabetes and all covariates; BMI= body mass index; WC=waist circumference; for all associations the reference category was Q1

Table 35. Associations at each age between average daily glycaemic index and type 2 diabetes between age 53 and 60-64

	Model 1		**Model 2**		**Model 3**		**Model 4**		**Model 5**	
	Adjusted for kcal intake and sex		Adjusted for SEP and education		As Model 2 + physical activity, smoking history		As Model 3 + BMI		As Model 4 + WC	
Quintiles of GI	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age 36 (N=1804)										
Q2	1.11 (0.65, 1.88)	0.68	1.20 (0.70, 2.06)	0.49	1.20 (0.70, 2.06)	0.49	1.32 (0.76, 2.29)	0.32	1.30 (0.75, 2.26)	0.34
Q3	1.10 (0.65, 1.86)	0.71	1.14 (0.66, 1.96)	0.62	1.14 (0.66, 2.96)	0.62	1.14 (0.65, 1.99)	0.64	1.11 (0.63, 1.94)	0.70
Q4	1.44 (0.86, 2.42)	0.16	1.49 (0.86, 2.58)	0.14	1.49 (0.86, 2.58)	0.14	1.61 (0.91, 2.85)	0.09	1.58 (0.89, 2.78)	0.11
Q5	1.58 (0.94, 2.66)	0.08	1.61 (0.92, 2.81)	0.09	1.61 (0.92, 2.81)	0.09	1.46 (0.82, 2.62)	0.19	1.43 (0.80, 2.55)	0.22
P for trend	0.05		0.09		0.18		0.17		0.18	
Age 43 (N=2267)										
Q2	1.48 (0.86, 2.54)	0.15	1.49 (0.86, 2.56)	0.14	1.44 (0.84, 2.49)	0.18	1.42 (0.81, 2.48)	0.20	1.38 (0.79, 2.41)	0.25
Q3	1.82 (1.07, 3.07)	0.02	1.80 (1.06, 3.04)	0.02	1.72 (1.01, 2.91)	0.04	1.64 (0.96, 2.81)	0.06	1.60 (0.93, 2.74)	0.08
Q4	2.13 (1.27, 3.57)	<0.01	2.09 (1.24, 3.51)	<0.01	2.91 (1.13, 3.22)	0.01	1.71 (1.00, 2.93)	0.04	1.67 (0.98, 2.85)	0.05
Q5	2.66 (1.61, 4.40)	<0.001	2.54 (1.52, 4.25)	<0.001	2.28 (1.35, 3.83)	<0.01	1.98 (1.16, 3.38)	0.01	1.90 (1.11, 3.25)	0.01
P for trend	<0.001		<0.001		<0.01		0.01		0.01	
Age 53 (N=1477)										
Q2	0.87 (0.40, 1.90)	0.74	0.86 (0.40, 1.88)	0.72	0.86 (0.39, 1.87)	0.71	0.83 (0.37, 1.85)	0.66	0.82 (0.37, 1.82)	0.63
Q3	2.25 (1.17, 4.35)	0.01	2.24 (1.16, 4.33)	0.01	2.22 (1.15, 4.30)	0.01	1.83 (0.92, 3.65)	0.08	1.70 (0.90, 3.59)	0.09
Q4	3.26 (1.73, 6.12)	<0.001	3.18 (1.68, 6.03)	<0.001	3.13 (1.64, 5.95)	<0.001	2.73 (1.40, 5.32)	<0.01	2.65 (1.36, 5.17)	<0.01
Q5	2.16 (1.11, 4.20)	0.02	2.09 (1.06, 4.14)	0.03	2.04 (1.02, 4.07)	0.04	1.65 (0.81, 3.37)	0.16	1.65 (0.81, 3.37)	0.16
P for trend	<0.001		<0.001		<0.01		<0.01		<0.01	

Note: analyses restricted to those with non-missing data for dietary intake at each age, type 2 diabetes and all covariates; GI=glycaemic index; BMI= body mass index; WC=waist circumference; for all associations the reference category was Q1

Table 36. Associations between total dietary fat density intake and type 2 diabetes at age 53 to 60-64 by sex at each age

	Men*				Women**				
	Model a		Model b		Model a		Model b		
Quintiles of fat density intake	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	P value for interaction
Age 36 (N=1804)									
Q2	1.00 (0.55, 1.81)	0.99	1.11 (0.60, 2.03)	0.73	1.19 (0.46, 3.07)	0.71	1.29 (0.49, 3.41)	0.59	
Q3	0.96 (0.50, 1.82)	0.90	0.98 (0.50, 1.90)	0.96	1.81 (0.77, 4.25)	0.17	1.91 (0.80, 4.68)	0.14	0.30
Q4	0.65 (0.31, 1.33)	0.24	0.68 (0.33, 1.42)	0.31	1.68 (0.70, 3.98)	0.23	1.82 (0.75, 4.41)	0.18	
Q5	0.91 (0.44, 1.88)	0.81	0.96 (0.46, 2.03)	0.93	1.59 (0.68, 3.71)	0.28	1.81 (0.75, 4.32)	0.18	
P for trend	0.43		0.48		0.23		0.15		
Age 43 (N=2267)									
Q2	0.97 (0.53, 1.75)	0.92	1.06 (0.57, 1.95)	0.84	2.42 (1.05, 5.61)	0.03	2.52 (1.06, 5.97)	0.03	
Q3	0.96 (0.52, 1.75)	0.89	0.99 (0.53, 1.86)	0.99	1.69 (0.69, 4.11)	0.18	1.84 (0.74, 4.57)	0.18	
Q4	0.98 (0.53, 1.82)	0.96	1.02 (0.54, 1.92)	0.94	2.78 (1.20, 6.42)	0.02	2.73 (1.15, 6.49)	0.02	0.04
Q5	1.12 (0.61, 2.07)	0.69	1.09 (0.58, 2.04)	0.78	3.10 (1.37, 7.00)	0.01	2.96 (1.27, 6.87)	0.01	
P for trend	0.71		0.85		<0.01		0.02		
Age 53 (N=1477)									
Q2	0.79 (0.36, 1.75)	0.56	0.89 (0.38, 2.07)	0.79	1.90 (0.61, 5.87)	0.26	2.50 (0.74, 8.41)	0.13	
Q3	0.91 (0.42, 1.97)	0.81	0.77 (0.33, 1.75)	0.55	2.34 (0.77, 7.10)	0.13	2.82 (0.86, 9.26)	0.18	
Q4	1.00 (0.46, 2.14)	1.00	0.89 (0.39, 2.03)	0.78	4.06 (1.42, 11.6)	<0.01	4.85 (1.55, 15.17)	<0.01	<0.01
Q5	0.48 (0.19, 1.20)	0.12	0.54 (0.21, 1.41)	0.21	3.18 (1.09, 9.24)	0.03	3.35 (1.05, 10.68)	0.04	
P for trend	0.29		0.28		0.01		0.02		

Note: analyses restricted to those with non-missing data for dietary intake at each age, type 2 diabetes and all covariates; for all associations the reference category was Q1; Model a: adjusted for kcals, social class, education, physical activity, smoking history; Model b= as Model a + adjusted for BMI and waist circumference.
* At age 36 n=856, at age43 n=1080, at age 53 n=668; ** At age 36 n=946, at age 43 n=1187, at age 53 n=809

Table 37. Associations between saturated fat density intake and type 2 diabetes at age 53 to 60-64 by sex at each age

	Men*				Women**				
	Model a		Model b		Model a		Model b		
Quintiles of SFA density intake	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	P value for interaction
Age 36 (N=1804)									
Q2	0.91 (0.50, 1.67)	0.77	1.05 (0.57, 1.95)	0.85	1.42 (0.60, 3.37)	0.41	1.68 (0.69, 4.08)	0.24	
Q3	0.65 (0.33, 1.29)	0.22	0.70 (0.35, 1.40)	0.32	0.87 (0.34, 2.21)	0.77	1.10 (0.42, 2.85)	0.84	0.48
Q4	0.86 (0.44, 1.67)	0.65	0.89 (0.45, 1.77)	0.75	1.73 (0.76, 3.96)	0.18	2.16 (0.92, 5.07)	0.07	
Q5	0.92 (0.45, 1.88)	0.83	0.91 (0.44, 1.89)	0.81	1.41 (0.62, 3.22)	0.40	1.74 (0.74, 4.07)	0.19	
P for trend	0.66		0.60		0.32		0.16		
Age 43 (N=2267)									
Q2	1.06 (0.57, 1.94)	0.84	1.27 (0.67, 2.37)	0.45	1.12 (0.52, 2.42)	0.76	0.93 (0.42, 2.09)	0.87	
Q3	0.93 (0.51, 1.71)	0.83	0.98 (0.53, 1.83)	0.96	1.15 (0.53, 2.50)	0.70	1.19 (0.54, 2.64)	0.66	
Q4	0.86 (0.46, 1.62)	0.65	1.11 (0.57, 2.13)	0.75	1.91 (0.93, 3.95)	0.07	1.77 (0.83, 3.74)	0.13	0.33
Q5	1.27 (0.70, 2.13)	0.41	1.33 (0.72, 2.45)	0.35	1.29 (0.60, 2.75)	0.50	1.30 (0.59, 2.85)	0.50	
P for trend	0.64		0.50		0.23		0.18		
Age 53 (N=1477)									
Q2	0.64 (0.28, 1.45)	0.29	0.60 (0.25, 1.44)	0.25	2.60 (0.88, 7.70)	0.08	3.08 (0.97, 9.82)	0.05	
Q3	1.34 (0.64, 2.79)	0.43	1.06 (0.48, 2.35)	0.87	3.39 (1.19, 9.60)	0.02	3.89 (1.27, 11.9)	0.01	0.01
Q4	0.55 (0.23, 1.31)	0.18	0.53 (0.21, 1.31)	0.17	0.94 (0.27, 3.29)	0.93	1.16 (0.31, 4.29)	0.82	
Q5	0.67 (0.31, 1.48)	0.33	0.63 (0.28, 1.49)	0.31	4.40 (1.54, 12.5)	<0.01	4.73 (1.53, 14.64)	<0.01	
P for trend	0.32		0.32		0.05		0.07		

Note: analyses restricted to those with non-missing data for dietary intake at each age, type 2 diabetes and all covariates; SFA= saturated fatty acids; for all associations the reference category was Q1; Model a: adjusted for kcals, social class, education, physical activity, smoking history; Model b= as Model a + adjusted for BMI and waist circumference. * At age 36 n=856, at age43 n=1080, at age 53 n=668; ** At age 36 n=946, at age 43 n=1187, at age 53 n=809

Table 38. Associations between fibre density intake and type 2 diabetes at age 53 to 60-64 by BMI and WC at each age

	BMI					WC				
	<25		≥25			Low risk*		High risk**		
Tertile of fibre density intake	OR (95% CI)	P value	OR (95% CI)	P value	P value for interaction	OR (95% CI)	P value	OR (95% CI)	P value	P value for interaction
Age 36 (N=1804)	n=1224		n=580			n=1289		n=515		
<4.9	1		1			1		1		
4.9-6.2	0.89 (0.50, 1.58)	0.76	0.53 (0.30, 0.93)	0.02	0.02	0.67 (0.39, 1.11)	0.14	0.69 (0.38, 1.24)	0.22	0.82
>6.2	0.81 (0.43, 1.50)	0.55	0.44 (0.23, 0.83)	0.01		0.63 (0.35, 1.13)	0.12	0.50 (0.25, 0.99)	0.04	
Age 43 (N=2267)	n=1225		n=1042			n=1497		n=770		
<5.0	1		1			1		1		
5.0-6.6	0.81 (0.41, 1.61)	0.55	0.94 (0.62, 1.43)	0.79	0.79	1,02 (0.52, 1.84)	0.92	0.83 (0.53, 1.29)	0.42	0.47
>6.6	0.72 (0.34 1.53)	0.40	0.61 (0.37, 1.00)	0.05		0.88 (0.46, 1.69)	0.71	0.53 (0.30, 0.92)	0.02	
Age 53 (N=1477)	n=541		n=936			n=598		n=879		
<6.2	1		1			1		1		
6.3-8.2	3.61 (0.97, 13.42)	0.05	0.89 (0.55, 1.45)	0.66	0.02	2.09 (0.57, 7.59)	0.26	1.02 (0.63, 1.64)	0.92	0.33
>8.2	2.75 (0.64, 11.77)	0.17	0.39 (0.21, 0.73)	<0.01		2.09 (0.47, 9.30)	0.33	0.46 (0.25, 0.84)	0.01	

Note: analyses restricted to those with non-missing data for dietary intake at each age, type 2 diabetes and all covariates; all analyses adjusted for sex, kcals, social class, education, physical activity, smoking history; BMI and waist circumference. BMI=Body Mass Index; WC=waist circumference.

* Low risk category = Men: WC <94 cm; women: WC <80 cm; ** High risk category = Men: WC ≥94 cm; women: WC ≥ 80 cm (includes Very high risk category. Categories of WC were defined according to the National Institute for Health and Care Excellence (NICE) cut-offs for increased risk of type 2 diabetes (279).

Table 39. Associations between glycaemic index and type 2 diabetes at age 53 to 60-64 by BMI and WC at each age

	BMI					WC				
	<25		≥25			Low*		High**		
Tertile of mean daily GI	OR (95% CI)	P value	OR (95% CI)	P value	P value for interaction	OR (95% CI)	P value	OR (95% CI)	P value	P value for interaction
Age 36 (N=1804)	n=1224		n=580			n=1282		n=515		
<62.7	1		1			1		1		
62.7-66.0	1.05 (0.60, 1.84)	0.84	1.05 (0.54, 2.03)	0.87		1.14 (0.65, 1.98)	0.63	0.97 (0.50, 1.88)	0.93	
<66.0	0.68 (0.34, 1.35)	0.27	1.94 (1.01, 3.64)	0.04	0.02	0.92 (0.49, 1.73)	0.80	1.77 (0.92, 3.38)	0.08	0.27
Age 43 (N=2267)	n=1225		n=1042			n=1497		n=770		
<61.8	1		1			1		1		
>61.8-66.2	0.91 (0.43, 1.93)	0.81	1.87 (1.14, 3.08)	0.01		1.09 (0.60, 1.98)	0.75	1.94 (1.11, 3.40)	0.01	
>66.2	1.75 (0.87, 3.50)	0.11	1.51 (0.90, 2.51)	0.11	0.18	1.07 (0.57, 2.01)	0.81	2.01 (1.14, 3.52)	0.01	0.31
Age 53 (N=1477)	n=541		n=936			n=598		n=741		
<60.1	1		1			1		1		
60.1-63.7	1.10 (0.38, 3.20)	0.85	3.03 (1.73, 5.30)	<0.001		0.26 (0.05, 1.37)	0.11	3.22 (1.87, 5.54)	<0.001	
>63.7	1.57 (0.40, 6.16)	0.65	2.03 (1.03, 3.97)	0.03	0.49	3.05 (0.84, 11.01)	0.08	1.64 (0.83, 3.23)	0.14	0.46

Note: analyses restricted to those with non-missing data for dietary intake at each age, type 2 diabetes and all covariates; all analyses adjusted for sex, kcals, social class, education, physical activity, smoking history, BMI and waist circumference; BMI and waist circumference. BMI=Body Mass Index; WC=waist circumference, GI= glycaemic index.

* Low risk category = Men: WC <94 cm; women: WC <80 cm; ** High risk category = Men: WC ≥94 cm; women: WC ≥ 80 cm (includes Very high risk category. Categories of WC were defined according to the National Institute for Health and Care Excellence (NICE) cut-offs for increased risk of type 2 diabetes (279).

5.4 Discussion

5.4.1 Main findings

The main findings of this chapter are that dietary fibre and GI were associated with lower and higher later risk of type 2 diabetes (respectively), particularly in middle age. Greater dietary fat density, especially total fat rather than SFA was positively associated with type 2 diabetes risk, more so for women than for men.

The associations between dietary fibre and GI persisted after controlling for BMI and WC; however the effects of low fibre and high GI were stronger among overweight people and those with a raised WC.

1st and 2nd objective: To analyse the association between dietary fibre, GI and dietary fat intake at age 36, 43 and 53 years and to assess whether these association are mediated by BMI and WC.

It was hypothesised that low fibre intake, high GI and high fat and SFA intakes would be associated with increased risk of type 2 diabetes (1st hypothesis) and that associations would be partly meditated by BMI and WC, although direct associations would remain (2nd hypothesis). In support of the first hypothesis, at age 43 and 53 people who consumed more dietary fibre and had a low-GI diet were at reduced risk of type 2 diabetes incidence, with a significant dose-response trend across quintiles of intake for both fibre density and GI. Although weaker and mostly non-significant, associations for all dietary factors at age 36 followed a similar direction.

An interaction was found between dietary fats and sex, with the effect of both total fat density and SFA density being present only among women at age 43 and 53. A linear trend was observed across total fat quintiles while associations between SFA and diabetes were more inconsistent with no apparent trend. However, the confidence intervals in these associations were quite large, indicating lack of precision in the estimate. The difference in association between men and women is not readily explained. It might be the results of different eating patterns or it may be a consequence of the higher number of women in the sample at age 43 and particularly at age 53 (men 45.2%, women 54.8%).

For all dietary factors the associations were robust to adjustment for SEP, education, smoking and physical activity indicating minimal confounding. The associations were weakened by adjustment for BMI and WC, indicating a possible mediating effect of body weight and abdominal fat, as suggested in the literature. However, in agreement with the second hypothesis a direct association between fibre density, GI and fat (for women) and diabetes remained, especially when comparing extreme quintiles of intakes at age 43 and 53.

Thus, dietary factors seem to have a stronger association with type 2 diabetes during middle and late adulthood rather than during early adulthood. The weak association between fibre, GI and fats intake at age 36 and later diabetes is difficult to compare with previous studies since the majority of these analyses had a follow-up time of 10 years or less and used a sample of

middle-aged adults. It is possible that a 17-year follow-up might be too long to detect a diet-disease association since people are likely to change their diet during this period, especially in conjunction with important life events, such as starting a family or retirement. Indeed, as is clear from Figure 9, both men and women in the NSHD, on average, changed their dietary intakes with diet overall becoming healthier at age 53. Figure 10 suggests that while diet became healthier for the whole population, those who developed type 2 diabetes had less marked improvements. However, Figure 10 also shows that intakes of fibre density were already lower and GI was already higher at age 36 for those who did developed diabetes compared with those who did not, with the gap widening with age, especially between age 36 and 43. This suggests an accumulation pattern so that the effects of an adult life-long lower-fibre and higher-GI diet track and accumulate over time and become apparent from middle-age when diabetes starts to manifest as a clinical outcome, mainly because of the rising adiposity levels. Indeed this apparent pattern of accumulation seems to parallel those in chapters 3 and 4, with the negative effects of obesity and WC accumulating over time. It is also plausible that people improved their diet around age 53 to avert the negative consequences of overweight (partly fed by the high-GI, high-fat and low-fibre diet).

These findings are in agreement with several prospective studies reporting a strong inverse association between fibre intake and type 2 diabetes, independently of body weight (131, 137, 142, 145, 147, 162). These studies used mainly middle-aged white populations, thus paralleling the associations found in this chapter between diet at 43 or 53 years old and later diabetes incidence. As in most of these studies, in this chapter a linear trend was found across categories of fibre density; however, only the highest intake (the fourth, and once the mediating effects of BMI and WC were accounted for, only the fifth quintile) were significantly associated with diabetes. The median daily intake of dietary fibre in the highest quintile was 15.4g at age 36, 16g at age and 18.5g at age 53. The dietary reference value for the population using NSP as defined by the Englyst method (the same method used in this thesis) is 18g/day. Thus only the highest fifth of the population and only at age 53 reached adequate levels of intake for optimal disease prevention. This finding suggests that dietary fibre needs to be consumed in relatively large quantities to be significantly protective. This is in agreement with a dose-response meta-analysis (285) reporting a threshold effect for total dietary fibre, with only high intakes being significantly protective.

Consistent with this chapter, previous prospective studies and systematic reviews reported that people consuming high GI diets are at increased risk of type 2 diabetes (131, 137-142, 144, 146). However, in disagreement with these results some studies did not find a significant association (145-147). This could be due to differences in the sample age, sex and ethnicity as well as on carbohydrates and GI range of intakes. Furthermore, assignment of GI values differs according to the references used. The majority of studies used various forms of FFQs to measure diet. These questionnaires might not be appropriate to assess GI as they are not detailed enough to account for differences among subtypes of food items, which might belong to the same food category but have very different GI value.

A gender difference has not been demonstrated in other prospective studies reporting a positive association between dietary fat and diabetes (172-174). However, it is known that men and women metabolize and store dietary fat differently (324) and that men tend to oxidize more dietary fat than women (325). It is also possible that the lack of an association between fat and diabetes could be due to inaccurate dietary assessment as selective underreporting of dietary fat has been reported among obese men (175).

3rd objective: To investigate whether BMI and WC modifies the association between dietary factors and type 2 diabetes.

It was hypothesised that the positive association between GI and type 2 diabetes and the inverse relationship between fibre and diabetes would be stronger among overweight and obese people. In agreement with the third hypothesis the positive association between GI and incident type 2 diabetes was stronger among overweight and obese people than those with a normal BMI. This was particularly evident at age 36 and age 53. Indeed, for age 36 while non-stratified associations (Table 34) showed a weak effect of GI, when associations were stratified by BMI (Table 38) there was a 2-fold increased risk for the highest tertile compared with the lowest among overweight people. Similarly, the effect of GI was stronger among people with a raised WC, although no significant interactions were found. Among the high-risk WC category, even those in the second tertile of GI intake had significantly raised diabetes risk compared with the lowest tertile. It has been suggested that the adverse effect of a high-GI diet might increase with the level of insulin resistance, which is presumably higher in obese individuals and those with a larger WC (129, 282), although this could not be proved since insulin resistance was not measured directly.

Similarly, fibre density showed a stronger inverse association with incident type 2 diabetes in the overweight category than in those with normal BMI, with significant interactions at age 36 and 53. Among the high-risk WC category at age 43 and 53, those in the highest tertile of fibre intake had a significantly lower risk of diabetes compared with the lowest tertile, while no association was found among the low-WC group. These findings suggest that a low-GI, high-fibre diet has an important independent effect on type 2 diabetes incidence and might bring the greatest benefits to overweight individuals and those with a raised WC, who are more susceptible to type 2 diabetes because of their adiposity levels. Alternatively it could be possible that high BMI and WC were a consequence of a low-GI, high-fibre diet in the first place, since dietary choices tend to track over the life course; it is often difficult to untangle patterns of associations among variables that correlated and track simultaneously. These results are in agreement with some studies reporting a stronger effect of GI among overweight people (139, 142, 144), but in disagreement with others, that did not find a similar modifying effect of BMI (140, 141). In disagreement with the results in this chapter, one study (138) has reported that dietary fibre is more protective for type 2 diabetes among people with a BMI <25. These discrepancies are difficult to explain. They might be due to differences in age and ethnicity of the participants, although chance findings cannot be excluded.

5.4.2 Strengths

This chapter adds to the available literature a comprehensive analysis of key dietary factors that might be important contributors to increased type 2 diabetes risk, using data from a representative white British population.

One strength of this chapter is that, unlike most other prospective cohort studies, it uses diet diaries to assess dietary intake. Nearly all other studies rely on FFQ to assess dietary intake. The FFQ has been the preferred method in large-scale epidemiological studies because it is easy to administer, relatively inexpensive and less burdensome for study participants (289). However, FFQs are subject to significant measurement error that can affect the validity of diet-disease associations (234, 290). Over-reporting of certain foods, especially healthy foods, and recall bias can further reduce the validity of FFQs (234, 290). More detailed dietary assessment tools, such as prospectively recorded diet diaries, correlate significantly better with actual intakes as measured by biomarkers and are subject to substantially less regression dilution compared to FFQs (233, 291). Diet diaries are able to include individual's portion sizes, cooking methods and recipes, making them more precise than FFQs, which utilise 'generic' portion sizes, foods and recipes. To avoid misclassification and consequent attenuation of diet-disease associations, it is crucial to measure dietary exposure accurately; currently the use of diet records, although relatively expensive, is considered by some researchers as one of the most accurate tools for epidemiological studies.

Another strength of these analyses is that GI values were assigned based on a rigorous methodology, which was developed to calculate the GI of diets reported in food diaries of European study members taking part in the recently initiated Diogenes study (297). Where possible data sources were selected from the UK or from European studies. This ensured that the GI values in the NSHD were country-specific and as accurate as possible, which might explain the robust associations between GI and diabetes found in this chapter.

5.4.3 Limitations

Uncontrolled residual confounding remains a concern in all observational studies. Although more precise than FFQs, diet diaries can also be subject to measurement error and under- or over-reporting. Random error in dietary analyses usually tends to underestimate relative risk estimates and reduce power (310). This might have cause attenuation of some results, such as in fat-diabetes associations, as dietary fats are more likely to be underestimated.

Although effort was taken to ensure GI values were assigned in as a rigorous manner as possible, there remains some variability in the GI of many foods. GI is affected by many factors, such as the physical form of the food (i.e. the particle size), the methods of processing and preparation or the ripeness of fruit (311). The concomitant ingestion of protein and fat will also affect to some degree the GI of the meal, although studies have shown that the GI of mixed meals can be reliably calculated (298-301). Also for some foods there was no information available on their GI, therefore only estimates could be used. Nevertheless, the validity of the GI

values was relatively high: for more than 40% of foods the GI of an equivalent or similar item had been measured and only for 18% of the foods a nominal value had to be assigned.

As in previous chapters the analyses in this chapter were restricted to those with valid data for potential confounders (lifetime social class, educational attainment, smoking history, physical activity, BMI and WC). The number of participants with valid diet diaries was relatively low at age 53, a factor that might have decreased the power of the analyses, particularly stratified ones. However, significant associations were found for most dietary factors.

In addition to contributing to loss of power, the use of complete case analyses in this chapter might have resulted in bias. As is shown in Appendix 6 the sample with valid data for dietary intake was a healthier (i.e. less likely to be smoker and inactive) and more educated; this is not surprising considering the relatively high compliance necessary to compile diet diaries.

5.4.4 Conclusions

In conclusion, high dietary GI and low dietary fibre density were prospectively associated with increased type 2 diabetes risk independently of BMI and WC, supporting the view that these dietary factors have direct effects on type 2 diabetes incidence as well as indirect effects via body weight. The associations for dietary fibre density and dietary GI was more pronounced among overweight people and those with a larger WC, indicating that a low-fibre, high-GI diet might be particularly detrimental to those at greater risk of type 2 diabetes due to excess adiposity. Dietary fat and SFA seemed to be a more important risk factor for women. The next chapter will expand these results by using dietary pattern analyses to investigate the combined effect of dietary fibre, GI and dietary fat on incident type 2 diabetes and to identify food based guidance for reducing type 2 diabetes risk.

6 Chapter 6. Dietary patterns and type 2 diabetes

6.1 Introduction

Over the past decade, dietary pattern analyses have increasingly been used as an alternative method of studying associations between diet and disease risk. As stated in Chapter 1, dietary patterns may better describe the 'real world' eating habits of free-living people, where foods (and nutrients) are consumed together, and not in isolation (206). Separating the individual effects of single nutrients analyses is challenging, owing to the natural collinearity between dietary variables and their likely biologic interactions; looking at whole diets can help solve these problems, since potential synergistic effects of different nutrients are incorporated into the dietary pattern (210). Also, food-based dietary guidance is easier to interpret for the consumer than advice based on nutrients; therefore results from dietary patterns analyses might be more useful for public health recommendations.

Overall the literature suggests that dietary patterns defined as 'healthy' are associated with reduced type 2 diabetes risk (216-218, 220-229). These 'healthy' patterns have common characteristics: high intake of fruits, vegetables and wholegrain foods, and low consumption of red meat, added sugar and fried foods. Most of the evidence comes from studies that have used exploratory dietary pattern methods: either factor or cluster analyses (216, 223, 225-229) or diet quality scores (217, 218, 220-222, 224) and their limitations have been discussed in Chapter 1. The mechanisms or pathways between 'healthy' dietary patterns and type 2 diabetes risk are as yet, uncertain. Unlike factor and cluster analysis, RRR is a hypothesis-driven empirical method that allows exploration of possible biological pathways. Compared to exploratory methods, RRR has the advantage of combining a data-driven methodology with prior knowledge of the diet-disease relationship. The few studies that have so far applied RRR to examine diet and type 2 diabetes risk have mainly investigated dietary patterns related to inflammatory pathways (209, 230-232, 234). No study has used RRR to investigate dietary patterns characterised by dietary GI, fibre and fat intake, yet separately, these dietary factors have been linked with diabetes risk.

In chapter 5, the associations between type 2 diabetes risk and GI, fat and fibre intakes were analysed separately. These nutritional elements were hypothesised to be important determinants of later diabetes risk, both through their effect on body weight and independently through other pathways. However, as mentioned earlier, it is important to consider the synergistic effects of nutrients in the whole diet and to be able to give food-based rather than nutrient-based guidance to the public. Therefore, using RRR analyses, this chapter will investigate how the sum and interaction of these nutrients, as part of a dietary pattern, predict type 2 diabetes risk. Combinations of foods in dietary patterns studies have revealed stronger associations than single foods or nutrients studies (208). Therefore it is expected that dietary

patterns will show more robust and consistent associations with later type 2 diabetes risk than those presented in chapter 5.

Despite the increasing popularity of dietary patterns, most cohort studies use only a single measure of dietary intake at baseline. Only a few studies have used repeated dietary measurements to analyse individual changes in diet over time. These studies have investigated dietary patterns longitudinally either to assess stability of diet over time (326, 327) or to study the association between changes in dietary patterns and disease risk (328-331). Changes in diet over time may be due to alterations of dietary advice or food supply or they might be a consequence of major changes to life circumstances, such as pregnancy, altered health status or aging (332). It is important to study how these changes affect disease risk and to what extent changing diet at specific times in life will subsequently decrease or increase disease risk. So far most studies have focused on how diet affects change in BMI and obesity risk; to the author's knowledge no study has investigated how longitudinal changes in dietary patterns affect type 2 diabetes risk. This chapter will attempt to model how changes over adult life in the consumption of a high fat, high GI, low fibre dietary pattern affect the risk of type 2 diabetes and whether specific times of change are more important than others.

6.1.1 Research question

The main research question of this chapter is whether the consumption throughout adult life of a dietary pattern characterised by high GI, low fibre and high fat predicts type 2 diabetes risk in later life and how changes in scores for this pattern affect disease risk.

6.1.2 Objectives

1. To identify a dietary pattern characterised by high GI, low dietary fibre and high dietary fat
2. To assess how scores for this dietary pattern at age 36, 43 and 53 years predict type 2 diabetes incidence later in life
3. To ascertain to what extent the relationship between the derived dietary pattern and type 2 diabetes is mediated by BMI and WC
4. To investigate whether scores for the derived dietary pattern over the adult life course increase or decrease the risk of type 2 diabetes

6.1.3 Hypotheses

1. A higher score for a dietary pattern characterized by high GI, low dietary fibre, and high dietary fat is prospectively associated with higher odds of type 2 diabetes.
2. The association between the derived dietary pattern and type 2 diabetes will be mediated in part by BMI and waist circumference, since GI, fibre and fat can affect caloric intake, energy density and therefore body weight, which is a leading cause of type 2 diabetes. However, the association will not be entirely attenuated, since GI, fibre

and fat are hypothesised to affect type 2 diabetes through alternative biological pathways.

3. The risk of type 2 diabetes between age 53 and 64 years will be greater with greater increases in scores for the high fat, high GI, low fibre dietary pattern throughout adult life (from age 36 to age 53 years).

6.2 Methods

6.2.1 Explanatory variables

The main explanatory variables used in this chapter are z-scores quantifying intakes of a high fat, high GI, low fat dietary pattern at 36, 43 and 53 years. Details of how the dietary pattern and z-scores were derived are presented in section 6.2.4.1. A categorical variable converting score in quintiles of dietary pattern intake is used in prospective associations of dietary pattern and type 2 diabetes. Details of the dietary assessment method are given in chapter 2.

6.2.2 Outcome variables

The main outcome used in this chapter is the main outcome of this thesis, risk of type 2 diabetes between age 53 and 60-64 years. This is described in more detail in Chapter 2

6.2.3 Potential confounding variables

The potential confounders variables included in this chapter were the same as for chapter 5: SEP, education, smoking history and physical activity. The justification for each of these factors parallel that for confounding factors in the dietary factors-type 2 diabetes associations, details of which have been given in chapter 5. As in the previous chapter, BMI and WC were considered as mediators, since one of the objectives of this chapter was to assess the extent to which dietary patterns affect diabetes risk through body weight and abdominal fat accumulation.

SEP was based on lifetime socio-economic position based on the head of the household's occupational social class at age 15-53 years and highest level of educational qualification achieved by age 26 years. Self-reported measures of leisure time physical activity at 36, 43 and 53 years were used as potential confounders. Three categorical variables of smoking history up to 36, 43 or 53 were used as measures of cumulative smoking damage. More detailed descriptions of the potential confounding measures used in this chapter are given in Chapter 2.

6.2.4 Statistical analyses

6.2.4.1 Deriving dietary patterns

RRR was applied to identify a dietary pattern characterised by dietary GI, fibre density and fat density. RRR is a statistical method that derives dietary patterns by extracting successive linear

combinations of predictor variables (food groups) that explain as much variation as possible in another set of response variables. The response variables are hypothesised to be on the pathway between the predictor variables (food intake) and the outcome of interest (type 2 diabetes). Dietary GI, fibre density and fat density were chosen as the response variables because they are hypothesised to be important determinants of the risk of type 2 diabetes (explained in more detail in Chapter 1 and explored in Chapter 5). The function PROC PLS in the software SAS was used to conduct all RRR analyses.

The RRR model included 45 food groups (Table 40) as predictor variables (coded as g consumed per day) and dietary GI, fibre density and fat density as response variables. The procedure for calculating the GI for each food is explained in more details in Chapter 5.

Because there were some differences in the intakes of the response variables between men and women the dietary patterns were initially created for men and women separately. The patterns derived were substantially similar. Therefore a dietary pattern based on men and women combined was subsequently used.

Initially exploratory RRR analyses were conducted separately at each age. RRR derives as many dietary patterns as there are response variables, which in this case were three. Characteristics of the three dietary patterns first derived at age 36, 43 and 53 are outlined in Table 41. At all ages the first dietary pattern derived from RRR analyses explained the greatest variation in all three response variables (total variation accounted for was 29.8% at age 36, 31.8% at age 43 and 37.9% at age 53) compared with the second and third patterns, which explained around 12-15% and 5% respectively. Therefore, only the first dietary pattern was analysed further. This dietary pattern was very similar at all ages: at age 43 and 53 it was negatively associated with dietary fibre density (r=-0.73 at age 43, r=-0.70 at age 53) and positively associated with fat density (r=0.37 at age 43, r=0.44 at age 53) and GI (r=0.56 at age 43, r=0.55 at age 53). At age 36 the correlations were similar but in the opposite direction (high fibre and low GI). Factors loadings for the first dietary pattern extracted at age 36, 43 and 53 are shown in Appendix 9 and 10 and Figure 11.

To assess longitudinal associations between dietary patterns and type 2 diabetes a score for exactly the same dietary pattern (based on the same covariance matrix) at 36, 43 and 53 years was required. To achieve this confirmatory RRR analyses (236) were used to calculate dietary pattern scores at 36 and 43 years of age using scoring weights from the first dietary pattern identified at 53 years (which explained the greater variation in response variables). Each study member received a score calculating the degree to which their dietary intake reflected this dietary pattern at age 36, 43 and 53.

6.2.4.2 Descriptive and regression analyses

Descriptive analyses compared proportion of people diagnosed with type 2 diabetes between age 53 and 60-64 and selected nutrients intakes according to quintiles of the dietary pattern score. Associations of potential confounders with dietary pattern scores and outcome were then

examined using tests for trend and t test.

Multivariable logistic regression models were used to examine prospective associations between quintiles of dietary pattern scores and type 2 diabetes risk between age 53 and 64 years. There was no interaction between the dietary pattern score and gender at age 36 (p=0.85) and 53 (p=0.14) but a significant interaction at age 43 (p=0.01). The data were then analysed together for all ages and subsequently stratified by sex at age 43. Sequential adjustments were made for caloric intake, sex, socio-economic status, educational attainment, smoking and exercise. Additional models were adjusted for BMI and WC.

Changes in dietary pattern scores over the period between age 36 and 53 were obtained by subtracting the score at age 36 from the score at 53. These steps were repeated to obtain the change in score between age 36 and 43 and between age 43 and 53. These change score were plotted graphically to allow visual inspection. A conditional model of change (272) was used to estimate the association between periods of changes in dietary pattern scores and the odds of type 2 diabetes. Dietary pattern scores change for the periods 36–53, 36–43 and 43–53 years were calculated conditional on earlier score using the residual method, which has been described in chapter 3. These residuals were fitted in the same models, adjusting for energy intake, socio-economic status, educational attainment, smoking and physical activity. Additional models were adjusted for conditional BMI and conditional WC change. Interactions between sex and dietary pattern change were tested. There was a significant interaction between the dietary pattern score change at age 36-43 and 36-53 and sex (p=0.01) therefore analyses were presented separately for men and women.

6.2.5 Study population

All analyses were restricted to those with valid information for type 2 diabetes status. In prospective analyses the dietary pattern and type 2 diabetes, models were restricted to study members with valid data for dietary intake and for all confounders and mediators (SEP, education, smoking, exercise, BMI, WC). The final number was different depending on the year of the dietary assessment (N=1804 for age 36; N=2267 for age 43; N=1478 for age 53). For longitudinal analyses of changes in dietary pattern score, analyses were restricted to those with valid data for all three dietary collection years and all confounders (N=1180).

6.3 Results

6.3.1 Descriptive analyses of dietary patterns

Dietary patterns analyses were initially identified in the 1760 study members for whom diet diaries were available at age 53 years. Factor loadings for the high fat, high GI, low-fibre dietary pattern identified at age 53 are shown in Figure 11. A positive factor loading indicated that as the intake of that food increased, so did the dietary pattern score; whereas, foods with a negative factor loading decreased the score. The dietary pattern was characterised by low intake of fruit, vegetables, low-fat yogurt, wholemeal bread, high-fibre cereals and high intakes

of white bread, processed meat, fried potatoes, butter and animal fat and added sugar (Figure 11). A detailed description of the foods groups included in the dietary pattern is given in Table 40. Fifty-seven percent of the variation in dietary pattern score was explained by the top five and bottom five factor loadings, with fresh fruit explaining the most variation (23%), then white bread (8%), vegetables (6%), low-fat yogurt (5%), and processed meat (4%).

Confirmatory dietary pattern analyses were applied to the diet diaries completed at age 36 (n=2441) and 43 years (n=3187) of age. Table 42 shows the proportion of people diagnosed with type 2 diabetes between age 53 and 60-64 and the nutritional characteristics of the dietary pattern at age 36, 43 and 53 years. At all ages those with higher scores for the high fat, high GI, low fibre dietary pattern had higher intakes of energy (kcal), total fat and protein density, a greater average daily GI and lower intakes of dietary fibre density. Those with higher scores for the dietary pattern also consumed less carbohydrates density and more alcohol except for age 36. The distributions of fat, fibre and GI, to some extent, changed with age. The diet of the NSHD population appears to be becoming healthier on average. For example, those in the top quintile for the dietary pattern had a median daily fibre density of 4.3g (SD=1.6), an average daily fat density of 45.1g (SD=4.9) and an average daily GI of 66.5 (SD=2.9) at age 36 compared to respectively 5.5g (SD=1.5), 42.3g (SD=5.9) and 64.9 (SD=3.5) at age 53 (Table 42).

6.3.2 Investigation of potential confounders/mediators

Table 43 shows associations between possible confounding variables and dietary patterns z-scores at age 36, 43 and 53. A negative score signifies a ‘healthier’ diet. Men and those from a lower socio-economic class and with lower educational attainments had higher scores for the high fat, high GI, low fibre dietary pattern at all ages. Lifetime smokers and less active people had all significantly higher dietary pattern scores at all ages. There was a significant trend for z-scores at all ages to increase with higher WC tertiles. The association between BMI categories and dietary patterns was less clear; at all ages obese individuals had the lowest z-score for dietary pattern at age 36; those within the normal BMI category at age 43 and 53 had the lowest negative scores at age 43 and 53, but overweight people tended to have higher z-scores than the obese at age 43. This could be due to underreporting among the severely obese or it could be due to the smaller number of obese people compared with overweight, especially at age 36. Alternatively it could be possible that those people who were obese from a younger age had already modified their diet as a consequence of their weight.

Table 40. Description of food groups included in the dietary pattern analyses

Food group name	Foods included
Pizza	Pizza
Pasta	Pasta & pasta dishes
Rice	Rice & rice dishes
Cereals_other	Cereals other than pasta, bread and rice
High-fibre cereals	Breakfast/oat cereals with fibre content equal or >3g/40g portion;
Low-fibre cereals	Low-fibre cereals and breakfast bars
White bread	White bread
Wholemeal bread	Wholemeal, granary and brown bread
Crisp & other bread	Crisp bread (e.g. Rivita, grissini) and other bread
Biscuit, pastry, cakes	Biscuits, pastries, buns, pies and cakes
Whole milk	Whole milk (cow or goat)
Skimmed milk	Skimmed milk, semi-skimmed milk and milk 1%
Low-fat dairy desserts	Low fat dairy desserts, low-fat ice-cream and flavoured milk
Full-fat yogurt	Full-fat yogurt
Low-fat yogurt	Low-fat yogurt
Full fat dairy dessert	Full fat dairy desserts, ice-cream and milk pudding
Cream	Cream
Butter and animal fat	Butter and animal fat
Cheese	Cheese
Eggs	Eggs
Oils	Oils
Plant fat solid	Plant based fats (solid)
Plant fat solid low fat	Plant based fats (solid) reduced-fat and low-fat
Fish	White fish, oily fish and shellfish
Red meat, offal	Beef, lamb, pork and other red meat (including dishes)
White meat	Chicken, turkey and other game birds (including dishes)
Processed meat	Bacon, ham, meat pies, sausages and other processed meats
Vegetables	Raw and cooked vegetables
Pulses	Pulses, lentils and baked beans
Fruit	Fresh, canned and dried fruits
Potatoes	Potatoes (not fried or roasted)
Fried potatoes	Fried and roasted potatoes
Nuts and seeds	Nuts and seeds (including peanut butter)
Soups	Canned, fresh and dried soup
Dressing & sauces	Dressings, mayonnaise, cooking sauces and other sauces
Jam and chutney	Jam, marmalade, chutney and pickles
Table sugar	Sucrose
Honey and syrup	Honey, syrup and other sugars (not pure sugar)
Confectionery	Chocolate products, sugar-based products, sorbets and lollies
Savoury snacks	Savoury biscuits, crackers, potato-, cereal- and vegetable-based snacks
Alcoholic drinks	Wine, beer, spirits, Alco pops
Squashes & juices	Squashes & fruit concentrate, fruit juice drinks
Pure fruit juice	Pure fruit juice and smoothies
Soft drinks	Carbonated soft drinks
Coffee & tea	Coffee, tea, powdered beverages (e.g. ovaltine)

Table 41. Characteristics of the 3 RRR-derived exploratory dietary patterns at age 36, 43 and 53

Dietary patterns at age 36

Per cent Variation Accounted for in the response variables

Dietary pattern	Fibre Density*	Fat Density*	GI	Total variation accounted for
1	38.2	1.9	49.4	29.8
2	40.8	47.3	49.4	15.9
3	50.1	47.9	57.4	5.9

Correlation coefficients for Response variables

Dietary pattern	Fibre Density*	Fat Density*	GI
1	0.65	0.14	-0.74
2	-0.23	0.97	-0.01
3	0.72	0.18	0.66

Dietary patterns at age 43

Per cent Variation Accounted for in the response variables

Dietary pattern	Fibre Density*	Fat Density*	GI	Total variation accounted for
1	51.7	13.7	29.9	31.8
2	53.4	48.0	35.2	13.7
3	59.1	48.3	42.9	4.5

Correlation coefficients for Response variables

Dietary pattern	Fibre Density*	Fat Density*	GI
1	-0.73	0.37	0.56
2	0.19	0.91	-0.35
3	0.64	0.15	0.74

Dietary patterns at age 53

Per cent Variation Accounted for in the response variables

Dietary pattern	Fibre Density*	Fat Density*	GI	Total variation accounted for
1	56.2	22.2	35.2	37.9
2	56.7	48.7	45.4	12.3
3	64.9	50.2	52.3	5.5

Correlation coefficients for Response variables

Dietary pattern	Fibre Density*	Fat Density*	GI
1	-0.70	0.44	0.55
2	0.11	0.84	-0.52
3	0.70	0.30	0.64

*= g/1000kcal; GI= glycaemic index

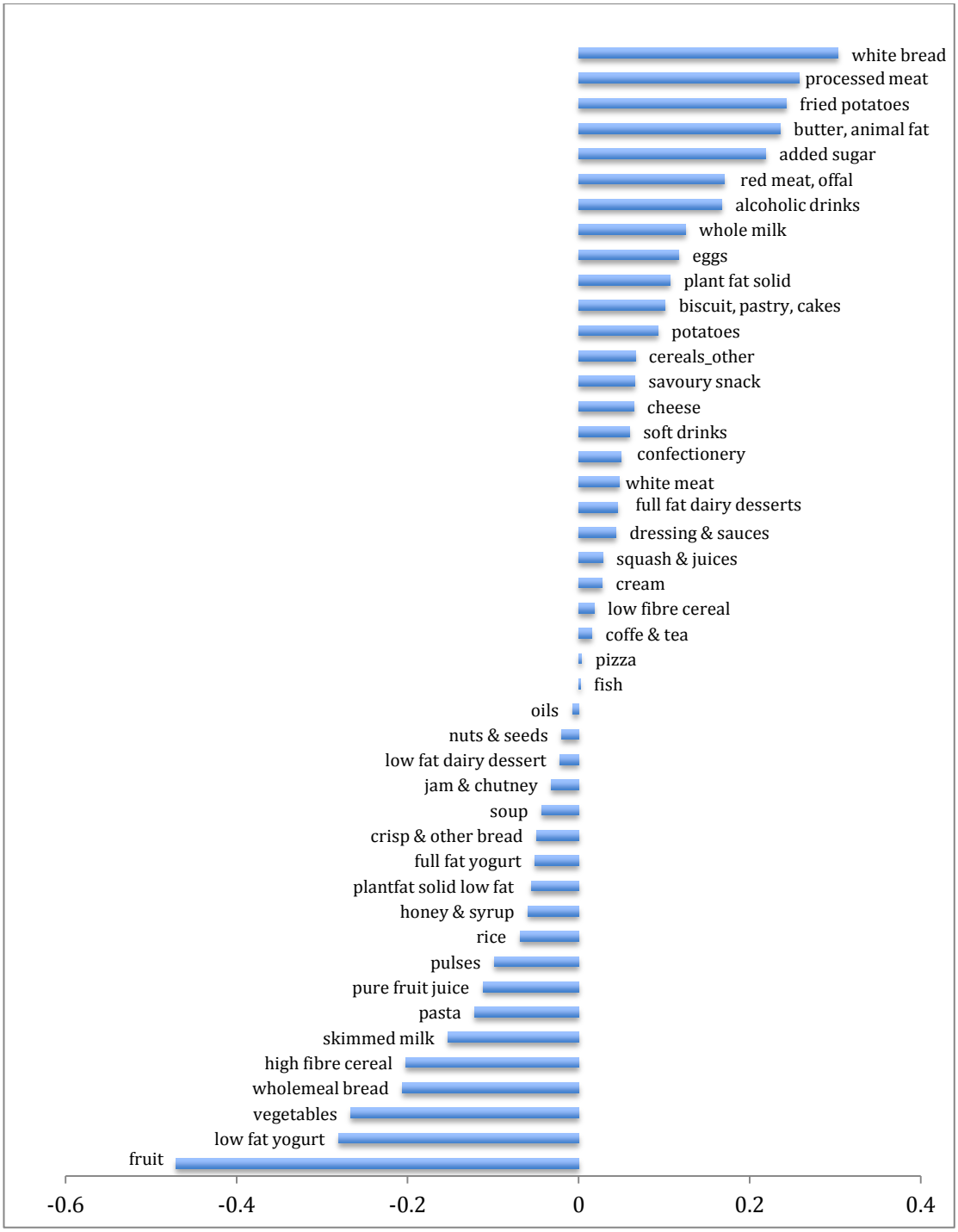


Figure 11. Factor loadings for the high-fat, high-GI, low-fibre dietary pattern at age 53 used in confirmatory dietary pattern analyses

Table 42. Mean (SD) or median (IQR) nutrient intakes by quintile of high-fat, high-GI, low-fibre dietary pattern z-score

	Quintile of dietary patterns z-score					
	1	2	4	3	5	p-value
Age 36						
n	361	489	489	488	488	
Diabetes[a] (%)	7.7	9.7	8.8	10.2	10.2	0.24
Energy, kcal	1785 ± 569	1940 ± 574	2004 ± 550	2065 ± 551	2373 ± 679	<0.001
Fat density*	41.6 ± 5.9	43.7 ± 5.4	44.3 ± 5.9	44.6 ± 5.2	45.1 ± 4.9	<0.001
CHO density*	110.8 ± 16.1	107.5 ± 16.1	109.0 ± 15.5	109.6 ± 14.7	110.6 ± 14.3	0.47
Protein density*	41.3 ± 10.2	37.5 ± 6.8	36.2 ± 6.5	35.9 ± 5.4	33.7 ± 4.5	<0.001
Alcohol (Median±IQR)	5.5 ± 15.3	6.7 ± 17.7	7.5 ± 18.0	8.2 ± 21.4	6.2 ± 21.3	0.34
Fibre density* (Median±IQR)	8.4 ± 3.4	6.6 ± 2.3	5.7 ± 2.0	5.1 ± 2.	4.3 ± 1.6	<0.001
GI	61.3 ± 10.0	63.1 ± 3.8	64.4 ± 3.3	65.5 ± 3.6	66.5 ± 2.9	<0.001
Age 43						
n	454	453	454	453	453	
Diabetes[a] (%)	7.9	6.6	10.5	10.1	12.1	<0.01
Energy, kcal	1833 ± 567	1934 ± 568	2078 ± 571	2129 ± 569	2424 ± 708	<0.001
Fat density*	38.6 ± 7.3	41.7 ± 5.6	43.3 ± 5.6	44.9 ± 5.7	46.5 ± 5.1	<0.001
CHO density*	118.2 ± 19.4	112.1 ± 15.4	109.7 ± 16.7	106.5 ± 15.3	106.6 ± 14.7	<0.001
Protein density*	41.6 ± 9.6	38.7 ± 7.1	37.2 ± 6.6	36.2 ± 5.6	34.4 ± 5.1	<0.001
Alcohol (Median±IQR)	5.4 ± 15.9	7.7 ± 18.0	6.4 ± 17.6	6.1 ± 17.3	6.8 ± 15.9	0.04
Fibre density* (Median±IQR)	7.6 ± 2.8	6.0 ± 2.0	5.6 ± 1.6	5.1 ± 1.2	4.6 ± 1.1	<0.001
GI	60.4 ± 4.8	63.0 ± 4.7	63.8 ± 4.5	65.1 ± 4.2	66.8 ± 3.8	<0.001
Age 53						
n	296	296	295	296	295	
Diabetes[a] (%)	5.7	7.4	7.4	11.4	13.2	<0.001
Energy, kcal	1867 ± 476	1913 ± 456	1999 ± 474	2031 ± 501	2117 ± 514	<0.001
Fat density*	32.6 ± 6.8	36.1 ± 5.6	38.8 ± 5.7	39.4 ± 5.4	42.3 ± 5.9	<0.001
CHO density*	131.7 ± 19.7	123.5 ± 14.7	118.1 ± 17.6	114.1 ± 16.9	109.3 ± 19.1	<0.001
Protein density*	42.1 ± 7.7	41.5 ± 6.6	39.4 ± 6.4	38.6 ± 6.2	37.9 ± 6.4	<0.001
Alcohol (Median±IQR)	7.5 ± 17.4	8.1 ± 17.5	9.7 ± 21.9	12.3 ± 25.6	9.2 ± 26.6	<0.001
Fibre density* (Median±IQR)	9.8 ± 3.3	8.2 ± 2.3	7.0 ± 2.1	6.4 ± 1.9	5.5 ± 1.5	<0.001
GI	58.8 ± 3.5	60.3 ± 3.2	61.6 ± 3.3	63.5 ± 3.3	64.9 ± 3.5	<0.001

Note: analyses restricted to those with non-missing data for dietary intake at each age, type 2 diabetes and all covariates. Values are mean (SD) unless specified; p-value for trend across quintiles of dietary pattern score; a= type 2 diabetes diagnosed between age 53 and 60-64; *= g/1000kcal; CHO=carbohydrates; GI= glycaemic index;

Table 43. Associations between potential confounders/mediators and dietary patterns z-scores at age 36, 43 and 53

		Dietary pattern z-score		
	n	36 year	43 year	53 years
Sex				
Male	632	0.29 (0.9)	0.26 (1.0)	0.25 (0.9)
Female	765	-0.39 (0.8)	-0.36 (0.8)	-0.36 (0.9)
P-value		*<0.001*	*<0.001*	*<0.001*
Socioeconomic position				
I professional	112	-0.39 (0.9)	-0.31 (0.8)	-0.18 (0.9)
II intermediate	514	-0.22 (0.9)	-0.20 (0.9)	-0.20 (0.9)
III skilled (Non-Manual)	351	0.14 (0.9)	0.09 (0.9)	-0.22 (0.9)
III skilled (Manual)	206	0.24 (0.9)	0.22 (1.0)	0.37 (1.0)
IV partly skilled	149	0.07 (1.0)	0.08 (1.0)	0.05 (1.0)
V unskilled	59	0.22 (0.9)	0.34 (0.9)	0.02 (0.9)
P-value (trend)		*<0.001*	*<0.001*	*<0.001*
Education attained by age 26				
None attempted	379	0.32 (0.9)	0.27 (0.9)	0.19 (0.9)
Intermediate	394	0.30 (0.9)	0.09 (0.9)	-0.15 (1.0)
Highest	562	-0.27 (0.9)	-0.31 (0.9)	-0.23 1.0)
P-value (trend)		*<0.001*	*<0.001*	*<0.001*
BMI (kg/m2) at age 36				
Underweight or normal	983	-0.12 (0.9)		
Overweight	340	0.08 (1.0)		
Obese	60	-0.40 (0.9)		
P-value (trend)		*0.24*		
BMI (kg/m2) at age 43				
Underweight or normal	806	-0.12 (0.9)	-0.17 (0.9)	
Overweight	448	0.09 (0.9)	0.10 (0.9)	
Obese	133	-0.40 (1.0)	-0.11 (1.0)	
P-value (trend)		*0.85*	*<0.01*	
BMI (kg/m2) at age 53				
Underweight or normal	511	-0.13 (0.9)	-0.18 (0.9)	-0.20 (1.0)
Overweight	597	0.01 (0.9)	0.01 (1.0)	-0.02 (1.0)
Obese	276	-0.21 (1.0)	-0.07 (0.9)	0.00 (0.9)
P-value (trend)		*0.71*	*0.05*	*<0.01*
Waist circumference age 36				
Lowest tertile	538	-0.34 (0.8)		
Middle tertile	446	0.07 (0.9)		
Highest tertile	387	0.11 (1.0)		
P-value (trend)		<0.001		
Waist circumference age 43				

Lowest tertile	568	-0.30 (0.8)	-0.36 (0.8)	
Middle tertile	423	-0.00 (0.9)	0.05 (1.0)	
Highest tertile	355	0.15 (1.0)	0.20 (1.0)	
P-value (trend)		<0.001	<0.001	
Waist circumference age 53				
Lowest tertile	537	-0.28 (0.8)	-0.33 (0.9)	-0.37 (1.0)
Middle tertile	464	-0.01 (0.9)	-0.00 (0.9)	-0.02 (0.9)
Highest tertile	389	0.11 (1.0)	0.18 (1.0)	0.23 (0.9)
P-value (trend)		<0.001	<0.001	<0.001
Lifetime smoking trajectory				
Never smoker	442	-0.27 (0.8)	-0.22 (0.9)	-0.29 (0.9)
Predominantly non-smoker	528	-0.18 (0.9)	-0.17 (1.0)	-0.20 (1.0)
Predominantly smoker	257	0.21 (0.9)	0.12 (0.9)	0.15 (0.9)
Lifelong smoker	145	0.32 (0.9)	0.34 (0.9)	0.59 (0.9)
P-value (trend)		*<0.001*	*<0.001*	*<0.001*
Exercise at age 36				
Inactive	475	-0.00 (0.9)		
Less active	358	0.04 (0.9)		
Most active	563	-0.22 (0.9)		
P-value (trend)		<0.001		
Exercise at age 43				
Inactive	674		0.05 (0.9)	
Less active	364		-0.16 (1.0)	
Most active	359		-0.23 (1.0)	
P-value (trend)			<0.001	
Exercise at age 53				
Inactive	643			0.07 (1.0)
Less active	279			-0.07 (0.9)
Most active	473			-0.30 (1.0)
P-value (trend)				<0.001

Note: analyses restricted to those with non-missing data for dietary patterns scores at age 36, age 43 and age 53; maximum available sample size used with each indicator; educational attainment was categorised as none (none attempted), intermediate (GCE 'O' level or Burnam C or lower) or highest (GCE A level or Burnam B or higher); exercise at age 43 was coded as inactive (no participation), moderately active (participated one to four times) and most active (participated five or more times) per month. P-value=t test or ANOVA

6.3.3 Prospective associations between dietary patterns and type 2 diabetes

Prospective associations between dietary pattern scores at age 36, 43 and 53 and type 2 diabetes diagnosed between 53 and 60-64 years are shown in Table 44. In models only adjusted for energy intake and sex, at all ages there was an increasing trend in type 2 diabetes risk observed with increasing quintile of the high fat, high GI, low fibre dietary pattern score (Model 1, p for trend <0.05 at age 36, <0.001 at age 43 and <0.01 at age 53). Following adjustments for lifestyle and social confounders associations were no longer significant at age 36 (Model 3). After adjustment for BMI associations between the highest quintile of intake and diabetes were no longer significant at age 43 but significant trends across quintiles persisted (Model 4). After further adjustment for WC associations were weakened but remained significant at age 53 (OR=2.35, 95% CI 1.14, 4.87, p=0.02) (Model 5).

Modification by sex was investigated and significant interactions were observed between dietary pattern score and sex on diabetes but only at age 43 (p=0.01); therefore analyses were also presented by sex (Table 45). While no effect for the high-fat low-fibre high-GI dietary pattern was observed among men at age 43, among women there was a strong relationship between higher scores and type 2 diabetes incidence, which persisted after adjustment for BMI and WC (p for trend <0.01).

6.3.4 Longitudinal changes in dietary pattern scores and type 2 diabetes

Table 46 shows the mean change in scores for the high fat, high GI, low fibre dietary pattern during the follow-up period. On average, dietary pattern scores for the whole population decreased between age 36 and 53 years. There were no significant differences in average score change between men and women, although men tended to decrease their scores for the dietary pattern steadily, while on average, women increased it between 36 and 43 years and decreased it between 43 and 53 years. People who developed type 2 diabetes between age 53 and 60-64 increased their dietary pattern scores (on average) during both periods, with an overall change between age 36 and 53 of 0.26, compared to a change of -0.06 for the rest of the sample (p <0.01). Figure 12 shows that the difference in mean dietary pattern score change from age 36 to 43 (and consequently from age 36 to 53) between those who later developed diabetes and those who did not, was stronger in women than men.

A significant interaction was observed between dietary pattern score change from age 36-43 years and sex on diabetes (p=0.01) therefore analyses were presented by sex. Multivariable regression models (Table 45) showed that changes in dietary pattern scores between age 36 and 43 and between age 43 and 53 were significantly associated with type 2 diabetes risk among women but not men. After adjustment for BMI change, dietary pattern change at age 43-53 was no longer significant while change at age 36-43 remained borderline significant. However, long-term change between age 36 and 53 remained significantly associated with type 2 diabetes in all models among women: for a 1 SD unit increase in score between age 36 and 53, the OR for type 2 diabetes 1.62 (95% CI: 1.10, 2.39).

Table 44. Associations at each age between a high fat, high GI, low fibre dietary pattern z-score and type 2 diabetes between age 53 and 60-64

	Model 1		**Model 2**		**Model 3**		**Model 4**		**Model 5**	
	Adjusted for kcal intake and sex		As Model 1 + SEP and education		As Model 2 + physical activity, smoking history		As Model 3 + BMI		As Model 4 + WC	
Quintiles of dietary pattern intake	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age 36 (N=1804)										
Q2	1.24 (0.72, 2.12)	0.43	1.24 (0.72, 2.12)	0.43	1.24 (0.72, 2.13)	0.43	1.43 (0.82, 2.50)	0.43	1.41 (0.81, 2.47)	0.22
Q3	1.08 (0.61, 1.90)	0.77	1.07 (0.61, 1.89)	0.79	1.03 (0.58, 1.82)	0.90	1.11 (0.62, 1.99)	0.90	1.09 (0.61, 1.96)	0.75
Q4	1.52 (0.88, 2.61)	0.12	1.51 (0.87, 2.61)	0.13	1.44 (0.83, 2.51)	0.18	1.55 (0.88, 2.73)	0.18	1.51 (0.85, 2.66)	0.15
Q5	1.84 (1.03, 3.22)	0.03	1.79 (0.98, 3.27)	0.05	1.62 (0.88, 2.98)	0.11	1.75 (0.93, 3.29)	0.11	1.72 (0.91, 3.22)	0.09
P for trend	0.03		0.04		0.10		0.09		0.10	
Age 43 (N=2267)										
Q2	0.92 (0.56, 1.50)	0.74	0.91 (0.55, 1.49)	0.71	0.85 (0.51, 1.40)	0.53	0.87 (0.52, 1.46)	0.61	0.88 (0.53, 1.47)	0.63
Q3	1.46 (0.92, 2.33)	0.10	1.44 (0.91, 2.30)	0.11	1.35 (0.84, 2.16)	0.20	1.33 (0.82, 2.16)	0.23	1.29 (0.80, 2.10)	0.28
Q4	1.52 (0.94, 2.43)	0.08	1.47 (0.91, 2.38)	0.11	1.34 (0.82, 2.18)	0.23	1.36 (0.83, 2.25)	0.21	1.33 (0.80, 2.20)	0.25
Q5	2.09 (1.30, 3.37)	<0.01	1.93 (1.21, 3.24)	<0.01	1.67 (1.00, 2.77)	0.04	1.55 (0.92, 2.62)	0.09	1.52 (0.90, 2.57)	0.11
P for trend	<0.001		<0.01		0.01		0.03		0.04	
Age 53 (N=1477)										
Q2	1.47 (0.74, 2.92)	0.26	1.45 (0.73, 2.89)	0.28	1.46 (0.73, 2.91)	0.27	1.62 (0.79, 3.38)	0.18	1.60 (0.77, 3.30)	0.20
Q3	1.98 (1.03, 3.82)	0.03	1.94 (1.01, 3.75)	0.04	1.94 (1.00, 3.75)	0.04	1.68 (0.83, 3.35)	0.14	1.67 (0.83, 3.37)	0.14
Q4	2.32 (1.21, 4.43)	0.01	2.25 (1.17, 4.31)	0.01	2.23 (1.16, 4.31)	0.01	2.21 (1.10, 4.44)	0.02	2.15 (1.06, 4.32)	0.03
Q5	2.81 (1.46, 5.44)	<0.01	2.67 (1.36, 5.24)	<0.01	2.68 (1.35, 5.34)	<0.01	2.42 (1.17, 4.88)	0.01	2.36 (1.14, 4.87)	0.02
P for trend	<0.01		<0.01		<0.01		0.01		0.01	

Note: analyses restricted to those with non-missing data for dietary intake at each age, type 2 diabetes and all covariates; SEP=socioeconomic position; BMI= body mass index; WC=waist circumference; for all associations the reference category was Q1

Table 45. Associations between dietary pattern z-score at age 43 and type 2 diabetes at age 53 to 60-64 by sex

Age 43 (N=2267)

	Model a		Model b		Model a		Model b		
Quintiles of dietary pattern z-score	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	P value for interaction
	Men (n=1080)				**Women (n=1187)**				
Q2	0.61 (0.33, 1.13)	0.17	0.64 (0.34, 1.22)	0.18	1.33 (0.51, 3.47)	0.55	1.31 (0.49, 3.48)	0.58	
Q3	0.88 (0.49, 1.60)	0.58	0.89 (0.48, 1.65)	0.73	2.99 (1.28, 7.01)	0.01	2.63 (1.10, 6.38)	0.02	
Q4	0.91 (0.49, 1.71)	0.99	0.87 (0.45, 1.66)	0.68	2.81 (1.18, 6.66)	0.01	2.81 (1.16, 6.79)	0.02	0.01
Q5	0.89 (0.45, 1.73)	0.87	0.91 (0.46, 1.80)	0.79	4.03 (1.64, 9.85)	<0.01	3.36 (1.32, 8.52)	0.01	
P for trend	0.88		0.94		<0.01		<0.01		

Note: analyses restricted to those with non-missing data for dietary intake, type 2 diabetes and all covariates; for all associations the reference category was Q1; Model a: adjusted for kcals, occupational class, education, physical activity, smoking history; Model b= as Model a + adjusted for BMI and waist circumference.

Table 46. Mean change (95%CI) in dietary pattern z-score according to sex and type 2 diabetes diagnosed between age 53 and 60-64

		Change in dietary pattern z-score		
		36 to 43 years	**43 to 53 years**	**36 to 53 years**
	N	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Whole sample	1180	-0.006 (-0.066 – 0.052)	-0.022 (-0.082 – 0.037)	-0.029 (-0.092 – 0.037)
By sex				
Men	525	-0.036 (-0134 – 0.061)	-0.046 (-0.143 – 0.050)	-0.082 (-0.182 – 0.017)
Women	655	0.015 (-0.059 – 0.090)	-0.003 (-0.079 – 0.072)	0.011 (-0.069 – 0.093)
P-value		0.40	0.49	0.14
By type 2 diabetes				
Not diabetic	1074	-0.025 (-0.087 – 0.036)	-0.034 (-0.097 – 0.028)	-0.060 (-0.125 – 0.005)
Diabetic	106	0.170 (-0.052 – 0.393)	0.096 (-0.109 – 0.301)	0.266 (0.036 – 0.496)
P-value		0.05	0.21	<0.01

Note: analyses restricted to those with non-missing data for dietary intake, type 2 diabetes and all covariates; CI=confidence interval

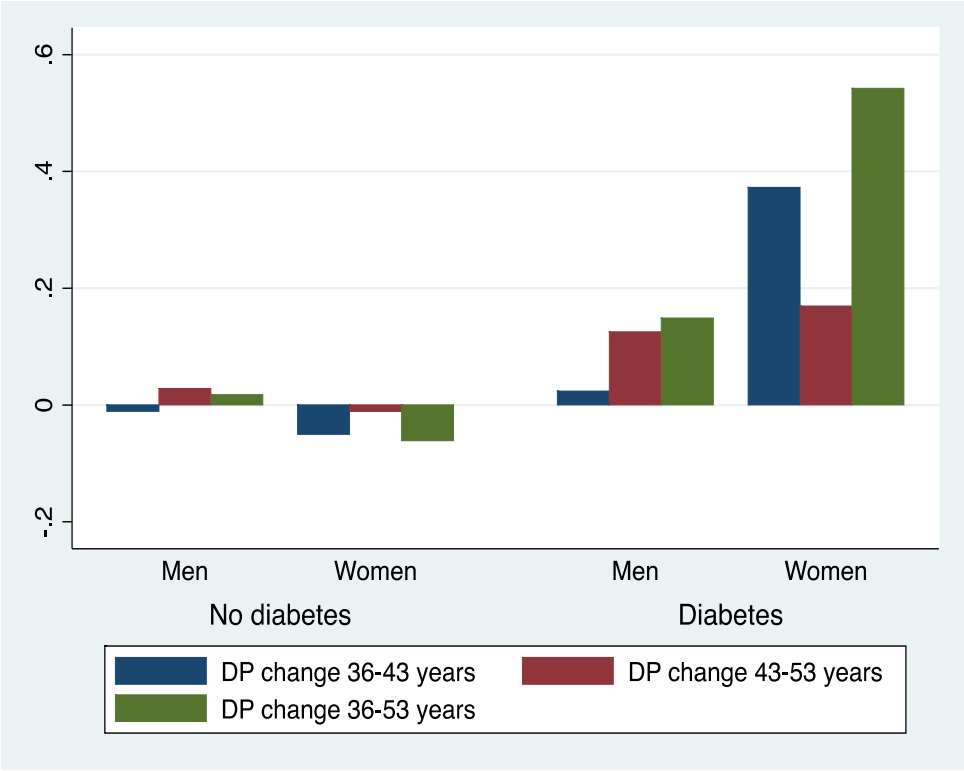


Figure 12. Mean change in dietary pattern score (SD) by sex and type 2 diabetes diagnosis

Note: analyses restricted to those with non-missing data for dietary intake, type 2 diabetes and all covariates (N=1180); DP= dietary pattern

Table 47. Associations between change in dietary pattern z-score and type 2 diabetes between age 53 and 60-64

	Model 1 Adjusted for, SEP, education, energy intake		**Model 2** As Model 1 + smoking and exercise		**Model 3** As Model 2 + BMI change*		**Model 3** As Model 3 + WC change**	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Change in dietary pattern z-score								
Men, N=525								
Age 36 to 43	1.08 (0.77, 1.53)	0.63	1.07 (0.76, 1.51)	0.67	1.09 (0.76, 1.59)	0.61	1.11 (0.77, 1.60)	0.56
Age 43 to 53	1.10 (0.79, 1.54)	0.53	1.07 (0.77, 1.50)	0.66	1.13 (0.81, 1.59)	0.45	1.05 (0.74, 1.48)	0.76
Age 36 to 53	1.12 (10.82, 1.53)	0.46	1.09 (0.79, 1.49)	0.59	1.17 (0.83, 1.63)	0.35	1.16 (0.83, 1.62)	0.37
Women, N=655								
Age 36 to 43	1.82 (1.22, 2.71)	<0.01	1.84 (1.23, 2.75)	<0.01	1.49 (0.99, 2.24)	0.05	1.50 (1.00, 2.27)	0.04
Age 43 to 53	1.55 (1.07, 2.25)	0.01	1.55 (1.06, 2.26)	0.02	1.43 (0.96, 2.13)	0.07	1.45 (0.98, 1.65)	0.06
Age 36 to 53	1.75 (1.23, 2.49)	<0.01	1.78 (1.24, 2.55)	<0.01	1.56 (1.07, 2.26)	0.01	1.62 (1.10, 2.39)	0.01

Note: analyses restricted to those with non-missing values for all covariates at all ages. OR of type 2 diabetes for a 1 SD increase in dietary patterns z-score in each interval conditional on previous dietary pattern z-score;
* conditional Body Mass Index change at age 36-43 and 43-53; ** conditional waist circumference change at age 36-43 and 43-53 waist circumference

6.4 Discussion

6.4.1 Main findings

A higher score for a dietary pattern characterised by high fat, high GI, low fibre at age 53 was associated with a greater type 2 diabetes risk in men and women; higher scores at age 43 were associated with diabetes among women but not men. These associations were independent of BMI and WC. Gradually increasing the score for this dietary pattern over the life course (36 to 53 years) is particularly detrimental for type 2 diabetes among women.

1st and 2nd objectives: To identify a dietary pattern characterised by high GI, low dietary fibre and high dietary fat and to investigate the association between this dietary pattern at age 36, 43 and 53 and type 2 diabetes incidence between age 53 and 60-64. It was hypothesised that a higher score for this dietary pattern would be prospectively associated with higher odds of type 2 diabetes.

Using RRR in this chapter, a high fat, high GI, low fibre dietary pattern was identified that was characterised by a high consumption of white bread, processed meat, fried potatoes, butter, animal fats and added sugar, and a low intake of fruits, vegetables, low-fat yogurt and high-fibre cereals. In agreement with the first hypothesis higher scores for this dietary pattern at age 53 were associated with an increased risk of type 2 diabetes diagnosed between age 53 and 60-64. This association was robust to adjustment for education, SEP, smoking, exercise, BMI and WC. At age 43 there was a significant sex interaction such that the dietary pattern was strongly associated with diabetes among women, for whom the association was independent of BMI and WC; however no association was observed among men. The associations between the dietary patterns at age 36 and diabetes were weaker and mostly non-significant. Therefore, it appears that this dietary pattern became more important for type 2 diabetes risk in middle and late adulthood and significantly more so in later adulthood. These results, in parallel with those in chapters 3-5, suggest a pattern of accumulation of lifestyle risk factors for type 2 diabetes across the adult life.

The results from this chapter are in agreement with the majority of previous findings from studies on type 2 diabetes and dietary patterns. Both the AHEI and the DASH diets, two diet quality scores that include fruits, vegetables, low-fat dairy and whole grains were protective against type 2 diabetes in White populations (218, 221). The Mediterranean diet, rich in vegetables and fruits and low in red meat, has also been linked with lower risk of type 2 diabetes (222, 224). Protective dietary patterns identified with factor and cluster analyses, often labelled ‘healthy’ or ‘prudent’, have also tended to include fruits, vegetables, whole grains, whole bread and low-fat dairy products, whereas, dietary patterns associated with increased type 2 diabetes risk have tended to be high in red and processed meat, refined grains, fried foods, high-fat dairy products and sweets (216, 225-228). Most of these protective and detrimental food groups loaded strongly on the high fat, high GI and low fibre dietary pattern identified in this chapter.

The results from this chapter build on previous findings by providing insight into the possible biological pathways that link these food groups with type 2 diabetes, as discussed in detail below. A few studies have attempted to do this by using RRR methodologies to examine pathways between food, inflammatory markers and type 2 diabetes (230-232, 234). Another study applied RRR to examine a dietary pattern based on fibre, alcohol, magnesium and a high ratio of PUFA to SFA in relation to type 2 diabetes risk (209). To the author's knowledge, no previous studies have used RRR to examine a dietary pattern characterised by fat density, GI and fibre density, for which, as outlined in chapter 1 and 5, there is some supporting evidence of a link with type 2 diabetes.

The stronger association between the dietary pattern at age 43 and diabetes among women could be due to several reasons. In chapter 5 a similar gender difference was observed for the association between fat (and SFA) and type 2 diabetes. Thus, there might be biological gender differences in the responses to certain nutrients, particularly fatty acids, and the way these are disposed of and stored in the postprandial state. For example it is known that sex-specific hormones can influence insulin receptors and lipid removal (324) and that men oxidise a higher percentage of ingested fat than women (325). However, the gender difference could also be due to different food choices; it is possible that this particularly dietary pattern explained greater variation in nutrients among women than men and that other food combinations might be more important for men. However, when dietary patterns were initially identified separately for men and women there were no major differences in the main foods characterizing the dietary patterns. Finally, accuracy in reporting dietary intake may also vary by sex (333).

Few studies have investigated men and women separately in the same cohort. In the Melbourne Collaborative Cohort Study (225) the association between a dietary pattern characterized by meats and fatty fried foods, and diabetes was significantly stronger among women, whose risk was in the highest quintile was nearly 4-fold compared to the lowest quintile. Conversely among men the risk was 2-fold and borderline significant. Other studies did not find significant interactions. However, in the Nurses' Health Studies the relative risks comparing quintiles of intakes of a RRR-derived dietary pattern high in processed meat, refined grains and soft drinks were particularly high (RR: 2.56, 95% CI: 2.10, 3.12 in the Nurses' Health Study and 2.93, 95% CI: 2.18, 3.92 in the Nurses' Health Study II) (234); on the contrary a similarly characterised dietary pattern had comparatively weaker associations in the Health Professionals Follow up Study (RR comparing quintiles: 1.59, 95%CI: 1.32 to 1.93) (228).

3rd objective: To ascertain whether the relationship between the derived dietary pattern and type 2 diabetes is mediated by BMI and WC. It was hypothesised that, since GI, dietary fibre and dietary fat can affect caloric intake and energy balance, the association would be partly mediated by BMI, but that an independent association between dietary pattern and diabetes would remain. The results in this chapter support this hypothesis. This was mainly true for the dietary pattern at age 43 (among women) and 53. Excess body weight, especially around the waist, is an established risk for type 2 diabetes; GI and fibre act on satiety signals while foods

high in fat are very energy-dense therefore affecting energy intake. Thus, it was expected that a dietary pattern high in fat and GI and low in fibre would act partly through its effect on energy intake and weight gain. The fact that an independent association remained after adjustment for BMI and WC (for dietary patterns at age 53) suggests that this dietary pattern might also act through alternative pathways. These pathways are discussed in more details in chapter 1 and 5. The postprandial hyperglycaemia induced by high GI foods can affect β-cells functions and insulin resistance both directly and indirectly by inducing a counter-regulatory hormone response, which increases circulating levels of free fatty acids (132, 133). Dietary fibre might reduce type 2 diabetes risk though its anti-inflammatory properties (157). Free fatty acids, which are elevated when excess calories and fat are consumed, increase insulin resistance by disrupting insulin signals in the gut and promote β-cells dysfunction though their lipotoxic effect in the pancreas (11). All these pathways are independent of excess body weight, although free fatty acids are particularly elevated in overweight individuals

Because RRR attempts to explain only the variation in chosen response variables, it is also possible that other nutrients and biological pathways might be important in the association between dietary patterns and type 2 diabetes.

4th objective: To investigate whether changes in the consumption of the high fat high GI low fibre dietary pattern over the adult life course are associated with type 2 diabetes incidence. It was hypothesised that the risk of type 2 diabetes would be greater with higher increases in dietary pattern score throughout adult life (from age 36 to age 53 years). The results from longitudinal analyses support this hypothesis, at least for women. Although, on average, the NSHD population decreased their scores over the entire follow up, thus improving their diet, those who developed type 2 diabetes between age 53 and 60-64 tended to increase their scores. The largest average increase was between age 36 and 43, when those who developed diabetes increased their score by 0.17 SD on average, compared to -0.02 SD for non-diabetics. This increase was mainly due to the large change observed among women in that period. Among women, results from regression analyses showed that long-term deterioration of the diet (increase in the dietary pattern score) from age 36 to 53 was particularly detrimental for type 2 diabetes risk rather than change at any particular time. This suggests that the cumulative influence of an unhealthy diet (as well as other lifestyle factors e.g. decreased physical activity) on body fatness and metabolic functions comes into play at an older age, which is when women become more susceptible to chronic diseases associated with aging. These findings parallel those in chapter 3 and 4, where it was shown that the detrimental effects of excess body weight and abdominal fat accumulate over the life course and that accumulation of excess weight around the waist is particularly detrimental for women.

6.4.2 Strengths

Because RRR incorporates hypothesised knowledge about pathways to disease, dietary patterns derived with this method may be more specific to the disease being analysed. This

allowed the author to investigate the synergistic action of dietary fibre, GI and dietary fat, key nutritional components hypothesised in the aetiology of type 2 diabetes. In this way our knowledge of the nutritional pathways linking dietary patterns and diabetes can be advanced. Furthermore, food-based public health recommendations based on key diabetes-relevant nutrients can be provided.

All the analyses accounted for a range of confounders (measures of SEP, education, smoking and physical activity) and results were similar after taking these into account. The mediating actions of BMI and WC were investigated and accounted for in separate models.

Another strength of these analyses is that repeated measures of dietary intake over the adult life were used to analyse longitudinal changes in diet in relation to type 2 diabetes. Although changes in diet might happen for different reasons, these are not commonly investigated. Most epidemiological studies of dietary patterns use only one measure of diet assuming eating behaviours remain stable over the adult life course.

6.4.3 Limitations

Although RRR is a more hypothesis-driven method than other exploratory dietary pattern methods, it requires previous knowledge of the biological pathways linking diet and disease. Based on the available evidence GI, fibre and fat were chosen as response variable for the RRR model. However, other nutritional components that were not included might have been important. Some of these, such antioxidants or polyphenols, are not easily recorded and are not listed in nutrition databases. For others there might not be enough evidence, but their biological role might still be important. Also, as with other dietary pattern methods, subjectivity can influence the RRR process at different stages, for example when deciding how to group foods and how to adjust for energy intake.

Although confirmatory RRR can be used to apply the same dietary pattern to other samples, the patterns derived with RRR, like other data-driven techniques, cannot be exactly reproduced in other cohorts. The food groups used in each cohort might be different or the foods consumed might vary according to season or country. In the NSHD sample, reproducibility of the high fat, high GI low fibre dietary pattern at age 36 had some limitations. Some foods commonly consumed in 1999 when the cohort was 53 did not exist in 1982 when the cohort was 36 e.g. skimmed milk and cereal bars were not consumed in 1982. Food formulation, meat fat content and portion sizes are also likely to have changed. In 1982 there was also a limited year-round supply of tropical and subtropical fruits and vegetables, the import of which only started in subsequent years. This might have contributed to greater seasonal variation in food consumed at age 36 (298). These factors might explain the weak associations found with type 2 diabetes in prospective analyses.

Although it is important to recognise the potential measurement error associated with dietary assessment, the use of food diaries generally provides more reliable estimates of food intakes (334) compared to food frequency questionnaires, which predominate in epidemiological

studies.

The analyses in this chapter were restricted to those with valid data for potential confounders (lifetime social class, educational attainment, smoking trajectory, physical activity, BMI and WC). Although this could have introduced bias, this restriction resulted in relatively small numbers of participants being excluded. However, loss to follow-up in NSHD might have introduced some bias and reduce the power of the associations, in particular in longitudinal analyses. The number of participants with valid diet diaries for all ages was 1397. However, we have no reason to suppose that this would have altered the pattern of results obtained. Nevertheless, as shown in Appendix 8, those providing dietary data were healthier and more likely to be women compared to those who did not complete diet diaries. Therefore results from these analyses might not be generalizable to all populations.

6.4.4 Conclusions

In conclusion, a dietary pattern characterised by high fat, high GI, low fibre is prospectively associated with type 2 diabetes risk especially among women and this association is partially independent of BMI and WC, indicating that this dietary pattern might be acting via alternative pathways as well as via body weight. Among women, this association was robust when the dietary pattern was examined longitudinally over the life course (36 to 53 years) suggesting that the cumulative effects of changes in diet over a long-term period are particularly important for type 2 diabetes for women.

7 Chapter 7 - Discussion

7.1 Research questions

This PhD project aimed to address the following research questions:

- How do longitudinal patterns of BMI throughout adult life affect type 2 diabetes incidence? (Chapter 3)
- How does WC throughout the adult life course affect type 2 diabetes incidence? (Chapter 4)
- Does consumption of dietary fibre, GI and dietary fats at different times of the adult life affect type 2 diabetes incidence? (Chapter 5)
- Is the consumption throughout the adult life of a dietary pattern characterised by high GI, low fibre and high fat associated with type 2 diabetes incidence and is this association mediated by BMI and WC? (Chapter 6)

7.2 Summary of main findings

The findings presented across this thesis consistently show that accumulating excess body weight and having a large WC, as well as eating an unhealthy diet (for women), throughout the adult life course increase the risk of developing type 2 diabetes later in life (53 to 60-64 years).

Chapter 3 showed that at any stage of the adult life course, overweight and obesity, as well as weight gain, were associated with later risk of type 2 diabetes. Early (26-36 years) and late adulthood (43-53 years) BMI gains were more important for men whereas gains in late adulthood had stronger associations for women. Chapter 3 also found evidence of the detrimental effect of accumulating weight across the life course, with those being overweight for longer durations reaching higher attained BMI and having the highest type 2 diabetes risk.

Chapter 4 expanded the results of chapter 3 by analysing abdominal obesity and its relationship with BMI. At any time of the adult life course, having a large WC was associated with type 2 diabetes incidence. The relative risk was particularly strong among women for whom the effect of having a large WC was independent of BMI. Chapter 4 also showed that long-term changes in WC (36-53) were associated with increased type 2 diabetes incidence, although only very large WC changes were independent of concomitant BMI change. Unlike BMI gains there was no period when WC gains were especially detrimental for later diabetes risk, although changes at age 36-43 were marginally more strongly associated with type 2 diabetes than later changes. Both abdominal obesity and changes in WC were particularly important for people with a normal BMI.

Chapter 5 and 6 showed that dietary choices across the adult life course are important for the prevention of type 2 diabetes, both through their effect on body weight and independently through other pathways. Chapter 5 found that dietary fibre, and GI, particularly at 43 and 53 years, was significantly associated with type 2 diabetes incidence (43 and 53 years), among whom the association persisted after controlling for BMI and WC. Excess dietary fat, especially total fat rather than SFA, had a stronger impact on women, and this association was independent of body weight and abdominal obesity. Chapter 5 also found that the effects of low fibre and high GI were stronger among overweight people and those with a raised WC suggesting that people already at risk might be more susceptible to the effects of an unhealthy diet.

Chapter 6 identified a high fat, high GI, low fibre dietary pattern that was characterised by high consumption of white bread, processed meat, fried potatoes, animal fats and added sugar, and a low intake of fruits, vegetables, low-fat dairy products and whole grain cereals. Higher scores for this dietary pattern at age 53 were associated with an increased type 2 diabetes incidence while at age 43 associations were strong for women but null for men. This association was only partly driven by the effect of diet on body weight and WC and was robust when the dietary pattern was examined longitudinally over the life course. In women, but not men, larger increases in this dietary patterns from age 36 to 53 years were associated with a higher risk of diabetes later in life independently of changes in BMI and WC over the same period.

All analyses were adjusted for adult social class, educational attainment, physical activity and smoking history, suggesting these results were unlikely to be confounded by these factors. Most of the analyses presented in this thesis extended previous work on obesity, diet and type 2 diabetes. However, few previous studies have analysed longitudinal patterns of excess body weight, WC and their association with type 2 diabetes risk and even fewer have examined longitudinal changes in dietary patterns over time. Indeed, a key strength of this thesis is the exploitation of repeated anthropometric and dietary measures to assess the interplay of these lifestyle factors and their effect on type 2 diabetes over the life course.

7.3 Implications of findings

As outlined in chapter 1, type 2 diabetes is a burdensome chronic disease, the prevalence of which is increasing worldwide. Diabetes complications are a major cause of morbidity and mortality and are extremely costly to handle, therefore prevention of the disease has become a public health priority. The findings from this thesis have a number of important implications for the prevention or delay of type 2 diabetes at the population level.

This thesis provided evidence that accumulating weight, especially around the waist, as well as consuming a diet increasingly characterised by high fat, high GI and low fibre, across adulthood is associated with higher type 2 diabetes incidence, particularly among women. Using a life course perspective this thesis showed that not only are these risk factors important individually, but that they are also deeply interconnected and should be approached jointly when planning

prevention strategies. To date, no other study has looked at concurrent longitudinal changes in BMI, WC and dietary patterns in relation to type 2 diabetes, therefore these findings provide meaningful new insights into the interrelated pathways of these risk factors in the development of diabetes.

Overall findings from this thesis point to a pattern of accumulation of metabolic insults brought about by repeated unhealthy life style choices over the life course. Results from chapter 3 and 4 underscore the importance of preventing weight gain as early as possible to avoid reaching a critically high body weight and WC peak in later life especially given that weight loss, or even weight maintenances, are rarely accomplished, as demonstrated by the NSHD cohort. Similarly, findings from chapters 5 and 6 indicate that a gradual worsening of the diet through the adult life is associated with type 2 diabetes. This is despite the fact that diet on average tended to improve for the NSHD cohort. The implications of these results are particularly relevant in the context of current obesity trends with people becoming overweight at increasingly younger ages and being exposed to longer durations of obesity than in previous decades (335). If, as argued by behavioural models of food choice (336), the most important dietary habits are those formed during the childhood years, which tend to track over the adult years, prevention should start as early as childhood. Furthermore, interventions to reduce even relatively small amounts of weight in later life tend to be costly, and maintenance of weight loss is typically poor. Shifting the focus from interventions solely aimed at at-risk individuals to a broader approach aimed at improving population lifestyle behaviours would probably be the most effective strategy to prevent diabetes and obesity in the future. The theory that effective prevention requires changes that involve the whole population, as initially proposed by Geoffrey Rose in its ‘Strategy of Preventive Medicine’ (337) and subsequently developed by the Marmot Reviews (25), is now a key focus of any public health policy.

Chapter 5 and 6 suggest that promoting a dietary pattern rich in fruit, vegetable and whole-grain cereals as well as choosing low-fat versions of diary products would help prevent type 2 diabetes, especially among women. Limiting processed and fried foods and reducing the consumption of added sugar and animal fat should also be encouraged. This is in agreement with findings from other studies. However, unlike other studies, this thesis has shed light on the nutritional pathways linking these food choices with diabetes development. By using a hypothesis-driven methodology it was found that dietary fibre, GI and dietary fats are key nutritional components underlying the metabolic effects of the above-mentioned food choices.

Furthermore, this thesis has helped elucidate whether the association between dietary factors and diabetes is mediated by BMI and WC both prospectively and longitudinally. The BMI-mediated pathways probably act through the high-energy density of fat-rich foods and low-satiating effect of diets poor in fibre and high in GI. There is also increasing evidence that high GI low fibre diets could preferentially facilitate visceral fat storage in the abdominal area (135, 136, 294-297). However, one important implication of this thesis is that consumption of a high-GI, low-fibre, high-fat dietary pattern can increase the risk of type 2 diabetes through alternative

biological mechanisms, independent of BMI and WC. The elevated postprandial insulin and glycaemic response brought about by a high GI-diet (i.e. one rich in refined carbohydrate) could lead to β-cells dysfunction if consumed for a long time (132); furthermore, high GI foods, after the initial glucose peak, lead to a quicker drop in blood glucose and a subsequent rise in FFA triggered by counter-regulatory hormones (132, 133). Raised FFA have been linked to insulin resistance and β-cell dysfunction. Two important mechanisms of dietary fibre, independent of body weight, are its strong anti-inflammatory action (157-159, 286), and its acute lowering effect on postprandial glycaemia (165); conversely, dietary fats when consumed in excess, increase inflammation and insulin resistance (182, 183). The results also suggest that the associations between these factors and diabetes might partly depend on gender differences in metabolism and food choices.

7.4 Overall strengths and limitations

Strengths and limitations specific to chapters 3-6 have already been discussed within each chapter. Only strengths and limitations common to the whole thesis will be discussed in this section.

7.4.1 Strengths

An important strength of this thesis was the use of a socially representative sample of the British population. The NSHD, with its longitudinal birth cohort study design, comprises a rich data set encompassing more than 65 years of life. Detailed information on prospectively obtained anthropometric measures, lifestyle behaviours, SEP and diabetes outcome enabled analyses to be adjusted for multiple potential confounder factors. The prospective nature of the study ensured that the temporal sequence of exposure and outcome in all analyses limited the risk of reverse causation.

A key strength of this thesis was the use of a life course perspective, which was essential to the identification of patterns of body weight, dietary choices and diabetes. Repeated measures of body weight, WC and diet were used in this thesis to address specific research questions, which would not have been possible using single measures. For example, repeated anthropometric measures were measures were used to identify periods of the adult life course when changes in BMI and WC were more detrimental for diabetes incidence and to investigate the cumulative damage of weight gain across the years. Repeated dietary measures were used to show the deleterious effects of adult changes in dietary patterns on diabetes risk, which have been rarely addressed in epidemiological studies. Furthermore, by modeling both anthropometric and dietary changes in one model the independent effect of dietary pattern on diabetes was shown. By addressing these issues, this thesis significantly contributes to the limited evidence on the longitudinal effects of diet and body weight on the risk of type 2 diabetes.

Another strength of this thesis was the use of a comprehensively measured diabetes outcome, which was ascertained by analyses of fasting blood glucose and HbA1c as well as by self-

report. Furthermore, the accuracy of participant-reported diabetes was validated using general practitioner information, which was collected by the author and used in a validation study (241).

7.4.2 Limitations

One of the main limitations of this thesis, as for many longitudinal studies, is represented by missing values due to loss to follow-up. In this thesis, the method chosen to address this problem was complete case analyses, with analyses restricted to those with valid data for all explanatory and confounding variables and the outcome. This method led to a reduced sample size with consequent reduction in statistical power. It may also have introduced bias if the excluded people differed substantially from those included with regards to the outcome and the main explanatory variables. However, as shown in Appendix 3, 4 and 6 this was not the case for analyses presented in chapter 3 and 4. However, as shown in Appendix 8, individuals providing dietary data were different from those not completing diet diaries with respect to social and lifestyle characteristics. In particular, the sample used for analyses in chapter 5 and 6 was a healthier one compared to the general population, making generalizations about findings more difficult.

The use of multiple imputation would have led to a larger sample size with consequent higher statistical power. However, multiple imputation assumes that data are missing at random, which happens when the difference between measured and missing values can be explained by differences within the observed data (338). However, when data are missing not at random (when the difference between measured and missing values depend on unmeasured variables), multiple imputation may give misleading results, resulting in potentially greater bias than complete case analyses (338).

Another potential limitation of this thesis is the use of self-reported measures of dietary intake, smoking and physical activity. Over reporting of healthy behaviours, such as fruit and vegetable intake and high-intensity exercise, and underreporting of unhealthy behaviours, such as smoking and fat intake, might have biased some results. However, if misreporting did happen this was likely to have resulted in bias towards the null and underestimation of relative risks.

A further limitation is the fact that some of the explanatory variables of interest, especially WC and dietary intakes, were collected only during the adult years limiting the scope of life course analyses. For example, it would have been of interest to explore at what time during an individual lifecourse unhealthy food choices associated with diabetes incidence start to develop; or whether they are influenced by specific life events in adolescence and early adulthood. Analysis of one-day recall diet records of 4-year olds in the NSHD (339) showed that compared with younger generations, the NSHD children were a healthier cohort mainly due to the availability of food items during the post war period. Availability of dietary data for later childhood and adolescence would have helped identify periods when dietary habits start to change and factors associated with this transition.

The generalisability of findings from this thesis to younger cohorts is questionable. Particularly, the prevalence of obesity in younger cohorts is higher than in the NSHD, while excess weight gain is increasingly starting earlier in life (261, 340). In the NSHD only few people were obese in childhood and adolescence, which prevented analyses of patterns of weight gain during these periods. It is possible that in younger cohorts significant weight gain in childhood might represent a sensitive period for the development of type 2 diabetes rather than accumulation of weight through the adult life course.

Reflecting the ethnic make-up of Britain in the 1940s, the NSHD is comprised exclusively of Caucasians. Therefore, the findings from this thesis might not be generalizable to cohorts of different ethnic groups. For example, the prevalence of type 2 diabetes is significantly higher among people of South Asian descent (1). Furthermore, because of the different body weight distribution and genetic background of these populations (341), the relative importance of BMI, WC and diet in modulating diabetes risk might differ from that of Caucasians.

7.5 Policy implications

Type 2 diabetes has reached epidemic proportions and will continue to rise worldwide, particularly among low-income countries. In an aging society, the older groups of the populations, those aged 65 years and more, are predicted to experience the greatest increase in type 2 diabetes (1), leading to a major public health impact on individuals' lives and governments spending.

As outlined in this thesis obesity and unhealthy diets are major determinants of this epidemic. These factors are highly interrelated and deeply imbedded in the culture of modern society. As illustrated by the social model of health of Dahlgren & Whitehead (342) health is determined not only by individuals choices but by a multitude of socio-economic, cultural and environmental factors, such as housing, employment and education. Targeting these wider determinants of health is a key priority for policies aiming at reducing obesity and diabetes. In fact, as noted in the Foresight report 'Tackling Obesities: Future Choices' (261), although individual responsibility plays a role in weight gain, the influence of the current 'obesogenic environment' with its abundant energy-dense foods and facilitation of sedentary life, has led to a state of near 'passive obesity'. This suggests that unhealthy lifestyles cannot be changed by policies solely aimed at the individual. Instead if policies are to be effective they need to involve various government departments and external stakeholders in an integrated fashion. These policies should target all opportunities for actions, including education, availability of food, food pricing and urban planning.

As suggested by the government's 'Healthy Lives, Healthy People: A call to action on obesity in England' (343), policy actions to reduce obesity and improve diets should involve the whole of society, including individuals, businesses and governments. The North Karelia Project in Finland (344), a 20-year long community-based programme aimed at reducing heart disease, provides evidence that such a whole-society approach would bring substantial population health

benefits. The Fleurbaix Laventie Ville Santé Study is a similar long-term community-based intervention started in two towns in France, which led to significant reductions in childhood obesity after 10 years. Based on the success of this study, the community-based project EPODE (345) (Ensemble prevenons l'obesite des enfants) aimed at preventing childhood obesity, was started in 2004 in 10 towns in France and is now implemented in 293 towns across Europe. These encouraging results demonstrated that a programme involving the whole town and based on political commitment, mobilization of resources, sustainability and continuous evaluation can successfully reverse the obesity trend (346). Similar progarmmes have not as yet been implemented in the UK. However, recently, government actions have been taken to involve various stakeholders to share the responsibility in reducing obesity levels, by for example encouraging food businesses to adopt the new government front of pack labeling system and to put calorie information on restaurant menus. On the other hand, awareness campaigns, such as the recently Change4Life programme (347), which uses social marketing to provides advice on healthy diet and physical activity aimed at families, have so far made little difference to people' behaviour (348). A better understanding of why people change their behaviour, as argued by social cognition theories, such as the Health Belief Model (349), might also be needed if such campaigns are to be more effective. However, ultimately, more research into the wider economic and social determinants of lifestyle behaviours is needed as well as more evaluations of the effectiveness of on-going interventions to support cost-effective decision-making. Finally, more emphasis needs to be placed on the importance of primary prevention of chronic diseases if policies are to be truly effective, since as demonstrated by this thesis, weight loss in adult life is rarely achieved and the negative effects of unhealthy choices accumulate over time.

7.6 Future research

This thesis has found that accumulation of body weight over the adult life course is a key determinant of type 2 diabetes and that weight and WC gains at any time are detrimental. Few studies have examined long durations of overweight or obesity and even fewer have looked at sensitive periods of weight and WC gains; thus replication of findings from this thesis would strengthen the conclusions from chapter 3 and 4. The replication of findings using longer life course trajectories and shorter time intervals between anthropometric measurements would be particularly informative. The use of data from cohorts with higher obesity prevalence in younger years would also allow more powerful analyses.

This thesis found that changes in dietary patterns are linked to type 2 diabetes, especially among women. Few studies have assessed diet longitudinally, therefore replicating results of dietary patterns analyses, particularly focusing on longitudinal changes of diet scores, either in Caucasians or in cohorts from different ethnic backgrounds would provide further insight on the link between diet and type 2 diabetes. More analyses of gender differences in the association between dietary patterns and diabetes could be conducted to ascertain the nature of this differential effect.

Future research could expand the findings from this thesis by exploring the combined effects of physical activity and diet in modulating the risk of type 2 diabetes, both directly though energy dynamics and independently via other pathways. The use of objectives measures of physical exertion would greatly advance research on exercise and metabolic outcomes.

Further investigations on the link between diet and diabetes could include genetic information to investigate genetic and nutritional interactions. Research on the interaction between dietary factors and genetic traits is a growing area of research, which would enhance the understanding of the interplay between environmental and genetic factors in modulating diabetes risk.

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Appendices

Appendix 1. Descriptive statistics of the main explanatory variables used in this thesis

						Centiles					
	N	Mean	SD	Min	Max	10	25	75	90	Median	IQR
Body Mass Index (BMI)	1860[a]										
BMI at age 26		22.8	3	13.8	50.4	19.6	20.8	24.4	26.4	22.3	3.6
BMI at age 36		23.9	3.4	14.1	44.3	20.1	21.5	25.8	28.2	23.5	4.3
BMI at age 43		25.2	3.9	17.0	49.3	21	22.5	27.9	30.3	24.6	4.7
BMI at age 53		27.3	4.6	17.1	57.1	22.3	24.1	29.7	33.2	26.5	5.6
Waist circumference (WC)	2007[b]										
WC at age 36		82.2	11.8	51.5	132.5	67	73	90.5	97.4	82	17.5
WC at age 43		83.9	12.2	54.5	130.1	68.6	74.2	92.5	100	83.5	18.3
WC at age 53		91.1	12.9	58.6	159.9	74.2	81.7	99.6	107.3	91	17.9
Dietary fibre density											
Dietary fibre at age 36	1804[c]	6	2.2	2	27.6	4.1	4.6	6.9	8.6	5.5	2.3
Dietary fibre at age 43	2267[d]	6.2	2.5	0.9	31.3	3.6	4.6	7.3	9.2	5.7	2.7
Dietary fibre at age 53	1477[e]	7.6	2.4	1.5	25.9	4.9	5.8	8.9	10.7	7.2	3
Glycaemic Index (GI)											
GI at age 36	1804[c]	64.2	4	41.5	75.8	58.7	61.8	67	69	64.5	5.2
GI at age 43	2267[d]	63.8	4.9	43.6	82	57.7	60.5	67.3	69.9	63.9	6.7
GI at age 53	1477[e]	61.8	4	45.1	74.4	56.6	59	64.5	66.9	61.9	5.5
Dietary fat density											
Dietary fat at age 36	1804[c]	43.9	5.3	4.7	62.3	37.2	40.7	47.3	50.4	44.2	6.6
Dietary fat at age 43	2267[d]	43	6.5	7.6	68	34.8	39.4	47.3	50.5	43.6	7.9
Dietary fat at age 53	1477[e]	378	6.7	10,7	59.5	29	33.4	42.6	46.3	38.2	9.1

a= sample used in chapter 3; b= sample used in chapter 4; c,d,e= samples used in chapter 5 and 6; IQR= interquartile range

Appendix 2. Descriptive statistics for the confounders variables used in this thesis

	Sample used in chapter 3		Sample used in chapter 4		Samples used in chapter 5 and 6					
	N=1860		N=2007		N=1804		N=2267		N=1477	
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
Sex										
Male	883	47.5	947	47.2	856	47.4	1080	47.6	668	45.2
Female	977	52.5	1060	52.8	948	52.5	1187	52.4	809	54.8
Socioeconomic position										
I professional	139	7.5	151	7.5	136	7.5	170	7.5	118	8
II intermediate	701	37.7	755	37.6	667	37.0	854	37.7	551	37.3
III skilled (Non-Manual)	460	24.7	488	24.3	464	25.7	534	23.6	365	24.7
III skilled (Manual)	300	16.1	327	16.3	282	15.6	374	16.5	226	15.3
IV partly skilled	187	10.1	206	10.3	188	10.4	246	10.8	158	10.7
V unskilled	73	3.9	80	4.0	67	3.7	89	3.9	59	4
Education attained by age 26										
None attempted	603	32.4	661	32.9	571	31.6	768	33.9	430	29.1
Intermediate	533	28.7	577	28.8	525	29.1	634	28	436	29.5
Highest	724	38.9	769	38.3	708	39.3	865	38.1	611	41.4
Smoking history up to age 36, 43 or 53										
Current smoker					478	26.5	582	25.7	247	16.7
Ex smoker					745	41.3	982	43.3	761	51.5
Never smoker					581	32.2	703	31	469	31.8
Lifetime smoking trajectory										
Never smoker	587	31.6	624	31.1						
Predominantly non-smoker	672	36.1	727	36.2						

Predominantly smoker	372	20.0	405	20.2						
Lifelong smoker	229	12.3	251	12.5	229	12.3				
Exercise at age 36										
Inactive	640	34.4	700	34.9	621	34.4				
Less active	495	26.6	528	26.3	493	27.4				
Most active	725	39.0	779	38.8	690	38.2				
Exercise at age 43										
Inactive	933	50.1	995	49.6			1126	49.7		
Less active	446	24.0	90	24.4			556	24.5		
Most active	481	26.9	522	26.0			585	25.8		
Exercise at age 53										
Inactive	843	45.3	910	45.4					655	44.4
Less active	266	19.7	393	19.6					299	20.2
Most active	650	35.0	703	35.0					523	35.4

Educational attainment categorised as none (none attempted), intermediate (GCE 'O' level or Burnam C or lower) or highest (GCE A level or Burnam B or higher); exercise was coded as inactive (no participation), moderately active (participated one to four times) and most active (participated five or more times) in the previous 4 weeks/ one month

Appendix 3. Comparison between study members with missing data on BMI and those with available data at age 26 and 36

	Age 26					Age 36				
	Missing		Non-missing			Missing		Non-missing		
	n	%	n	%	P value	n	%	n	%	P value
Sex										
Male	993	56.4	1822	50.5	<0.001	1183	56.2	1633	49.7	<0.001
Type 2 diabetes										
age 53 to 60- 64	29	8.3	230	10	0.32	34	12.2	225	9.5	0.15
SEP										
Manual	255	40.7	1276	35.7	0.01	394	42.1	1137	34.8	<0.001
Education (by age 26)										
None attempted	434	45.9	1331	38.3		578	44.4	1187	38.0	
Intermediate	278	29.4	938	26.9	<0.001	341	26.2	875	28	<0.001
Highest	233	24.6	1206	34.7		382	29.3	1057	33.8	
Lifetime smoking										
Never smoker	81	24.8	869	28.3		65	28.6	885	28	
Predominantly non-smoker	89	27.3	1012	33		54	23.7	1047	33.1	
					<0.001					0.02
Predominantly smoker	78	23.9	543	20.8		57	25.1	658	20.8	
Lifelong smoker	78	23.9	543	17.7		51	22.4	570	18	
BMI category*										
Overweight (25 -29.9 kg/m^2)		-				132	18.7	534	18.4	0.86
Obese (≥30 kg/m^2)						17	2.4	80	2.7	
WC category*										
High risk		-					-			
Very high risk										
Physical activity*										
Inactive										
Less active										
Most active										

BMI= body mass index; WC= waist circumference; educational attainment was categorised as none (none attempted), intermediate (GCE 'O' level or Burnam C or lower) or highest (GCE A level or Burnam B or higher); exercise was coded as inactive (no participation), moderately active (participated one to four times) and most active (participated five or more times) in the previous 4 weeks/ one month; * high risk category: WC of 94-102 cm for men, WC of 80-88 cm for women; very high risk category: WC>102 for men, WC>88 cm for women. * information from previous data collection used

Appendix 4. Comparison between study members with missing data on BMI and those with available data at age 43 and 53

	Age 43					Age 53				
	Missing		**Non-missing**			**Missing**		**Non-missing**		
	n	%	n	%	P value	n	%	n	%	P value
Sex										
Male	1198	56.0	1617	50.1	<0.001	1363	56.4	1452	49.2	<0.001
Type 2 diabetes										
age 53 to 60- 64	28	14.2	231	9.4	0.03	27	12	232	9.5	0.23
SEP										
Manual	422	42.3	1109	34.6	<0.001	536	42	995	34	<0.001
Education (by age 26)										
None attempted	641	46.2	1124	37		741	45	1024	36.8	
Intermediate	365	26.3	851	28.0	<0.001	444	27	772	27.8	<0.001
Highest	380	27.4	1059	34.9		459	27.9	980	35.3	
Lifetime smoking										
Never smoker	78	23.5	872	28.5		140	22.6	810	29.2	
Predominantly non-smoker	69	20.8	1032	33.7		152	24.6	949	34.2	
					<0.001					<0.001
Predominantly smoker	72	21.7	643	21		136	22	579	20.9	
Lifelong smoker	112	33.8	509	16.6		190	30.7	431	15.5	
BMI category*										
Overweight (25 -29.9 kg/m^2)	100	28.7	830	28.3	0.16	179	37.5	960	34.9	0.37
Obese (≥30 kg/m^2)	31	8.9	185	6.3		62	13	333	12.1	
WC category*										
High risk	80	22.6	570	19.3	0.04	108	22.5	601	21.9	0.08
Very high risk	51	14.4	337	11.4		78	16.3	352	12.8	
Physical activity*										
Inactive	151	42.3	1068	36.1		275	56.1	1424	51.3	
Less active	91	25.4	746	25.2	0.03	108	22	645	23.2	0.12
Most active	115	32.2	1138	38.5		107	21.8	703	25.3	

BMI= body mass index; WC= waist circumference; educational attainment was categorised as none (none attempted), intermediate (GCE 'O' level or Burnam C or lower) or highest (GCE A level or Burnam B or higher); exercise was coded as inactive (no participation), moderately active (participated one to four times) and most active (participated five or more times) in the previous 4 weeks/ one month; * high risk category: WC of 94-102 cm for men, WC of 80-88 cm for women; very high risk category: WC>102 for men, WC>88 cm for women. * information from previous data collection used

Appendix 5. Associations between conditional BMI changes at different age intervals and type 2 diabetes between age 53 and 60-64

	Model 1 Unadjusted		**Model 2** Adjusted for SEP and education		**Model 3** As Model 2 + adjusted for physical activity and smoking history	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Period of change						
Men, n=889						
26-43 years	1.48 (1.19, 1.83)	<0.001	1.46 (1.18, 1.81)	<0.001	1.50 (1.21, 1.87)	<0.001
43-53 years	1.57 (1.27, 1.94)	<0.001	1.56 (1.26, 1.93)	<0.001	1.64 (1.32, 2.05)	<0.001
P for difference between periods*	0.15		0.68		0.58	
Women, n= 984						
26-43 years	1.60 (1.28, 2.01)	<0.001	1.59 (1.27, 1.99)	<0.001	1.59 (1.26, 2.00)	<0.001
43-53 years	1.85 (1.46, 2.34)	<0.001	1.85 (1.46, 2.34)	<0.001	1.84 (1.45, 2.34)	<0.001
P for difference between periods*	0.42		0.39		0.41	

Note: analyses restricted to those with non-missing data for BMI at age 26, 36, 43 and 53, type 2 diabetes and all covariates. OR of type 2 diabetes for a 1 SD increase in BMI in each interval conditional on previous BMI;P for difference between periods estimated with Wald's test

Appendix 6. Comparison between subjects with information about type 2 diabetes between age 53 and 64 and those with non-missing data for all covariates

		Maximum sample		**Complete cases** (n= 1872)	
	Maximum N available	n	%	n	(%)
Male	*(N=2642)*	1,279	48.4	889	47.4
Type 2 diabetes status	*(N=2642)*				
Diagnosed between age 53 and 64		259	9.7	182	9.7
Socioeconomic position	*(N=2618)*				
Manual		827	31.5	562	30.0
Education attained by age 26	*(N= 2467)*				
None attempted		841	34.0	603	32.2
Intermediate		694	28.1	538	28.7
Highest		932	37.2	731	39.0
Lifetime smoking trajectory	(N=2462)				
Never smoker		747	30.3	594	31.7
Predominantly non-smoker		866	35.1	677	36.1
Predominantly smoker		511	20.7	372	19.8
Lifelong smoker		338	13.7	230	12.2
BMI Mean (95%CI)					
BMI at age 26	*(N=2294)*	22.7	(22.65, 22.90)	22.7	(22.65, 22.92)
BMI at age 36	*(N=2364)*	24.01	(23.87, 24.15)	23.9	(23.80, 24.11)
BMI at age 43	*(N=2445)*	25.2	(25.10, 25.41)	25.2	(25.07, 25.42)
BMI at age 53	*(N=2418)*	27.3	(27.17, 27.54)	27.3	(27.12, 27.54)
WC Mean (95%CI)					
WC at age 36	*(N=2375)*	82.5	(82.03, 82.98)	82.2	(81.73, 82.80)
WC at age 43	*(N=2438)*	84.0	(83.58, 84.56)	83.9	(83.39, 84.51)
WC at age 53	*(N=2429)*	91.1	90.64, 91,68)	91.1	(90.52, 91,70)

BMI= body mass index; WC= waist circumference

Appendix 7. Correlation between WC and BMI measures by BMI category

a) Males (n=947)		**a) Females (n=1060)**	
Correlation between BMI and WC at age 36			
BMI <25 kg/m^2	0.55	BMI <25 kg/m^2	0.41
BMI ≥25 – 29.9 kg/m^2	0.53	BMI ≥25 – 29.9 kg/m^2	0.36
BMI ≥30 kg/m^2	0.67	BMI ≥30 kg/m^2	0.58
Correlation between BMI and WC at age 43			
BMI <25 kg/m^2	0.50	BMI <25 kg/m^2	0.55
BMI ≥25 – 29.9 kg/m^2	0.56	BMI ≥25 – 29.9 kg/m^2	0.47
BMI ≥30 kg/m^2	0.70	BMI ≥30 kg/m^2	0.59
Correlation between BMI and WC at age 53			
BMI <25 kg/m^2	0.53	BMI <25 kg/m^2	0.74
BMI ≥25 – 29.9 kg/m^2	0.57	BMI ≥25 – 29.9 kg/m^2	0.69
BMI ≥30 kg/m^2	0.78	BMI ≥30 kg/m^2	0.78

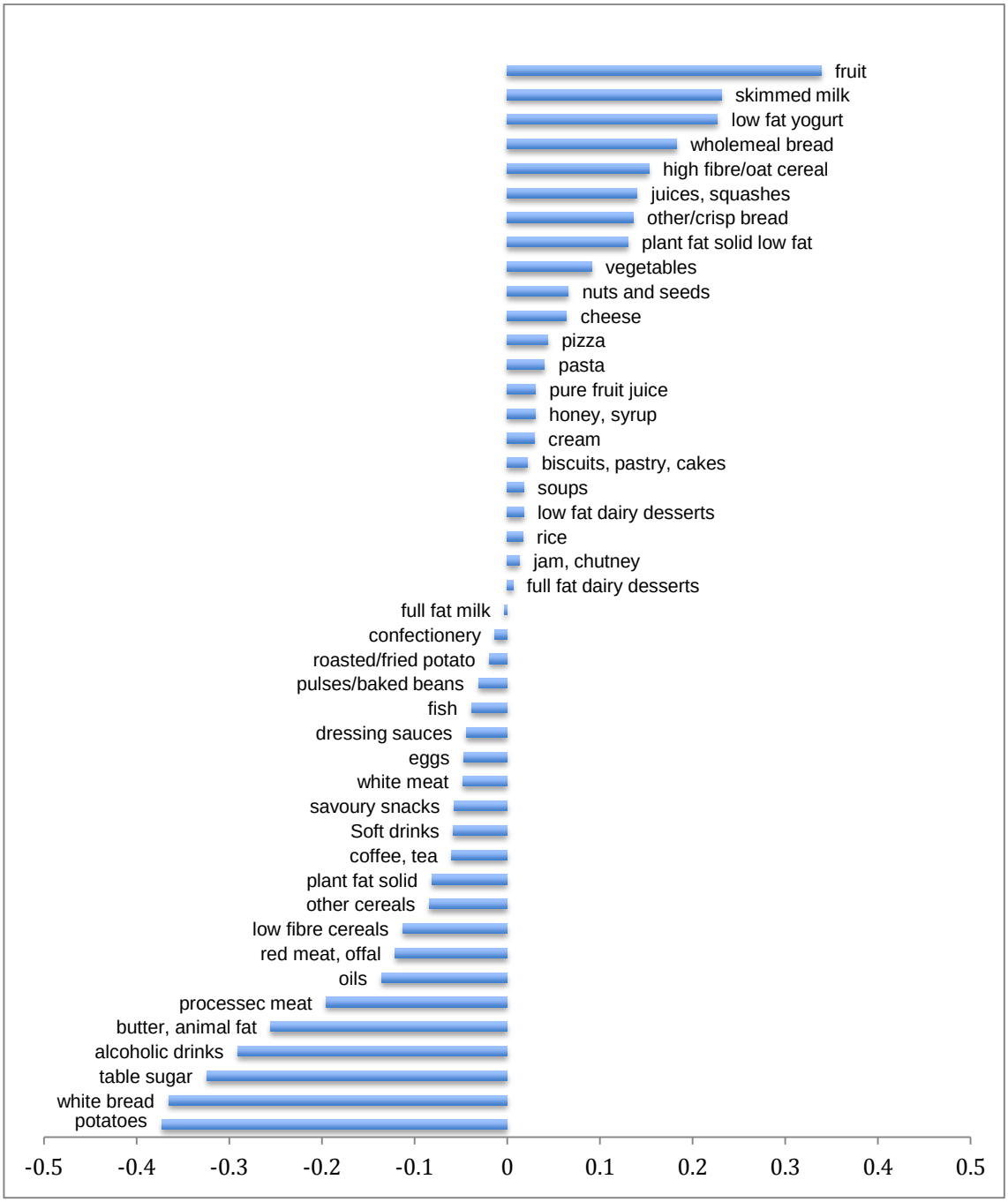
Note: Analyses restricted to those with non-missing data for WC and BMI at age 36, 43 and 53, type 2 diabetes and all covariates

Appendix 8. Comparison between study members who completed diet diaries and those who did not at each age

	Age 36					Age 43					Age 53				
	Non completers		Completers			Non completers		Completers			Non completers		Completers		
	n	%	n	%	P value	n	%	n	%	P value	n	%	n	%	P value
Male	1617	55.3	1198	49	*<0.001*	1229	56.5	1586	49.7	<0.001	1988	55.4	827	46.5	<0.001
Type 2 diabetes diagnosis															
age 53 to 60- 64	83	11.2	176	9.2	*0.11*	30	14	229	9.4	0.03	122	11.5	137	8.6	0.01
Socioeconomic position															
Manual	718	40.5	813	33.4	*<0.001*	436	42.1	1095	34.6	<0.001	983	40.2	548	31.1	<0.001
Education attained by age 26															
None attempted	959	45.8	806	34.6		653	45.9	1112	37		1249	45.3	516	30.9	
Intermediate	544	25.9	672	28.8	*<0.001*	379	26.6	837	27.9	<0.001	737	26.7	479	28.7	<0.001
Highest	591	28.2	848	36.4		390	27.4	1049	34.9		767	27.8	672	40.3	
Lifetime smoking trajectory															
Never smoker	249	24.6	701	29.5		91	24.5	859	28.4		427	25	523	31.1	
Predominantly non-smoker	251	24.8	850	35.7	*<0.001*	76	20.5	1025	33.9	<0.001	475	27.8	626	37.2	<0.001
Predominantly smoker	258	25.4	457	19.2		78	21	637	21.1		382	22.3	333	19.8	
Lifelong smoker	254	25.1	367	15.4		125	24.8	496	16.4		424	24.8	197	11.7	
BMI category															
Overweight (25 -29.9 kg/m^2)	275	31.8	655	27.1	*<0.001*	23	37.1	1116	35.2	0.32	508	42.5	749	42.6	<0.001
Obese (≥30 kg/m^2)	72	8.3	144	5.9		11	17.7	384	12.1		352	29.5	362	20.6	
WC category															
High risk	183	21	467	19.2	*0.01*	12	20.3	697	22.0	0.48	380	31.7	559	31.6	<0.001
Very high risk	123	24.1	265	10.9		11	18.6	419	13.2		445	37.1	487	27.6	
Physical activity															
Inactive	345	39.6	874	35.8		42	56	1657	51.9		660	54.3	817	46.1	
Less active	199	22.8	638	26.1	*0.07*	13	17.3	740	23.2	0.48	179	14.7	339	19.1	<0.001
Most active	327	37.5	926	37.9		20	26.6	790	24.7		376	30.9	615	34.7	

BMI= body mass index; WC= waist circumference; educational attainment categorised as none (none attempted), intermediate (GCE 'O' level or Burnam C or lower) or highest (GCE A level or Burnam B or higher); exercise was coded as inactive (no participation), moderately active (participated one to four times) and most active (participated five or more times) in the previous 4 weeks/ one month; * high risk category: WC of 94-102 cm for men, WC of 80-88 cm for women; very high risk category: WC>102 for men, WC>88 cm for women

Appendix 9. Factor loadings for the first dietary pattern (high-fibre, low-fat, low-GI) extracted at age 36 using exploratory RRR analyses.



Appendix 10. Factor loadings for the first dietary pattern (low-fibre, high-fat, high-GI) extracted at age 43 using exploratory RRR analyses.