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**Understanding the Role of Integrated Grip Strength,
Physical Activity, Diet, and Adiposity-related Body
Composition in the Development of Type 2
Diabetes: Insights from the UK Biobank Cohort**

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Submitted in fulfilment of the requirement for the

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Abstract

Type 2 diabetes (T2D) is a major contributor to cardiovascular disease risk and global mortality. T2D develops through complex biological pathways influenced by modifiable lifestyle behaviours and sociodemographic context. Accordingly, this thesis explores the relationship between traditional and emerging cardiometabolic risk factors, such as grip strength, physical activity (PA), dietary patterns, and obesity-related indicators, with the incidence of T2D.

This research uses data from the UK Biobank, a large-scale population-based prospective study encompassing over 500,000 participants from across the UK. Dietary exposures were self-reported, while PA was objectively quantified using wrist-worn accelerometers. Grip strength was assessed using a hand dynamometer, and obesity-related indicators were derived from anthropometric measurements taken by trained personnel. The incidence of T2D was obtained from primary care and hospital records. Cohort analyses were conducted using harmonised methods across exposures, including multivariable Cox regression, subgroup analysis, and mediation modelling.

The findings of this thesis reveal that lower absolute or relative (kg, or kg/body mass) grip strength is linked with an increased risk of developing T2D in both women and men, compared to those with normal grip strength. Notably, relative grip strength exhibits a more pronounced association with T2D risk than absolute grip strength (12% for men and 20% for women vs. 11% for men and 12% for women). Furthermore, low grip strength may serve as an early indicator of heightened T2D risk. In terms of PA, adherence to the WHO's PA guidelines, as measured by accelerometers, is associated with a reduced risk of T2D (50%-70% depending on intensity and time spent). The magnitude of these associations is significantly greater than those reported in previous studies based on self-reported PA. Dietary analysis indicates that fish eaters (pesco-vegetarians) and those consuming fish and poultry have a lower risk of T2D (42% and 28%, respectively) compared to omnivores, while vegetarian diets show no significant association. This discrepancy may be due to a poor quality of diet, underreporting, or misclassification. Additionally, among 11 obesity-related markers evaluated for T2D risk prediction, 9 demonstrate an association, with

the waist-to-height ratio (WHtR) showing the strongest predictive value, which could potentially benefit clinical screening practices. Sociodemographic factors, such as sex, age, and ethnicity, modified both exposure levels and T2D risk.

These findings offer new insights into the roles of both emerging and established risk factors for T2D, supporting the existence of a shared biological pathway in which poor diet, low muscle strength, and physical inactivity contribute to central adiposity, systemic inflammation, and muscle insulin resistance. These interrelated exposures act synergistically, often beyond what is captured by body mass index-based models, to drive the development of T2D.

Integrated prevention strategies should therefore address behavioural, physiological, and sociodemographic dimensions to effectively reduce the burden of T2D. Among the behavioural and phenotypical factors investigated, central adiposity, particularly WHtR, emerged as one of the strongest risk factors for T2D.

However, caution is warranted when interpreting these results due to the observational nature of the study, which limits causal inference. Future research should focus on clarifying the potential causal relationships underlying these associations.

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Publications

Publications included in the thesis for the PhD

Boonpor J, Parra-Soto S, Petermann-Rocha F, et al. Associations between grip strength and incident type 2 diabetes: findings from the UK Biobank prospective cohort study. *BMJ Open Diab Res Care* 2021;9:e001865. doi:10.1136/bmjdr-2020-001865.

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Boonpor, J., et al. 2020. The combined associations of walking pace and obesity with diabetes incidence: Findings from the UK Biobank prospective cohort study. 27th European and International Congress on Obesity: ECO-ICO 2020, 1-4 September 2020. Presentation format: E-poster (video presentation).

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Author's Declaration

I declare that this thesis is the result of my own work. In those cases where the contributions of others were used, explicit references were included. The manuscripts included are open-access; therefore, they can be openly shared in this thesis.

The contents of this thesis have not been submitted for any other degree at the University of Glasgow or any other institution.

Jirapitcha Boonpor

August 2025

Definitions/Abbreviations

ABSI	A Body Shape Index
ARI	Anthropometric risk index
ADA	American Diabetes Association
BMI	Body mass index
CI	Confidence interval
CVD	Cardiovascular disease
FFQ	Food frequency questionnaire
HbA1c	Glycated haemoglobin
HR	Hazard ratio
HI	Hip index
ICD	International Classification of Diseases
IDF	International Diabetes Federation
IQR	Interquartile range
MR	Mendelian randomisation
MVPA	Moderate-to-vigorous physical activity
NDE	Natural direct effect

NIE	Natural indirect effect
NCD	Noncommunicable disease
OR	Odds ratio
PA	Physical activity
RAP	Rate advancement period
RR	Relative risk/risk ratio
TE	Total effect
T2D	Type 2 diabetes
VAI	Visceral adiposity index
WC	Waist circumference
WHR	Waist-hip ratio
WHtR	Waist-to-height ratio
WHO	World Health Organization

Chapter 1 Introduction

1.1 Definition

1.1.1 Diabetes

Diabetes is a chronic disease that is one of the first four noncommunicable disease (NCD) deaths worldwide (Bennett et al., 2018, World Health Organization, 2022). It is a chronic medical condition characterised by increased levels of blood glucose, in combination with impaired metabolism of fats and proteins (Roglic, 2016). The increase in blood glucose levels, known as hyperglycaemia, occurs as a result of the inability of cells to metabolise glucose due to insufficient insulin secretion by the pancreas or the cell's restricted capacity to use insulin (Roglic, 2016).

The American Diabetes Association (ADA) classified diabetes into four categories (American Diabetes, 2020):

1. Type 1 diabetes: Characterised by the autoimmune destruction of β -cell, resulting in a complete lack of insulin, including latent autoimmune diabetes in adults.
2. Type 2 diabetes (T2D): Characterised by the gradual decline in the ability of β -cell to secrete sufficient insulin, usually in the presence of insulin resistance.
3. Specific forms of diabetes caused by other conditions, such as diseases of the exocrine pancreas (e.g., cystic fibrosis and pancreatitis), monogenic diabetes syndromes (e.g., neonatal diabetes and maturity-onset diabetes of the young), and drug-or chemical-induced diabetes (e.g., with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation)
4. Gestational diabetes mellitus: Refers to the occurrence of diabetes during the second or third trimester of pregnancy, which was not obvious as overt diabetes earlier to the onset of gestation.

Prediabetes is a term used to denote an intermediate state between normal blood glucose (normoglycemia) and diabetes when abnormal blood glucose levels are observed. Professional associations, namely the World Health Organization (WHO), the ADA and the International Expert Committee (IEC), have released the definitions of prediabetes. The phenotypes of these definitions are identified based on several tests for hyperglycaemia, including fasting blood glucose (FBG), 2-hour plasma glucose (2-h PG) and haemoglobin A1c (HbA1c), as shown in **Table 1-1** (Echouffo-Tcheugui and Selvin, 2021).

Table 1-1 Prediabetes definitions

Tests	American Diabetes Association	World Health Organization	International Expert Committee
Fasting plasma glucose (FPG)	5.6-6.9 mmol/L (100-125 mg/dl)	6.1-6.9 mmol/L (110-125 mg/dl)	NA
2-hour plasma glucose (2-h PG) on 75-g oral glucose tolerance test (OGTT)	7.8-11.0 mmol/L (140-199 mg/dl)	7.8-11.0 mmol/L (140-199 mg/dl)	NA
Haemoglobin A1c (HbA1c)	39-47 mmol/mol (5.7-6.4%)	NA	42-47 mmol/mol (6.0-6.4%)

Note: NA, not applicable

Source: Adapted from Echouffo-Tcheugui and Selvin (2021) and American Diabetes (2020)

1.1.2 Type 2 Diabetes

T2D is a global public health problem. Previously referred to as non-insulin-dependent diabetes, it is currently the most common form of diabetes, accounting for over 90% of all diagnosed diabetes cases (International Diabetes Federation, 2021). T2D is characterised by a state of inadequate insulin levels, due to pancreatic β -cell dysfunction and insulin resistance in target organs (ChatterjeeKhunti and Davies, 2017).

Insulin production and secretion

β -cells are located in the islets of Langerhans within the pancreas (Wilcox, 2005, Galicia-Garcia et al., 2020). They play an important role in maintaining glucose homeostasis by producing and secreting insulin. Insulin is encoded from the INS gene, which is located on the short arm of chromosome 11, and produced in the β -cells of the pancreatic islets of Langerhans as its precursor, proinsulin. Proinsulin is produced in the ribosomes of the rough endoplasmic reticulum (RER) from mRNA as pre-proinsulin. And then, pre-proinsulin undergoes structural changes in the RER to form proinsulin. Proinsulin is then transported from the RER to the Golgi apparatus (GA). In the GA, proinsulin enters immature secretory vesicles and is cleaved into insulin and C-peptide. Insulin and C-peptide are kept inside the granules until insulin secretion is induced (Wilcox, 2005, Galicia-Garcia et al., 2020).

Insulin secretion is initially triggered by hyperglycaemia. When hyperglycaemia occurs, pancreatic β -cells uptake glucose via glucose transporter 2 (GLUT2). Upon glucose entry, glucose is detected by glucokinase, which converts glucose into glucose 6-phosphate (G6P). It undergoes metabolism through glycolysis and mitochondria processes, resulting in elevating cytosolic adenosine triphosphate (ATP) and reducing cytosolic adenosine diphosphate (ADP) (increasing ATP/ADP ratio). This increase prompts the closure of ATP-dependent potassium channels in the plasma membrane. When the ATP-dependent potassium channels close, the cell membrane is depolarised and activates voltage-dependent calcium channels, allowing Ca^{2+} to enter the cell. This leads to a rise in intracellular Ca^{2+} concentration. The elevation of the intracellular Ca^{2+} concentration stimulates the priming and fusion of insulin-containing granules with the plasma membrane, leading to exocytosis, where insulin is released (Wilcox, 2005, Galicia-Garcia et al., 2020, AshcroftLloyd and Haythorne, 2023).

B-cell dysfunction

The latest evidence suggests that B-cell dysfunction is due to complex mechanisms involving many interactions between the various biochemical processes and the environment (Galicia-Garcia et al., 2020), which is driven by various factors, including inflammation induced by cytokines, insulin resistance, obesity, and excessive intake of free fatty acids and saturated fats (Cerf, 2013, Galicia-Garcia et al., 2020)

Insulin resistance

Insulin resistance describes a reduction in the metabolic response of cells that react to insulin, which relates to three conditions: (1) declined insulin secretion, (2) insulin competitors in the plasma and (3) impaired response to insulin in target organs, i.e. skeletal muscle, liver and adipose tissue. Insulin resistance is thought to develop at the cell level due to post-receptor abnormalities in insulin signalling. In the fed state, the action of insulin is influenced by its interaction with other hormones, including IGF-1 and growth hormone. Growth hormone is released in response to insulin to prevent insulin-induced hypoglycaemia. During the fasting state, additional counter-regulatory hormones, including glucagon, glucocorticoids, and catecholamines, play a key role in regulating metabolic activities to prevent hypoglycaemia. Glucagon stimulates glycogenolysis, gluconeogenesis and ketogenesis. Glucocorticoids stimulate gluconeogenesis, muscle catabolism and lipolysis. Catecholamines stimulate glycogenolysis and lipolysis. Over-secretion of these hormones can contribute to developing insulin resistance in specific conditions (Wilcox, 2005). Insulin resistance occurs primarily in three extra-pancreatic insulin-sensitive organs: skeletal muscle, adipose tissue, and liver. A malfunction in the action of insulin in these tissues frequently precedes the onset of systemic insulin resistance (Galicia-Garcia et al., 2020).

1.2 Diagnosis of Type 2 Diabetes

The diagnosis of T2D is based on plasma glucose or HbA1c criteria. The diagnosis screening is equally proper for FPG, 2-h PG during 75-g oral glucose tolerance test (OGTT), and HbA1c (American Diabetes, 2020). Based on the ADA document, T2D is diagnosed with at least one of the criteria listed in **Table 1-2** (American Diabetes, 2020). To confirm the diagnosis, it is necessary to obtain the two abnormal test results for diagnosis, either from the same sample or two separate test samples (American Diabetes, 2020).

Table 1-2 Type 2 diabetes diagnosis criteria

Criteria	Cut-off point
Fasting plasma glucose (FPG)	≥7.0 mmol/L (126 mg/dL)
OR	
2-h plasma glucose (2-h PG) during 75-g oral glucose tolerance test (OGTT)	≥11.1 mmol/L (200 mg/dL)
OR	
Haemoglobin A1c	≥48 mmol/mol (6.5%)
OR	
Random Plasma glucose in the presence of classic symptoms of hyperaemia or hyperglycaemic crisis	≥11.1 mmol/L (200 mg/dL)

Note: FPG should be tested after fasting for at least 8 hours (fasting means no dietary intake for at least 8 hours). 2-h PG during the 75-g OGTT should be taken using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water, as the World Health Organization described. Haemoglobin A1C should be using the standard methods in a laboratory.

Source: Adapted from American Diabetes (2020)

1.3 Epidemiology, Prevalence and Projections of Diabetes

Over several decades, diabetes cases have had a significant increase, with the number of individuals affected rising from 108 million in 1980 to 422 million in 2014 worldwide. In 2019, diabetes was identified as the primary cause of 1.5 million deaths and it was observed that 48% of all diabetes-related deaths occurred prior to people reaching the age of 70. Between 2000 and 2019, the age-standardised death rate due to diabetes had a 3% increase globally (World Health Organization, 2023).

The International Diabetes Federation (IDF) published global estimates of the prevalence of diabetes for the period 2021 to 2045. It projects that the number of people aged between 20-79 years old with diabetes will reach 783 million by 2045 (International Diabetes Federation, 2021), accounting for 12.2% of the worldwide population in this age group (Sun et al., 2022). As a subset of the estimated data, the prevalence of diabetes in Europe is projected to reach 69 million, accounting for a 13% increase from 2021 to 2045 (**Figure 1-1**).

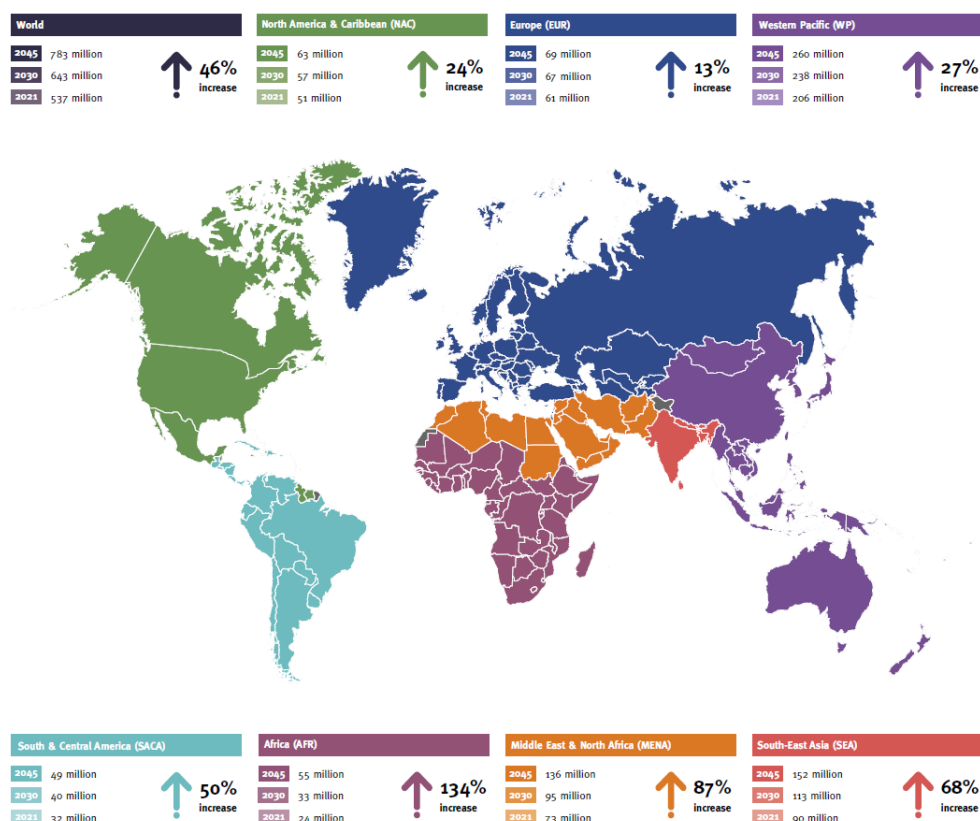


Figure 1-1 Number of people with diabetes worldwide and per IDF Region in 2021–2045 (aged 20–79 years)

Source: Figure from International Diabetes Federation (2021)

The projected increase in T2D prevalence is estimated to increase across the world from 7,079 people per 100,000 by 2023 to 7,862 people per 100,000 by 2040. (Khan et al., 2020).

In the UK, similarly, the prevalence rate of T2D showed an upward trend, rising from 3.21% (95% Confidence Interval [CI] 3.19-3.22) in 2004 to 5.26% (95% CI 5.24-5.29) in 2014 (Zghebi et al., 2017). Currently, the number of people diagnosed with diabetes within the UK population is approximately 4.3 million. The registration statistics for 2021-2022 have revealed an increase of 148,591 individuals compared to 2020-2021. Furthermore, there are more than 2.4

million individuals currently identified as being at higher risk of developing T2D. (Diabetes UK, 2023, Jacqui, 2023).

Importantly, it is predicted that one in ten individuals in the UK may be affected by diabetes by 2030 unless the government allocates a significant investment towards prevention services. However, around 33% or one in three individuals, up to 17 million adults, may have an increased risk of T2D over the next ten years without further financial support from the government (Gareth, 2021).

To conclude, data sources clearly show that T2D is increasing significantly in the UK and around the world with a considerable number of people already affected by T2D. Therefore, further investigation to understand the development of T2D is required to help determine what factors and measures can prevent it.

1.4 Risk Factors of Type 2 Diabetes

A complex combination of risk factors for T2D, including genetic, metabolic and environmental factors, interacts with one another. Of those, risk factors can be broadly categorised into non-modifiable and modifiable factors. Among the non-modifiable risk factors, age is particularly influential. For instance, a study of the effect of age on the prevalence of T2D with different BMI ranges in 296,824 individuals aged between 18-90 years old found that a statistically significant age-related increase in the prevalence of T2D was observed, including among individuals with a normal BMI. This study also found that the ageing impact became more pronounced at the age of 40, at which point a statistically significant inflection occurred (FazeliLee and Steinhauser, 2019). Other key non-modifiable factors include biological sex, ethnicity, and family history of T2D, all of which may interact with and influence modifiable lifestyle-related risk factors (Tabák et al., 2012, FletcherGulanick and Lamendola, 2002). For instance, individuals of South Asian, African-Caribbean, or Hispanic descent have a higher predisposition to T2D, independent of BMI, possibly due to genetic susceptibility and differences in fat distribution (Haffner, 1998, Sattar and Gill, 2015). A narrative review of sex differences in T2D revealed that there were differences

between women and men in the risk of T2D. For example, women had greater skeletal muscle and hepatic insulin sensitivity compared to men. Meanwhile, men manifested T2D at an earlier age and with a lower BMI than women. This review also emphasised that sex difference was influenced by age and ethnicity, and separating these interrelationships may enable more tailored approaches to diabetes management (Kautzky-WillerLeutner and Harreiter, 2023). The prevalence of T2D in people with a familial history was around fourfold greater than that of individuals without such a history. It was also strongly correlated with the number of parents affected. Furthermore, the prevalence of T2D among individuals with a mother with T2D (16.5%) exceeded that of persons with a father with T2D (12.4%). In addition, the prevalence of familial history in adults varied according to numerous variables such as age, ethnicity or BMI (Annis et al., 2005).

Among the modifiable risk factors, obesity, particularly central adiposity, is considered the most important determinant of T2D development, given its strong association with insulin resistance and pancreatic β -cell dysfunction (KahnHull and Utzschneider, 2006). In addition to obesity, several other lifestyle and behavioural factors significantly contribute to T2D risk, including diet, physical activity (PA), smoking, sleep quality and sleep duration, and gut microbiome (Salzberg, 2022, Shan et al., 2015, Reutrakul and Cauter, 2018, Lynch and Pedersen, 2016). The cumulative effect of these factors can accelerate metabolic dysfunction and chronic inflammation, key mechanisms in T2D pathogenesis.

Emerging evidence also emphasises the critical role of social determinants of health (SDOH) in shaping diabetes risk. These determinants include socioeconomic status (e.g., education level, income, and occupation), the neighbourhood and physical environment (e.g., housing quality, built environment, exposure to pollutants), and the food environment (e.g., food security, access to affordable healthy foods). For instance, socioeconomic status (SES), a multifaceted term including educational, economic, and occupational status, is a robust and consistent predictor of both the onset and progression of

diabetes across all SES levels. It is closely intertwined with nearly all recognised SDOH, influencing individuals' and communities' access to essential material resources such as healthcare and nutritious food as well as social resources such as political influence, social participation, and control. (Hill-Briggs et al., 2020). In addition, barriers in healthcare access and affordability, along with social and community context, such as social support networks, social capital, and community cohesion, can significantly influence an individual's ability to adopt and maintain healthy behaviours. Addressing these broader determinants is essential to reduce health disparities and promote equitable prevention strategies for T2D. These social determinants are also likely to operate through the lifestyle and behavioural factors discussed above.

Interestingly, a comprehensive umbrella review of 86 systematic reviews and meta-analyses based on observational data revealed that T2D is influenced by a broad range of risk factors spanning dietary, lifestyle, psychosocial, environmental, clinical, and biological domains (Bellou et al., 2018). The review categorised the strength of evidence for each risk factor into four levels: convincing, highly suggestive, suggestive, and weak, based on methodological quality, heterogeneity, and presence of bias.

Among the risk factors supported by convincing evidence for increased T2D risk were obesity, low whole grain intake, low adherence to healthy dietary patterns (referred to as decreased intake of red and processed meats, moderate alcohol intake, minimal use of sugar-sweetened drinks, and heightened intake of whole grain items), high consumption of sugar-sweetened beverages, and increased sedentary time. In addition to lifestyle and dietary behaviours, several biomarkers and clinical factors were also strongly associated with increased T2D risk. These included low serum vitamin D levels, elevated serum uric acid, increased serum alanine aminotransferase, and exposure to high levels of fine particulate matter (PM₁₀). Notably, psychosocial and early life factors such as low conscientiousness and preterm birth were also identified as convincing risk factors (Bellou et al., 2018). These findings highlight the complex interplay of biological, behavioural, and environmental determinants in the development of

T2D and reinforce the need for an integrated, multi-sectoral approach to prevention. However, the factors were used to study in the present research based on data available in the UK Biobank, as shown in **Figures 1-2**.

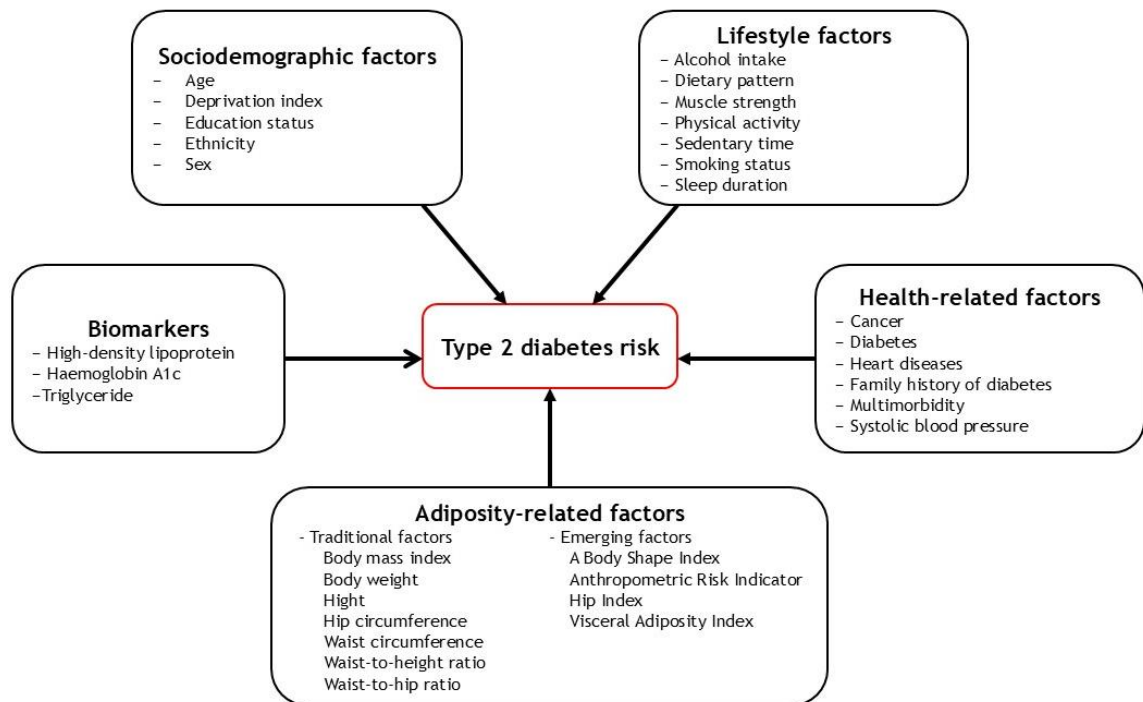


Figure 1-2 Factors of type 2 diabetes studied in the present study

Source: Adapted from Bellou et al. (2018)

1.4.1 Physical Activity, Muscle Strength and Type 2 Diabetes

1.4.1.1 Physical Activity in Glucose Regulation

PA is defined as any bodily movement produced by skeletal muscles that results in a significant increase in energy expenditure above resting levels. Individuals engage in a spectrum of physical activities ranging from light-intensity daily tasks to vigorous structured exercise. In epidemiological research and public health guidelines, PA intensity is commonly expressed using the metabolic equivalent of task (MET), a standardised physiological measure that quantifies

energy expenditure. One MET corresponds to the energy expended while sitting quietly at rest. Activities between 1.5 and <3 METs are generally considered light intensity, those between ≥ 3 and <6 METs as moderate intensity, and activities ≥ 6 METs as vigorous intensity (Gill, 2022).

Biologically, the link between PA and reduced T2D risk is well established. Extensive research has established that aerobic exercise promotes physiological adaptations at both the molecular and systemic levels. These adaptations are particularly evident within the cardiovascular and musculoskeletal systems, which exhibit enhanced oxygen delivery, increased endurance capacity, and improved functional performance. When practised consistently over time, aerobic training facilitates chronic adaptations that are associated with positive clinical outcomes (Farrell and Turgeon, 2023).

Regular aerobic exercise promotes adaptations in skeletal muscles, leading to acute and chronic effects on T2D. Acute effects include increased hepatic glucose, increased glucose uptake in muscle, increased lipolysis of free fatty acids from adipose cells, decreased insulin secretion due to increased epinephrine secretion from adrenal medulla, increased glucagon (secreted by pancreatic alpha cells, this substance promotes glycogenolysis in the liver, resulting in the release of 75% of the liver's glucose), increased growth hormone, and increased cortisol from the adrenal cortex. Chronic effects include lower circulating insulin, improved glucose tolerance, reduced insulin resistance, increased number of insulin receptors in skeletal muscle in individuals with T2D, increased insulin-like effect of muscle contraction (increases GLUT4 transporter), and increased insulin sensitivity in individuals with T2D (Rod K. Dishman et al., 2022).

1.4.1.2 Physical Activity and Type 2 Diabetes: Epidemiological Evidence and Methodological Advances

The health benefits of PA are well established, particularly in reducing the burden of non-communicable diseases (NCDs) such as cardiovascular disease

(CVD), obesity, and T2D (Reiner et al., 2013). In relation to T2D, a comprehensive systematic review and dose-response meta-analysis of 78 cohort studies and three randomised controlled trials demonstrated that total PA, as well as specific types and intensities of PA, were inversely associated with T2D risk (Aune et al., 2015). Compared to individuals with low levels of PA, the relative risk (RR) of developing T2D among those with high levels of activity was 0.65 (95% CI: 0.59-0.71) for total PA. Specific PA types also showed protective effects: walking (RR: 0.85; 95% CI: 0.79-0.91), leisure-time activity (RR: 0.74; 95% CI: 0.70-0.79), moderate activity (RR: 0.68; 95% CI: 0.52-0.90), low-intensity activity (RR: 0.66; 95% CI: 0.47-0.94), and vigorous activity (RR: 0.61; 95% CI: 0.51-0.74).

Subsequently, Smith et al. (2016) conducted another dose-response meta-analysis based on 28 prospective cohort studies, confirming the protective association between PA and T2D risk. Their findings indicated that individuals engaging in 150 minutes per week of moderate-intensity PA, aligned with current public health guidelines, had a 26% lower risk of developing T2D (RR: 0.74; 95% CI: 0.69-0.80) compared to inactive individuals. Notably, doubling this amount of activity further reduced the risk by 36% (95% CI: 27%-46%) (Smith et al., 2016).

In line with this evidence, the 2020 WHO Guidelines on Physical Activity and Sedentary Behaviour recommend that all adults engage in 150-300 minutes of moderate-intensity aerobic activity per week, or 75-150 minutes of vigorous-intensity aerobic activity, or an equivalent combination of both. Additionally, adults should perform muscle-strengthening activities involving all major muscle groups on two or more days per week. For further health benefits, adults are encouraged to exceed 300 minutes of moderate-intensity PA per week, where feasible and appropriate (Bull et al., 2020).

However, the majority of data used in these large-scale epidemiological studies and subsequent PA recommendations have been derived from self-reported measures of PA, which are subject to various limitations (Gill et al., 2023, Bull et al., 2020). These include recall bias, social desirability bias, overestimation of

moderate-to-vigorous physical activity (MVPA), underreporting of light-intensity activity, and the inability to detect short sporadic bouts of movement. To address these limitations, device-based PA measurement tools, such as accelerometers and pedometers, are increasingly used in both research and clinical contexts (Jin et al., 2023, Timothy James et al., 2023).

Device-based tools offer more objective, continuous, and fine-grained assessments of PA. Importantly, they capture actual movement patterns across the full intensity spectrum and provide insights into activity duration, frequency, and context that are not typically available from self-report data (Gill et al., 2023). Accelerometers, one of the most widely used devices, employ motion-sensing technology to record raw acceleration data across three axes. These data are typically collected at high sampling frequencies (up to 100 Hz) and can be integrated with additional sensors (e.g., heart rate monitors) and digital devices (Sasaki et al., 2016). Accelerometers can be worn on different body locations (e.g., wrist, hip, thigh) depending on the research protocol and population characteristics. Raw data are later processed and calibrated to derive meaningful PA metrics such as energy expenditure, step count, and time spent in different intensity domains (ArvidssonFridolfsson and Börjesson, 2019).

Despite the methodological advantages of device-based PA measurement, few longitudinal studies have examined the relationship between objectively measured PA and health outcomes such as T2D. Most available studies have focused on CVD and all-cause mortality. For instance, a 10-year follow-up of young adults found that replacing sedentary time with light or moderate-to-vigorous PA (as measured by accelerometer) was associated with improved cardiometabolic health (Whitaker et al., 2019). Similarly, Ramakrishnan et al. (2021) reported that middle-aged and older adults with higher quartiles of device-measured MVPA had a significantly reduced risk of incident CVD. Ballin et al. (2021) also observed protective effects of light and moderate PA, measured using a hip-worn accelerometer, against CVD and all-cause mortality in 70-year-olds (Ballin et al., 2021).

With regard to T2D, a large U.S.-based prospective cohort study of 7,280 participants aged 18-74 employed hip-worn accelerometers to evaluate MVPA levels (Chen et al., 2020). The results showed that individuals aged 50 years and older in the highest quartile of MVPA had a 44% lower risk of developing T2D compared to those in the lowest quartile (RR: 0.56; 95% CI: 0.38-0.82), after adjusting for a wide range of confounders, including demographics, lifestyle behaviours, and accelerometer wear time (Chen et al., 2020). However, no significant association was found among younger adults ($P = 0.68$). A key limitation of this study was the exclusive focus on MVPA, with no analyses of light, total, or vigorous PA, thereby limiting the comprehensiveness of the findings.

In summary, although device-based PA measurements offer clear advantages over self-reports and have improved the precision of PA epidemiology, the evidence linking these measures specifically to T2D risk remains limited and is still emerging. There is a need for more well-powered, prospective cohort studies using standardised device-based assessments that can capture the full spectrum of PA intensities. These studies should also include diverse populations, longer follow-up periods, and harmonised data processing protocols to enable cross-study comparisons. Strengthening the evidence base in this area will be critical for refining future PA guidelines and advancing T2D prevention strategies based on objective PA metrics.

1.4.1.3 Muscular Strength in Glucose Regulation

Muscular strength is a key component of muscular fitness, alongside muscular endurance and power, and is defined as the ability of a muscle or muscle group to exert force against resistance (Rod K. Dishman et al., 2022). It is influenced by both PA, particularly resistance training, and genetic factors (Roth, 2012, Grgic et al., 2018) . Although the volume of research on muscular strength in relation to T2D remains limited compared to aerobic activity, a growing body of evidence supports its potential role in metabolic health.

Skeletal muscle plays a central role in maintaining glucose homeostasis, particularly in the postprandial state. Approximately 80% of glucose uptake following a meal is facilitated by insulin-dependent mechanisms in skeletal muscle. Glucose disposal into muscle tissue requires several coordinated steps: (1) delivery of glucose via the bloodstream, (2) diffusion of glucose through the extracellular matrix to the muscle cell membrane, (3) uptake via glucose transporters, either constitutively expressed or translocated in response to insulin or muscle contraction, and (4) the presence of a glucose gradient driven by intracellular metabolism. Given that skeletal muscle is a major target for systemic glucose disposal, impairments at any of these stages can contribute to whole-body insulin resistance. In individuals with T2D, skeletal muscle exhibits multiple pathological changes that impair glucose transport, uptake, and metabolism, underscoring its pivotal role in T2D pathogenesis (HulettScalzo and Reusch, 2022).

Individuals with higher muscular strength generally have greater muscle mass and improved muscle quality, which are associated with increased insulin sensitivity and more efficient glucose metabolism (Dishman et al., 2021). Resistance training, which enhances muscular strength, has been shown to upregulate GLUT4 expression and increase mitochondrial density in muscle fibres, adaptations that support enhanced glucose transport and oxidation. Furthermore, resistance training is associated with reduced systemic inflammation and improved lipid profiles, both of which are important in T2D prevention (Dishman et al., 2021).

Importantly, muscle contraction itself stimulates the translocation of GLUT4 to the plasma membrane, promoting glucose uptake independent of insulin. This insulin-independent pathway is mediated through several intracellular signalling mechanisms. Muscle contraction induces calcium influx, activating protein kinase C (PKC) and Ca²⁺/calmodulin-dependent protein kinases (CaMK), which contribute to GLUT4 mobilisation. In parallel, contraction increases the AMP/ATP ratio, activating AMP-activated protein kinase (AMPK), a key energy sensor that enhances glucose transport through multiple pathways. AMPK

activation may also stimulate p38 mitogen-activated protein kinase (MAPK), further facilitating GLUT4 translocation and glucose uptake (Rod K. Dishman et al., 2022).

Figure 1-3 illustrates that muscle strength and its contraction enhance glucose metabolism, thereby improving insulin sensitivity.

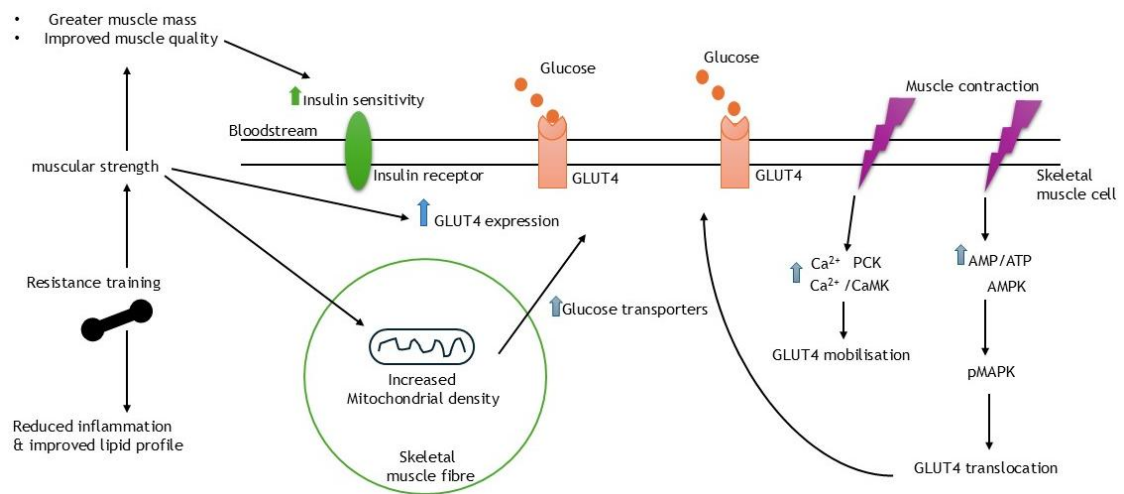


Figure 1-3 Linking muscular strength, resistance training, and glucose transport in skeletal muscle

Consistent with these mechanisms, stronger muscles are often a marker of better glycaemic control and lower insulin resistance. Skeletal muscle abnormalities, such as impaired insulin signalling and reduced oxidative capacity, are commonly observed in individuals with T2D, further highlighting the central role of muscle strength in metabolic regulation.

1.4.1.4 Muscular Strength and Type 2 Diabetes: Epidemiological Evidence and Methodological Advances

Epidemiological studies have also found an inverse association between muscular strength and all-cause mortality (VolaklisHalle and Meisinger, 2015, Jochem et al., 2019). These associations remain significant even after controlling for

cardiorespiratory fitness, body composition, age, alcohol consumption, and smoking status, suggesting that muscular strength is an independent predictor of long-term health outcomes. In recognition of its health relevance, muscular strength has been included in recent PA guidelines, particularly in relation to the prevention of chronic diseases. Despite this, research examining the direct association between muscular strength and incident T2D remains relatively scarce. Muscle strength can be assessed using various methods, including isometric, isotonic, and isokinetic dynamometry, one-repetition maximum (1-RM) tests, and functional tests such as chair stands or timed up-and-go. Among these, handgrip strength is the most widely used indicator in large epidemiological studies due to its simplicity, low cost, and minimal burden on participants (Bohannon, 2019). Standardised protocols, such as the Southampton Protocol, have been developed to ensure the reproducibility and accuracy of grip strength measurement. According to this protocol, participants are seated in a standard chair with forearms resting on the chair arms. Using a calibrated handgrip dynamometer, individuals perform three maximal contractions with each hand, holding each for 3-5 seconds. The highest value from the six measurements is typically used for analysis (Beudart et al., 2019).

A systematic review and meta-analysis by Tarp et al. (2019) examined the association between muscular strength and the risk of developing T2D. Thirteen studies were included in the systematic review, with 11 studies contributing to the meta-analysis. Their results showed that each 1-standard deviation (SD) increase in muscular strength was associated with a 24% reduced risk of incident T2D (RR: 0.76; 95% CI: 0.64-0.91). After adjusting for adiposity, the association remained significant but was attenuated to a 13% lower risk (RR: 0.87; 95% CI: 0.81-0.94). Notably, when muscular strength was normalised to body mass, stronger associations were observed (RR: 0.83; 95% CI: 0.79-0.86) compared to absolute strength (RR: 0.95; 95% CI: 0.87-1.04), suggesting that relative muscular strength may be a more sensitive indicator of metabolic risk (**Figure 1-4**) (Tarp et al., 2019).

Despite these promising findings, several limitations in the current evidence base should be acknowledged. Studies included in the meta-analysis varied in their confounder adjustment, with some failing to control for key variables such as baseline PA or dietary intake. There was also notable heterogeneity in population characteristics, sample size, and methods of strength assessment. Moreover, the possibility of reverse causation, where preclinical T2D may lead to reduced muscle strength, was not fully addressed, as few studies excluded participants who developed T2D shortly after baseline assessment. Some studies were also restricted to specific subgroups, such as only men or women, limiting generalisability.

In summary, muscular strength appears to be inversely associated with the risk of T2D, supported by both biological mechanisms and observational data. However, the existing evidence is limited by methodological variability and a small number of longitudinal studies. Given that skeletal muscle is a major site of glucose uptake, handgrip strength, as a practical and scalable proxy for muscle function, may serve as a useful marker for T2D risk (Bohannon, 2019). Future research is needed to clarify the dose-response relationship, assess causality, and explore the potential for strength-based interventions in diabetes prevention strategies.

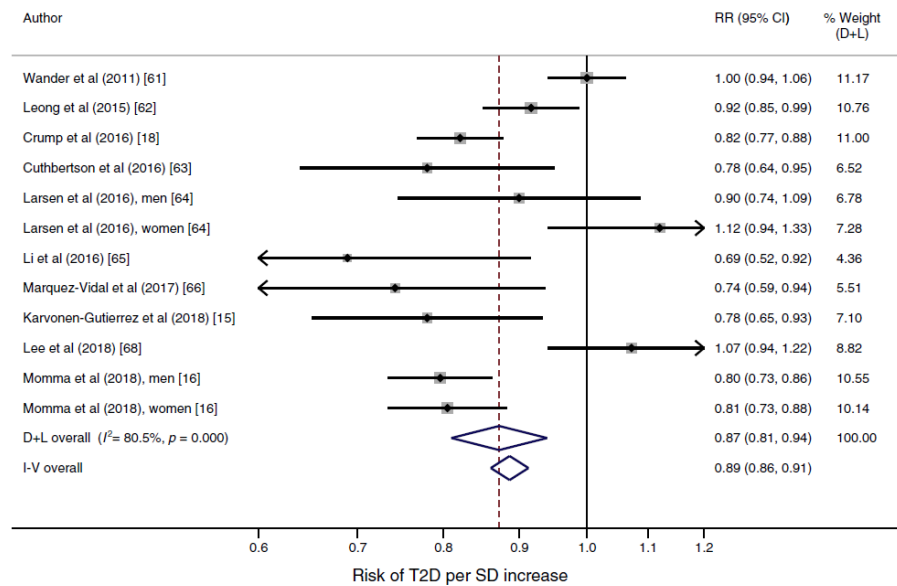


Figure 1-4 Association between 1-SD increase in muscular strength and type 2 diabetes risk in adiposity adjustment model

Source: Figure from Tarp et al. (2019)

1.4.2 Dietary Intake and Type 2 Diabetes

1.4.2.1 Dietary Intake and Its Association with Type 2 Diabetes

Diet plays a critical role in the development, progression, and prevention of T2D. An unhealthy dietary pattern, characterised by excessive intake of saturated fats, refined carbohydrates, added sugars, and energy-dense, nutrient-poor foods, has been consistently identified as a major modifiable risk factor for T2D (Ley et al., 2014, Imamura et al., 2015). Chronic overnutrition contributes to key metabolic disturbances, including hyperglycaemia, hyperlipidaemia, low-grade systemic inflammation, as well as a metabolic inflammatory condition (metaflammation) in metabolic cells due to an overload of nutrients and energy (status of obesity), all of which are central to the pathophysiology of insulin resistance (Gregor and Hotamisligil, 2011). Elevated circulating free fatty acids, due to intake of energy-dense diets rich in fat,

especially saturated fat, can also trigger ER stress and oxidative damage, impairing pancreatic β -cell function and insulin secretion (Cnop et al., 2005, Gregor and Hotamisligil, 2011). Collectively, these metabolic effects increase the risk of T2D in individuals consuming poor-quality diets.

The evidence supporting the relationship between diet and T2D risk is extensive and continues to expand. A landmark umbrella review of 53 meta-analyses of prospective observational studies found robust associations between specific dietary components and incident T2D (Neuenschwander et al., 2019). Increased consumption of whole grains (Hazard Ratio [HR]: 0.87; 95% CI: 0.82-0.93) and cereal fibre (HR: 0.75; 95% CI: 0.65-0.86) was associated with a significantly lower risk of T2D. Similarly, moderate alcohol consumption was associated with reduced risk (HR: 0.75; 95% CI: 0.67-0.83). Conversely, a higher intake of processed meat (HR: 1.37; 95% CI: 1.22-1.54), red meat (HR: 1.17; 95% CI: 1.08-1.26), sugar-sweetened beverages (HR: 1.26; 95% CI: 1.11-1.43), and bacon (HR: 2.07; 95% CI: 1.40-3.05) was associated with significantly increased T2D risk.

Despite these clear patterns, Neuenschwander et al. (2019) highlighted several methodological limitations in the current literature. Dietary exposure assessments often rely on self-reported instruments with limited validity, and definitions of dietary components (e.g., “red meat”) are not consistently applied across studies. The authors also called for more research using substitution models, dietary patterns, network meta-analyses, and mediation analyses, especially those considering potential interactions among food groups and the mediating role of factors such as BMI. Additionally, there is a need to distinguish between the effects of unprocessed versus processed food items and to explore under-researched exposures, such as types of fish (e.g., oily vs. lean) (Neuenschwander et al., 2019).

Further complexity arises from inconsistencies in the evidence on macronutrients, particularly carbohydrates and saturated fats, in relation to T2D. The most recent reports by the Scientific Advisory Committee on Nutrition (SACN) identified conflicting findings and substantial limitations in this area

(Scientific Advisory Committee on Nutrition, 2015, Scientific Advisory Committee on Nutrition, 2019, Scientific Advisory Committee on Nutrition, 2021). As summarised in **Table 1-3**, these limitations include heterogeneity in macronutrient classification, varying dietary assessment methods, and differences in follow-up durations (short-term interventions vs. long-term cohort studies). Moreover, many of the reviewed studies were conducted in populations already diagnosed with T2D, limiting their relevance to primary prevention.

SACN (2021) emphasised the need for higher-quality evidence using standardised definitions, improved dietary assessment tools, and prospective designs that can better isolate the effects of individual macronutrients and dietary patterns in T2D development. These improvements are essential for advancing the scientific basis of dietary recommendations for diabetes prevention and public health policy.

Table 1-3 Evidence on the association of saturated fat (SACN, 2019) and carbohydrate (SACN, 2015) with type 2 diabetes and its biomarkers

Nutrients	Evidence from Randomised controlled trials	Evidence from Prospective Cohort Studies
Saturated fats and type 2 diabetes		
Reduced intake of saturated fats	No evidence	No association Adequate evidence
Saturated fats and glucose tolerance		
Reduced intake of saturated fats	Insufficient evidence	No evidence
Saturated fats and insulin resistance assessed by Homeostatic model assessment		
Reduced intake of saturated fats	Insufficient evidence	No evidence
Saturated fat substitution and type 2 diabetes		

Substitution with carbohydrates	Insufficient evidence	No evidence
Substitution with polyunsaturated fatty acid (PUFA)	No evidence	Insufficient evidence
Saturated fat substitution and fasting glucose		
Substitution with PUFA	- Effect - Adequate evidence	No evidence
Substitution with monounsaturated fatty acid (MUFA)	- No effect - Adequate evidence	No evidence
Substitution with carbohydrate	- No effect - Adequate evidence	No evidence
Saturated fat substitution and fasting insulin		
Substitution with PUFA	- No effect - Adequate evidence	No evidence
Substitution with MUFA	- Effect - Adequate evidence	No evidence
Substitution with carbohydrates	- Effect - Adequate evidence	No evidence
Saturated fat substitution and glycated haemoglobin		
Substitution with PUFA	- Effect - Adequate evidence	No evidence
Substitution with MUFA	- Effect	No evidence

	- Adequate evidence	
Substitution with carbohydrates	- No effect - Adequate evidence	No evidence
Saturated fat substitution and glucose tolerance		
Substitution with PUFA	- No effect - Adequate evidence	No evidence
Substitution with MUFA	- No effect - Adequate evidence	No evidence
Substitution with carbohydrates	- No effect - Adequate evidence	No evidence
Saturated fat substitution and insulin resistance assessed by HOMA		
Substitution with PUFA	- Effect - Adequate evidence	No evidence
Substitution with MUFA	- Effect - Adequate evidence	No evidence
Substitution with carbohydrates	- No effect - Adequate evidence	No evidence
Saturated fat substitution and insulin resistance assessed by infusion		
Substitution with PUFA	- No effect - Adequate evidence	No evidence

Substitution with MUFA	- No effect - Adequate evidence	No evidence
Substitution with carbohydrates	- No effect - Adequate evidence	No evidence
Carbohydrate and type 2 diabetes		
Total carbohydrate (% energy or g/day)	No data	- No association - Moderate evidence
Carbohydrate and glycaemia		
Total carbohydrate (% energy or g/day)	Difference in the proportion of carbohydrate to fat and/or protein about measures of glycaemia	- No association - Moderate evidence
Carbohydrate and oral glucose tolerance test		
Higher total carbohydrate diets	- No effect - Adequate evidence	No data
Carbohydrate and fasting blood glucose concentration		
Higher carbohydrate, lower fat diets	- No effect - Adequate evidence	No data
Higher carbohydrate, average protein diets	- No effect - Adequate evidence	No data
Higher carbohydrate, low fat, average protein diets	- No effect - Adequate evidence	No data

Carbohydrate and fasting blood insulin concentration		
Higher carbohydrate, low fat diets	- No effect - Adequate evidence	No data
Higher carbohydrate, average protein diets	- No effect - Adequate evidence	No data
Higher carbohydrate, low fat, average protein diets	- No effect - Adequate evidence	No data
Carbohydrate and insulin response to oral glucose tolerance test		
Higher carbohydrate, low-fat diets	- No effect - Adequate evidence	No data
Carbohydrate and insulin resistance/sensitivity		
Higher carbohydrate, low fat diets	- No effect - Adequate evidence	No data
Higher carbohydrate, low fat, average protein diets	- No effect - Adequate evidence	No data
Carbohydrate and haemoglobin A1c concentration		
Higher carbohydrate diets	- No effect - Adequate evidence	No data
Sugar and type 2 diabetes		
Sugars (g/day)	No data	- No association

		- Limited evidence
Sugar and blood insulin concentration		
Sugars	- No effect - Limited evidence	No data
Sugars-sweetened beverages and type 2 diabetes		
Sugars-sweetened beverages (ml/day)	No data	- Association - Moderate evidence

Source: Adapted from Scientific Advisory Committee on Nutrition (2015) and Scientific Advisory Committee on Nutrition (2019).

1.4.2.2 Dietary Assessment

Accurate assessment of dietary intake is essential for investigating associations between diet and health outcomes. Traditionally, dietary intake is assessed through self-reported questionnaires, which estimate food and beverage consumption over a specified time period. Food frequency questionnaires (FFQs), 24-hour dietary recalls and dietary records are commonly used methods to collect dietary data (Garcia-Aloy et al., 2017, Neuhouser et al., 2023).

FFQs ask participants to report how often they consume particular food items from a pre-defined list, along with portion size estimates, over a specified time period (e.g., past month or year). They are widely used in large-scale studies due to their relatively low cost and minimal participant burden. In contrast, 24-hour dietary recalls require individuals to recall all food and drink consumed over the previous 24 hours. These are typically administered via in-person or telephone interviews, using paper-based or computer-assisted tools. Self-administered versions are increasingly common (Thompson and Subar, 2017).

Dietary records, also known as food diaries, involve participants recording all foods and beverages consumed—ideally at the time of consumption—over one or more days. Portion sizes may be estimated using household measures, digital scales, or food models/images. Data are typically collected over 3 to 7 consecutive days (Neuhouser et al., 2023). While this method can provide detailed intake information, its high cost and participant burden limit its use in large epidemiological studies (Thompson and Subar, 2017, Neuhouser et al., 2023).

Notably, FFQs and 24-hour dietary recalls rely on participants' memory and self-reporting, making them prone to recall bias and misreporting (NaskaLagiou and Lagiou, 2017). To address these issues, researchers have increasingly turned to dietary biomarkers—biological samples that reflect the consumption or metabolism of specific dietary components or overall nutritional status. These biomarkers have been instrumental in both validating dietary assessment tools and offering independent insights into dietary patterns. Dietary biomarkers are generally classified into two categories: direct biomarkers, which reflect specific nutrient intake, and biomarkers of nutritional status, which are influenced by metabolic processes and interactions among nutrients. Both types are frequently utilised to estimate the intake of particular nutrients, foods, or food groups. In recent years, the growing use of metabolomics has significantly advanced this field. As the comprehensive analysis of small molecules produced within an organism, metabolomics enables a detailed examination of metabolites in biological samples, many of which are directly linked to dietary intake (Liang et al., 2022).

Although nutrient biomarkers provide objective measures, their ability to fully capture the complexity and diversity of dietary intake, approaching individual foods, food groups, and whole dietary patterns, remains limited (Neuhouser et al., 2023). To improve the accuracy of dietary assessments, some studies recommend combining multiple dietary questionnaires and incorporating biomarker data (NaskaLagiou and Lagiou, 2017). Others suggest that repeated

24-hour dietary recalls used in conjunction with FFQs offer a practical and effective approach for nutritional epidemiology (Carroll et al., 2012).

1.4.2.3 Plant-based Diets and Its Association with Type 2 Diabetes

A plant-based diet is defined as one having minimal consumption of animal-based foods that includes vegetarian diets. Several categories of vegetarian diets are possible. Vegan diets exclude the consumption of all meat and animal products. Lacto-vegetarians excluded other animal products but consumed dairy products. Lacto-ovo vegetarians excluded other animal foods but consumed eggs and dairy. Pesco-vegetarians (also known as pescatarians) excluded poultry and red meat but consumed eggs, dairy and fish (Satija and Hu, 2018). Regarding benefits, plant-based diets were associated with lower risk of CVD and enhanced cardiovascular risk profiles such as HDL (Satija and Hu, 2018).

A systematic review and meta-analysis from 9 prospective studies found that higher adherence to a plant-based dietary pattern was associated with 23% (RR: 0.77; 95% CI: 0.71-0.84) lower risk of T2D compared to poorer adherence. This study indicated that the association was stronger if dietary patterns were rich in vegetables, fruits, legumes, whole grains, and nuts (Qian et al., 2019). However, only three studies compared adhering to the types of vegetarian diets, such as vegans or vegetarians. The author also suggested that additional studies may bring an understanding of other specific pathways that mediate the positive relationship between a plant-based diet and T2D (Qian et al., 2019).

A study of vegetarian diets and incident T2D in the Adventist Health Study-2 defined participants as vegans, lacto-ovo vegetarians, pesco-vegetarians, semi-vegetarians (consuming eggs and/or dairy products, and red meat and poultry) and non-vegetarians (consuming eggs, milk and dairy products, fish, poultry, and red meat) (Tonstad et al., 2013). They found that compared to non-vegetarians, vegans (Odd Ratio (OR): 0.381; 95% CI: 0.236-0.617), semi-vegetarians (OR: 0.486; 95% CI: 0.312-0.755), and lacto-ovo vegetarians (OR: 0.618; 95% CI: 0.503-0.760) were associated with lower risk of incident T2D after adjusting for age,

sex, income, education, smoking, alcohol intake, television watching, sleep, PA and BMI (Tonstad et al., 2013).

According to a plant-based diet review, the authors are concerned about the lack of a precise definition of the concept of a plant-based diet as well as their inconsistent implementation may cause uncertainty among scientists and the public. As a result, studies may be hard to replicate and difficult to compare. Therefore, the term plant-based diet should be declared with dietary detail (Storz, 2022).

1.4.2.4 Animal-based Diets and Association with Type 2 Diabetes

There are many studies of an association between animal products and incident T2D. A systematic review and meta-analysis from eleven cohort studies showed that a high total animal protein consumption was associated with a 14% higher risk of T2D (RR: 1.14; 95% CI: 1.09-1.19) (Tian et al., 2017). Similarly, a dose-response meta-analysis of dietary protein consumption and the risk of T2D indicated that high animal protein consumption had an 11% (RR: 1.11; 95% CI: 1.07-1.15) higher risk of T2D compared to low animal protein intake (Fan et al., 2019). However, there was heterogeneity in some food groups regarding sex, age, geographic location, follow-up time and number of cases (Fan et al., 2019).

Considering the association between food types and the risk of T2D, processed meat (RR: 1.39; 95% CI: 1.29-1.49), red meat (RR: 1.22; 95% CI: 1.09-1.36), egg (RR: 1.03; 95% CI: 0.64-1.67) and fish (RR: 1.03; 95% CI: 0.89-1.17) were associated with a higher risk of T2D, while total dairy products (RR: 0.89; 95% CI: 0.84-0.94), whole milk (RR: 0.87; 95% CI: 0.78-0.96), and yoghurt (RR: 0.83; 95% CI: 0.70-0.98) were associated with a lower risk of T2D (Tian et al., 2017). Additionally, meat intake (e.g. red meat, fish, poultry) had a higher risk of T2D when compared to those who did not or avoided meat intake (BarnardLevin and Trapp, 2014).

A few years later, a dose-response meta-analysis of twenty-eight prospective cohort studies revealed that total meat (RR: 1.33; 95% CI: 1.16-1.52), red meat

(RR: 1.22; 95% CI: 1.16-1.28) and processed meat (RR: 1.25; 95% CI: 1.13-1.37) were associated with the risk of T2D compared to those with the lowest intake (Yang et al., 2020). However, poultry (RR: 1.00; 95% CI: 0.93-1.07) or fish (RR: 1.01; 95% CI: 0.93-1.10) were not significantly associated with a higher risk of T2D compared to those with the lowest intake (Yang et al., 2020).

In reality, people integrate diverse food components into a meal. Therefore, the study of dietary intake has been changed from a single food item to the overall food consumption, such as dietary patterns. For example, a systematic review and meta-analysis of dietary patterns from sixteen cohort studies found that a diet of refined grains, red and processed meat, eggs, high-fat dairy, and fried products was associated with a higher risk of T2D (RR: 1.44; 95% CI: 1.27-1.62), while dietary described by fruits, vegetables, legumes, fish and poultry was associated with a lower risk of T2D (RR: 0.84; 95% CI: 0.77-0.91) (JannaschKröger and Schulze, 2017).

Once considering the findings of systematic reviews and meta-analyses mentioned above, there is a combination of positive and negative dietary risks in individual dietary patterns. However, diets rich in fats, particularly saturated fat, such as red meat, processed meat, and bacon, are associated with incident T2D. As a result, healthier food habits (e.g., avoiding processed meat) and plant-based diets should be considered to reduce dietary risk factors associated with T2D. As previously stated, there are limitations to the food type definition, heterogeneity in other factors such as sex, age, or region, and dietary detail within the food group. Therefore, additional research is necessary to investigate healthier diets that can help prevent T2D.

1.4.3 Adiposity and Type 2 Diabetes

1.4.3.1 Adiposity and Its Association with Type 2 Diabetes

Understanding the role of adiposity in the development of T2D begins with the concept of energy balance. This principle is grounded in the first law of thermodynamics, which states that energy cannot be created or destroyed but can be transformed from one form to another (Hall et al., 2012). In humans, energy balance is achieved when the chemical energy derived from food and beverages matches the energy expended through basal metabolism, diet-induced thermogenesis, and PA. This relationship can be summarised by the equation (King, 2022):

$$\text{Energy intake} = \text{Energy expenditure} \pm \text{Energy storage (fat, protein, carbohydrate)}$$

Note: + denotes that energy expenditure is more than energy storage. - denotes that energy expenditure is less than energy storage.

When energy intake equals expenditure, body mass remains stable. However, sustained imbalance, where intake consistently exceeds expenditure (+), results in energy being stored, primarily as fat, leading to body weight gain and potentially obesity (King, 2022, Champagne et al., 2013).

The health consequences of adiposity depend not only on the amount of fat stored but also on its anatomical distribution. Adipose tissue in the human body is anatomically categorised into three distinct compartments: superficial subcutaneous adipose tissue (SSAT), deep subcutaneous adipose tissue (DSAT), and visceral adipose tissue (VAT). The **adipose tissue overflow hypothesis** posits that SSAT, typically found in the hips, thighs, and upper arms, is the primary storage site for excess fat. Once its capacity is exceeded, fat begins to accumulate in visceral areas (VAT) and ectopically within organs (DSAT) such as the liver, pancreas, and skeletal muscle. While SSAT exhibits relatively low metabolic activity, DSAT and VAT demonstrate increased transmembrane fatty

acid flux, thereby contributing more significantly to metabolic disturbances such as dyslipidaemia and dysglycaemia (Sniderman et al., 2007).

Excess adiposity contributes to insulin resistance through several biological pathways. Adipose tissue in individuals with obesity often shows increased infiltration by macrophages and other immune cells, in part due to adipocyte death and tissue remodelling. These immune cells secrete proinflammatory cytokines that exacerbate systemic inflammation and disrupt insulin signalling. Visceral adipose tissue, in particular, has been mechanistically linked to key metabolic abnormalities and poor health outcomes (Heymsfield and Wadden, 2017).

Adipocytes also secrete various hormones and adipokines, the balance of which is influenced by both the amount and distribution of fat. In obesity, the excess release of proinflammatory adipokines promotes chronic low-grade inflammation. Additionally, the hydrolysis of triglycerides within adipocytes releases free fatty acids (FFAs) into circulation, which are taken up by non-adipose tissues. Elevated levels of FFAs, inflammatory cytokines, and lipid intermediates in ectopic sites contribute to impaired insulin signalling and insulin resistance (Heymsfield and Wadden, 2017). **Figure 1-5** illustrates the pathways linking excess adiposity to insulin resistance and β -cell dysfunction, both of which are central to the development of T2D.

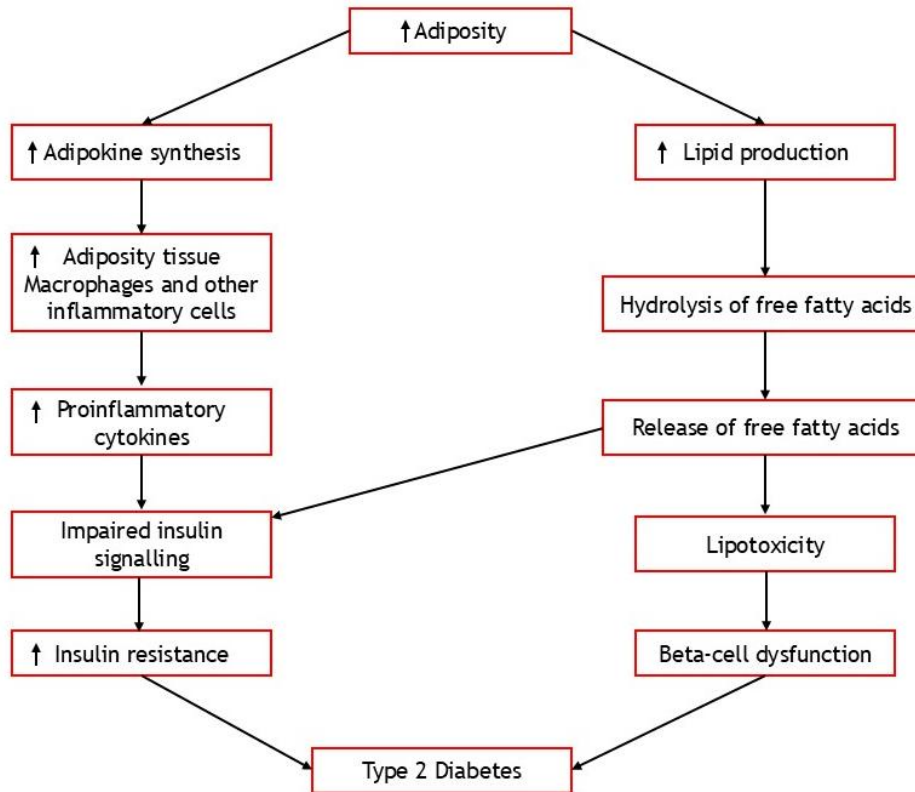


Figure 1-5 Some pathways through which excess adiposity contributes to the development of type 2 diabetes

Source: Adapted from Heymsfield and Wadden (2017)

Beyond energy balance, it is essential to consider the role of macronutrient balance in shaping body composition. Even when energy balance is maintained, imbalances between macronutrient intake and utilisation can affect fat and lean mass. For example, exercise can promote fat oxidation, creating a negative fat balance and reducing adiposity, even if total body weight remains unchanged (King, 2022).

Body composition can be analysed across five distinct but interconnected levels: atomic, molecular, cellular, tissue-organ, and whole-body levels (Heymsfield et al., 2005) (**Figure 1-6**). This five-level model forms the basis of human body composition analysis and highlights the cross-level interactions that are relevant

for both clinical and research applications. Measuring body composition provides insights into an individual's metabolic status, disease progression, and the effectiveness of interventions (Dalili et al., 2020).

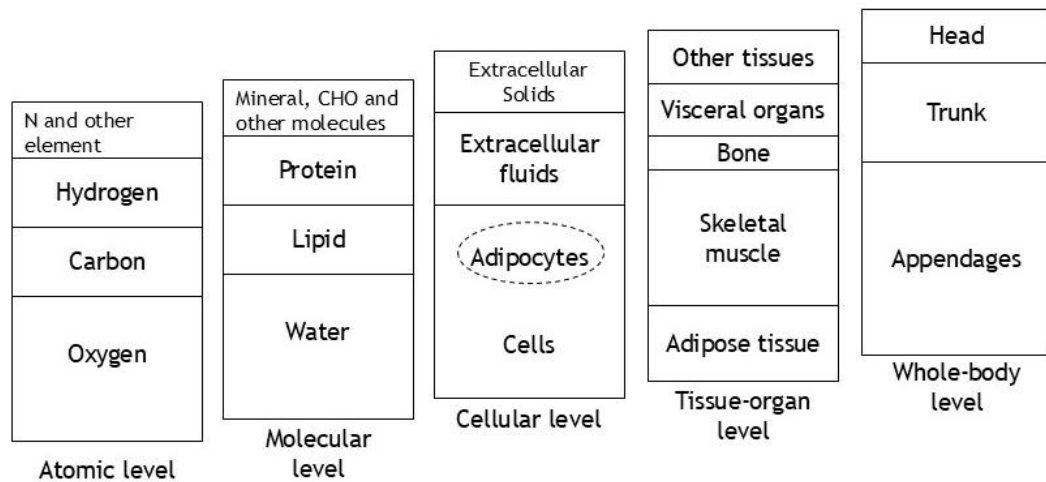


Figure 1-6 Major body components at each of the five levels of body mass

Source: Adapted from Heymsfield et al. (2005)

Anthropometric methods are widely used to assess body composition in both clinical and epidemiological settings. Common measures include height, body mass, BMI, WC, hip circumference, and skinfold thickness (Casadei and Kiel, 2024). While more precise methods, such as dual-energy X-ray absorptiometry (DEXA), underwater weighing, magnetic resonance imaging (MRI), and computed tomography (CT), offer greater accuracy in estimating fat distribution, they are less feasible for large-scale or routine use (Purnell, 2023). Consequently, BMI and WC remain practical and informative indicators of overall and central adiposity.

Although assessment of body mass, the sum of fat-free mass and fat mass, should be a routine component of every clinical evaluation, as it serves as a general indicator of overall energy reserves, fluctuations in body mass often reflect changes in an individual's energy and protein status. A single body mass

measurement, in isolation, provides limited clinical insight. For instance, a body mass alone does not indicate whether an individual is underweight, normal weight, or overweight. Consequently, it is essential to assess recent trends in body mass, including the magnitude and rate of change over days, weeks, or months. Rapid fluctuations in body mass are often indicative of substantial losses in lean body mass. Additionally, body mass should not be interpreted independently, as it can be misleadingly influenced by factors such as dehydration or fluid retention (Elliott, 2009). Therefore, BMI is used instead of body mass measurement alone to assess health outcomes.

BMI, calculated as body weight in kilograms divided by height in meters squared, is a cost-effective and relatively straightforward indirect method for evaluating obesity, offering a standardised approach across height variations. The thresholds used to define obesity are grounded in well-documented associations with increased cardiometabolic risk and early mortality. Despite its strong correlation with more precise measures of body fat, BMI lacks the ability to differentiate between fat and lean tissue and does not provide insights into fat distribution. Compared to direct assessment techniques, BMI demonstrates high specificity (0.90) but limited sensitivity (0.50) in identifying obesity.

Furthermore, the relationship between BMI, total adiposity, and cardiometabolic risk, especially in the context of T2D, varies across ethnic groups, prompting the need for ethnicity-specific BMI cut-offs (AdabPallan and Whincup, 2018). The WHO defines obesity using BMI thresholds, which vary by population. For European adults, BMI is categorised as <18.5 kg/m² (underweight), 18.5-24.9 kg/m² (normal weight), 25-29.9 kg/m² (overweight), and ≥ 30 kg/m² (obese). For Asian populations, the cut-offs are more conservative, with obesity defined as BMI ≥ 25 kg/m² (WHO Expert Consultation, 2004, Weir and Jan, 2023). Central obesity is defined by WC >88 cm in women and >102 cm in men (World Health Organization, 2011).

Indicators of central obesity, such as WC, waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR), may offer superior predictive value for visceral fat accumulation, cardiometabolic conditions, and mortality risk compared to BMI.

However, evidence highlights the strong correlation between these central obesity metrics and BMI, suggesting that their associations with CVD risk are similar and may not provide substantial additional prognostic value. Despite this, central adiposity measures have been shown to predict morbidity and mortality independently of BMI and are thus recommended for clinical use, especially in individuals with lower BMI (AdabPallan and Whincup, 2018).

Adiposity is a well-established and potent risk factor for T2D (Leong and Wilding, 1999, Verma and Hussain, 2017, Klein et al., 2022). Numerous studies have quantified this risk using various measures of adiposity. For example, a meta-analysis combining eight studies across 13 cohorts found that abdominal obesity, defined by WC, WHR, iliac circumference, or intra-abdominal fat area, was associated with a 2.1-fold increased risk of T2D (OR: 2.14; 95% CI: 1.70-2.71) (Freemantle et al., 2008).

A more recent systematic review and meta-analysis of 84 prospective cohort studies involving 2.69 million adults across 20 countries further confirmed these associations. Using WHO's ethnic-specific BMI thresholds, overweight and obesity were associated with a 24% increased risk of prediabetes (RR: 1.24; 95% CI: 1.19-1.28), while severe obesity conferred a 23-fold higher risk of T2D (RR: 22.97; 95% CI: 13.58-38.86) (Yu et al., 2022). However, heterogeneity across studies, due to differences in region, follow-up duration, and confounder adjustments, should be acknowledged.

In recent years, novel anthropometric indices have been developed to improve upon traditional measures like BMI. These include the A Body Shape Index (ABSI), Anthropometric Risk Index (ARI), Hip Index (HI), and Visceral Adiposity Index (VAI) (Amato et al., 2010, Krakauer and Krakauer, 2012, Krakauer and Krakauer, 2016, Bawadi et al., 2019). These indices aim to better capture fat distribution and predict obesity-related health risks, including T2D.

A comprehensive dose-response meta-analysis from 216 cohort studies (over 26 million participants) found that all anthropometric measures, BMI, WC, WHR,

WHtR, VAI, percentage body fat, and body adiposity index, were positively and linearly associated with T2D risk (Jayedi et al., 2022). WHtR appeared to have greater predictive value than traditional measures, while body adiposity index and percentage body fat were the strongest predictors overall. However, the analysis also revealed high between-study heterogeneity ($I^2 = 71\%-99\%$) and limited data for certain measures such as ABSI ($n=5$) and VAI ($n=9$), particularly in sex-stratified analyses.

As highlighted, assessing body composition can aid in disease monitoring and risk stratification. Cross-level measures such as VAI, derived from BMI, WC, triglycerides (TG), and high-density lipoprotein (HDL) cholesterol, offer a sex-specific tool for evaluating fat distribution and functionality. While many indices have shown promise, more research is needed to determine the most reliable predictors of T2D risk across diverse populations.

1.4.3.2 Adiposity as a Mechanism of Type 2 Diabetes

Adiposity and T2D are intricately linked through shared pathophysiological and molecular mechanisms. Key elements in this relationship include adipose tissue distribution, levels of free fatty acids, chronic inflammation, adipokines (e.g., adiponectin), gut microbiota composition, and dyslipidaemia, as illustrated in **Figure 1-7**. Understanding these complex interconnections is essential for the effective prevention and management of T2D.

The development of both obesity and T2D is influenced by a combination of genetic, epigenetic, and environmental factors, particularly unhealthy lifestyle behaviours. Visceral adiposity plays a central role in the pathogenesis of T2D by promoting the release of proinflammatory cytokines, adipokines, and non-esterified fatty acids (NEFA), all of which contribute to β -cell dysfunction, alterations in gut barrier integrity, and dysbiosis. Moreover, inflammatory signalling in the hypothalamus has been implicated in the development of T2D, while T2D itself may disrupt central energy homeostasis by overstimulating

regulatory neurons and surrounding microglia (Chandrasekaran and Weiskirchen, 2024).

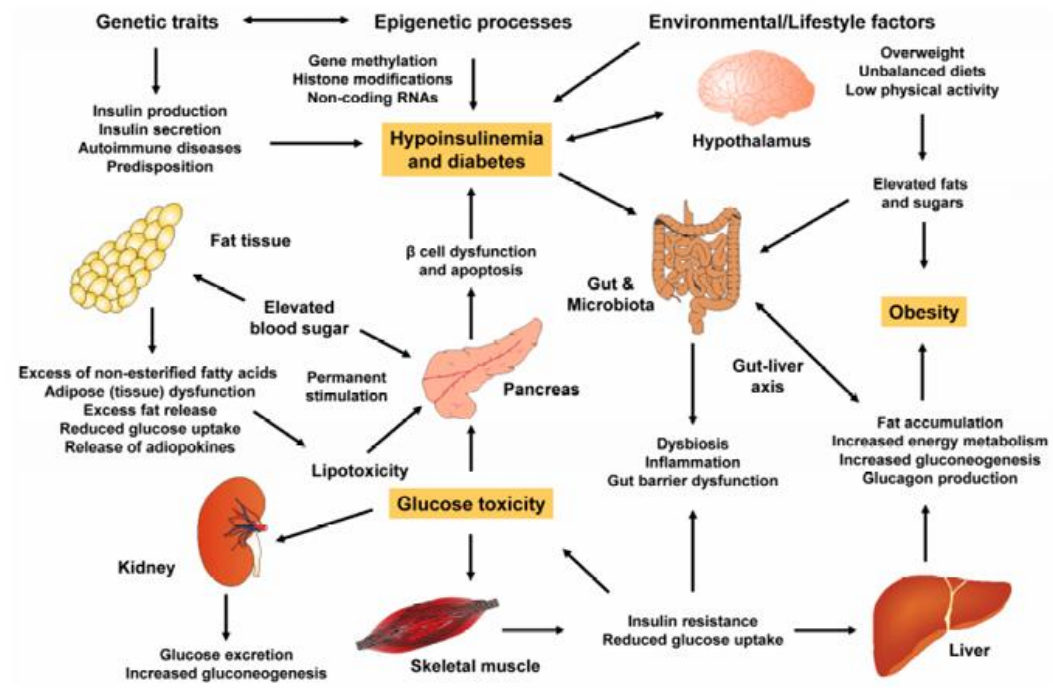


Figure 1-7 Interconnected pathophysiology and molecular processes of type 2 diabetes and adiposity

Source: Figure received from Chandrasekaran and Weiskirchen (2024)

For example (Figure 1-8), individuals with obesity who may exhibit a limited capacity to store excessive nutrient load, become incapable of storing additional lipid effectively. Consequently, excess lipids begin to accumulate in other peripheral tissues, including skeletal muscle, liver, and pancreas (Overflow). SSAT can undergo expansion in two ways: through the enlargement of existing adipocytes (hypertrophy) or by generating new adipocytes (hyperplasia). While hyperplastic expansion appears to protect against SSAT dysfunction, hypertrophic growth is closely linked to a higher risk of developing T2D. When lipid storage is redirected to ectopic fat deposition, it contributes significantly to insulin resistance and the onset of T2D. This inappropriate fat accumulation

leads to the buildup of lipid intermediates in these tissues, which can disrupt insulin signalling pathways (Chadt et al., 2018).

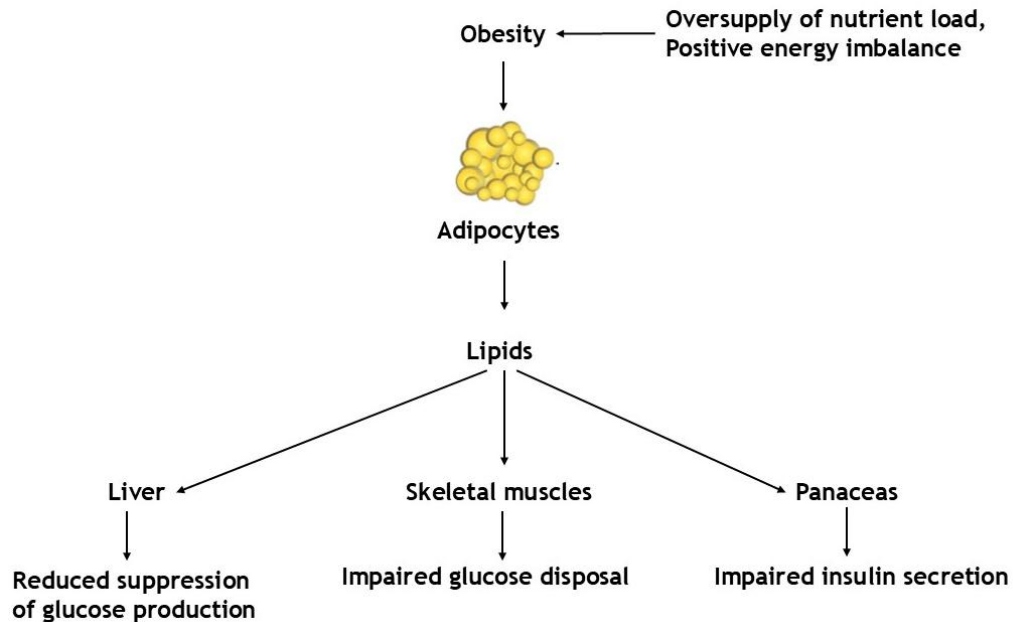


Figure 1-8 Underlying biological mechanisms by which obesity-driven ectopic lipid accumulation contributes to peripheral insulin resistance and dysfunction of pancreatic β -cells

Source: Adapted in a modified form Chandrasekaran and Weiskirchen (2024) and Chadt et al. (2018)

Interestingly, in terms of obesity, apart from pharmacological and surgical treatments, loss of body mass through lifestyle interventions remains the most effective strategy for reducing the complications and comorbidities associated with T2D. A gradual reduction in adipocyte size through body weight loss can downregulate oxidative stress pathways and lipogenesis. Exercise is also a critical component of lifestyle interventions, shown to improve insulin sensitivity, glycaemic control, and lipid profiles. Importantly, combining PA with an energy-restricted diet has been found to yield greater metabolic improvements than either strategy alone (Chandrasekaran and Weiskirchen,

2024). These findings highlight that adiposity may mediate the effects of both dietary intake and PA on T2D incidence.

Mendelian randomisation studies support a causal role of adiposity, measured through BMI and WC, in the development of T2D (Bellou et al., 2018). Two cross-sectional studies investigating the dietary inflammatory index and red meat consumption found associations with markers of insulin resistance, mediated by general and central adiposity. However, these studies did not quantify the proportion of the mediation effect (Mtintsilana et al., 2019, Mazidi et al., 2021).

In prospective analyses, similar patterns emerge. For example, in the EPIC-Norfolk study, which included 21,984 participants followed for a median of 10.2 years, fish and seafood consumption were associated with incident T2D, but this association was attenuated after adjusting for BMI and WC. The authors suggested that adiposity may have mediated this relationship, although no formal mediation analysis was conducted (Patel et al., 2009).

Other studies have quantified the mediation effect. In the Nurses' Health Studies I and II, BMI accounted for 42% and 57% of the association, respectively, between a 40 g increase in whole grain intake and reduced T2D risk (de Munter et al., 2007). Similarly, a 20-year prospective cohort study of 70,991 women found that the protective effect of an anti-inflammatory diet, measured using the dietary inflammatory index, was mediated by BMI in 58% of the total effect (Laouali et al., 2019). In France, a cohort of 79,205 adults found that adherence to national dietary guidelines was associated with reduced T2D risk, with BMI mediating 20% to 27% of this relationship (Kesse-Guyot et al., 2021).

Adiposity may also mediate the well-established relationship between PA and T2D risk. Although PA is inversely associated with incident T2D, individuals with obesity who engage in PA often remain at higher risk than normal-weight individuals. For example, a 16-year follow-up of 68,907 women in the Nurses' Health Study revealed that obesity substantially increased T2D risk, even among those who were physically active. Compared to normal-weight women with

active PA, those with obesity had a 10.7-fold higher risk when physically active (RR: 10.74; 95% CI: 8.74-13.18) and a 16.8-fold higher risk when physically inactive (RR: 16.75; 95% CI: 13.99-20.04) (Rana et al., 2007).

Similar findings were reported from the HUNT study in Norway, involving 38,231 adults followed for 11 years. Compared to normal-weight individuals with high PA levels, those with obesity had markedly higher T2D risks, regardless of their activity level. Among women with obesity, the risk ratios were 13 (95% CI: 7.42-21) for high PA and 15 (95% CI: 9.18-25) for low PA. Among men, the corresponding values were 13 (95% CI: 6.92-26) and 17 (95% CI: 9.52-30) (Kirsti VikJo and Tom, 2017).

More recent studies have formally examined the mediating role of adiposity. In a cohort of 9,757 English adults aged ≥ 50 years, increased cumulative PA was associated with lower T2D risk, and this association was partially mediated by adiposity. Specifically, WC explained 17% of the effect, BMI 10%, and change in BMI 9%. However, PA was assessed using self-reported questionnaires, which may introduce measurement error (Li et al., 2021).

In summary, obesity leads to insulin resistance and β -cell dysfunction, primarily due to factors such as chronic inflammation, altered adipokine secretion, increased free fatty acids, and oxidative stress. These changes impair insulin signalling and glucose metabolism, leading to the development of T2D. Also, adiposity appears to be a key mediator linking both diet and PA to T2D risk. However, few studies have quantified the extent of mediation, and most rely on self-reported exposures. Further research is needed to clarify these pathways using robust mediation models and device-based assessments of PA and adiposity.

1.5 Research Gaps in Understanding Risk Factors for Type 2 Diabetes

Current evidence highlights important gaps in our understanding of the complex relationships between muscular strength, PA, diet, body composition, adiposity, and the risk of developing T2D, as summarised in **Figure 1-9**.

Unhealthy dietary patterns, particularly those high in red and processed meat, have been linked to increased T2D risk through mechanisms involving inflammation and oxidative stress. Additionally, an imbalance between overload of energy intake and less expenditure (via PA) leads to a positive energy balance, resulting in changes in body composition and, over time, increased adiposity and obesity. PA is known to reduce T2D risk by improving insulin sensitivity and muscular function (e.g. muscle contraction, which enhances glucose uptake). Conversely, physical inactivity contributes to insulin resistance and increased disease risk.

Muscular strength has also emerged as a potential predictor of T2D; however, there is limited evidence to support this, and the role of strength remains underexplored. Obesity is a well-established risk factor for T2D, yet the distribution of adipose tissue, particularly visceral and ectopic fat, is increasingly recognised as more predictive of T2D risk than overall adiposity alone. Various methods have been developed to assess body composition and fat distribution, but uncertainty remains regarding which are most accurate or practical for predicting T2D in clinical or population settings.

Furthermore, as shown in **Figure 1-9**, adiposity may mediate the associations between both dietary intake and PA and the risk of developing T2D. This potential mediating role underscores the need for studies that better characterise these pathways using formal mediation analysis.

Several key research limitations have been identified and are summarised below:

Muscular Strength and Type 2 Diabetes Risk

Research on the association between grip strength and incident T2D is limited. Most studies rely on absolute grip strength without accounting for relative strength or body size. In addition, few studies adjust for key confounding factors, explore gender-specific effects, or address the potential for reverse causality.

Device-Based Physical Activity Measurement

While wearable devices offer more objective assessments of PA, evidence on device-measured PA and its association with T2D remains limited. Most current guidelines are based on self-reported PA, which is prone to measurement error. There is a clear need for robust evidence using device-based methods to examine the effects of specific PA types and durations. Furthermore, the extent to which adiposity mediates these associations remains unclear.

Dietary Patterns and Adiposity

Inconsistencies in how dietary patterns are described contribute to mixed findings in the literature. Studies often fail to distinguish clearly between different diet types (e.g. vegetarian, pescatarian, or poultry-based) that may reduce T2D risk. Additionally, limited research has assessed whether adiposity mediates the relationship between dietary patterns and T2D incidence.

Body Composition and Prediction of T2D Risk

Although many body composition metrics (e.g. BMI, WC, body fat percentage) have shown associations with T2D, their ability to accurately predict disease risk remains limited. More research is needed to compare existing metrics and develop novel, reliable approaches, especially in large, diverse cohorts, to guide clinical and public health interventions.

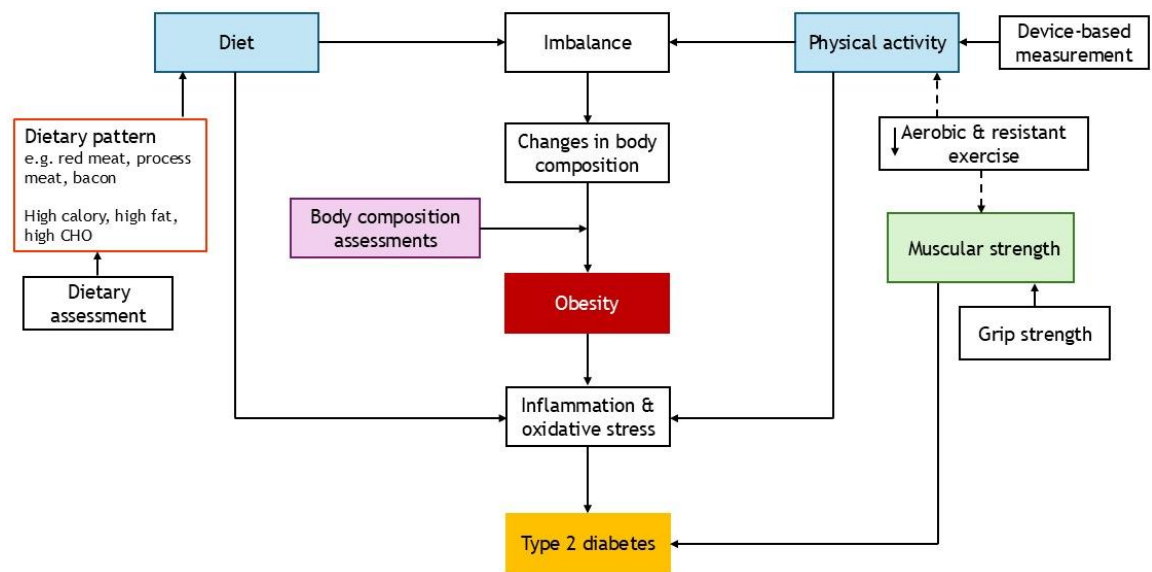


Figure 1-9 Summary of existing literature

1.6 Aims

1.6.1 General Aims

This thesis presents a prospective cohort study aimed at investigating the associations between emerging risk factors and the incidence of T2D. Specifically, it focuses on muscular strength (assessed by handgrip strength), PA (measured using wearable devices), dietary patterns, and body composition (assessed using multiple methods). The study also explores the potential mediating role of adiposity in these associations, using large-scale data from the UK Biobank.

1.6.2 Specific Objectives

1. To examine the association between grip strength and incident T2D, and to assess potential interactions with sociodemographic characteristics, lifestyle factors, and adiposity.

2. To evaluate the association between device-based PA measurement and incident T2D, and to determine the mediating role of adiposity in this relationship.
3. To assess the association between different dietary patterns and incident T2D, and to explore the mediating effect of adiposity.
4. To investigate the association between traditional and novel body composition measurements and incident T2D, and to evaluate their predictive performance in identifying individuals at risk.

All analyses are based on secondary data from the UK Biobank—a large prospective cohort study comprising approximately 500,000 participants.

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Chapter 2 General Methods

The study in this thesis used data from UK Biobank, a large population-based prospective study.

2.1 UK Biobank

UK Biobank has been developed by multidisciplinary scientific experts and stakeholders. It aims to provide a comprehensive data resource for scientists to investigate the development of major diseases due to the multiple interactions of various factors, including lifestyle, environment, and genetic factors (UK Biobank, 2007, Collins, 2012). Its data and samples are open, on application, to all bona fide researchers, such as academic, public and commercial sections, and charities across the world (Sudlow et al., 2015).

The full protocol of the UK Biobank and information on variables are published online on the UK Biobank website (www.ukbiobank.ac.uk/) (UK Biobank, 2019).

2.2 Designs and Methods

2.2.1 Population and Recruitment

UK Biobank includes data from more than 500,000 people in England, Scotland and Wales. The sample size was calculated from the number of events required for the reliable quantification of several different factors on different diseases (UK Biobank, 2007). This sample size shows that the data obtained in the UK Biobank has sufficient power to identify a high odds ratio (1.3-1.5) of the diseases in the next 20 years of the follow-up period (Palmer, 2007).

The age of participants was targeted between 40 and 69 years old, allowing scientists to study the risk of developing diseases (UK Biobank, 2007). This means that participants are young enough to allow the first diagnosis to be taken before subsequent illnesses are affected by exposures, and participants are old enough to detect the health outcomes during the initial stages of follow-up (Sudlow et al., 2015).

UK Biobank recruited the participants by sending invitation letters to approximately 9,238,453 people across the UK. Of those, 503,317 participants agreed to join the study. Afterwards, they were invited to 1 of 22 local assessment centres (within 25 miles) between 2006 and 2010. Individuals' response rate to participate in the study was 5.45% (Fry et al., 2017).

At the assessment centres, participants were assessed in different scientific stations where they electronically signed consent to collect baseline data, including touch-screen questionnaires, interviews, functional and physical measurements, and biological sample collection (Sudlow et al., 2015).

2.2.2 Cohort Characteristics

In recruited and active participants, the cohort characteristics showed that the average age was 56.5 years old, and women were 54.5% of participants. More than 90% were of the white ethnicity (Table 2-1).

Table 2-1 Characteristics of the UK Biobank cohort and data available at the time the study began

Sociodemographic variables available at the UK Biobank	Numbers of participants with data available	Data available for individuals without diabetes at baseline	Data available for individuals with diabetes at baseline
N	502,536	473,502	26,402
Age	502,520	473,502	26,402
Mean age (SD)	56.5 (8.1)	56.4 (8.1)	59.6 (7.2)
Sex	502,520	473,502	26,402
women	273,391 (54.5%)	261,788	10,400

Men	229,129 (45.6%)	211,714	16,002
Deprivation index	501,897	472,921	26,363
Low index	167,432	160,321	6,666
Middle index	167,196	158,676	7,932
High index	167,269	153,924	11,765
Ethnicity	499,743	471,921	26,260
Whites	472,709	448,659	22,925
Mixed	7,517	6,781	642
South Asians	9,882	7,979	1,692
Blacks	8,061	7,060	909
Chinese	1,574	1,442	92
Education qualification	492,382	465,173	25,693
College or University degree	161,174	154,699	6,171
A levels/AS levels or equivalent	55,324	52,795	2,413
O levels/GCSEs or equivalent	105,193	99,890	5,057
CSEs or equivalent	26,885	25,545	1,254
NVQ or HND or HNC or equivalent	32,729	30,445	2,162

Other professional qualifications e.g. nursing, teaching	25,804	24,223	1,518
None of the above	85,273	77,576	7,118

Note: Table presents the number of participants

A levels/AS levels, Advance/Advanced Subsidiary level; GCSEs, General Certificate of Secondary Education; HNC, Higher National Certificate; HND, Higher National Diploma; NVQ, National Vocational Qualification; O levels, Ordinary level; SD, Standard deviation

However, evidence on a comparison between UK Biobank participants and nonparticipants concluded that UK Biobank was not representative of the general public in several sociodemographic factors (age, sex, ethnicity, deprivation index, property ownership, and region of residence), lifestyle characteristics (smoking status, and alcohol intake), physical characteristics (height, body mass, WC, and BMI) and self-reported health conditions (CVD, stroke, diabetes, chronic kidney disease, hypertension, and respiratory disease). For instance, UK Biobank individuals seemed to be older, to be women, and to live in less socioeconomically deprived areas compared to nonparticipants. Similarly, when compared to the general population of the same age, UK Biobank participants were less likely to be obese, to smoke, to drink alcohol daily and to have fewer self-reported health conditions (Fry et al., 2017). Nonetheless, the comparison suggested that the considerable number of participants and diverse range of exposure metrics enabled scientific conclusions regarding the relationship between exposures and health outcomes which can be applied to general populations (Fry et al., 2017).

This was extended by a study that examined risk factor associations in the UK Biobank compared with regular response rates in other national surveys (from 18 studies). The results showed similar associations between risk factors and mortality in UK Biobank against other national surveys. For instance, participants in UK Biobank who ever smoked cigarettes had a 2.04 times higher risk of CVD

mortality (HR: 2.04; 95% CI: 1.87-2.24) compared to those who never smoked cigarettes, while those in population-representative studies showed people who ever smoked cigarettes had 1.99 times higher risk of CVD mortality (HR: 1.99; 95% CI: 1.78-2.23) compared to those who never smoke cigarettes. Therefore, the author concluded that risk factors associations in UK Biobank were likely to be generalisable (Batty et al., 2020).

2.3 Data Collection

More than 500,000 participants provided baseline data between 2006 and 2010. Over the follow-up period, further assessments were conducted to collect additional information from participants as shown in **Table 2-2**.

Table 2-2 Data collections in UK Biobank

Data type	Number of participants	Collection date
Baseline questionnaire	Whole cohort at baseline	2006-2010
First resurvey	20,000	2012-2013
Target Imaging visit	100,000	2014
Target repeat imaging	60,000	2019
Baseline physical measures	Whole cohort at baseline	2006-2010
First resurvey	20,000	2012-2013
Target Imaging visit	100,000	2014
Target repeat imaging	60,000	2019
Web-based questionnaires	210,000	2011
Physical activity monitor	100,000	2013-2016

Repeat assessment	2,500	2018
Imaging assessment	100,000	2014

Source: Adapted from Bešević et al., 2022

2.3.1 Questionnaires

A questionnaire was developed based on the potential risk factors for outcomes. It covered the following topics of interest, i.e. sociodemographic and occupation; lifestyle exposures; family history of illness; early life exposures; cognitive function; psychological state; and medical history and general health (UK Biobank).

At the assessment visit, the questionnaire was provided on a touch-screen computer. Participants completed the touch-screen questionnaire to collect the majority of information. However, for example, if a participant had a particular medical condition, they were interviewed by the train staff about that medical condition (UK Biobank, 2007).

2.3.2 Physical Measurements

Physical measurements were developed based on other epidemiological studies that were found to be risk factors for several health outcomes. The measurements consisted of blood pressure (and pulse rate), body mass, height, WC, hip circumference, bioelectrical impedance, handgrip strength, spirometry, and bone densitometry (UK Biobank, 2007).

2.3.3 Biological Samples

The protocol of biological sample collections was developed by conducting a comprehensive study of existing literature and taking part in significant consultation and peer review within the scientific community. Blood (45 ml.) and urine (9 ml.) were collected at the baseline assessment centres (Elliott and Peakman, 2008).

2.4 Outcomes Used in This Thesis

The health outcome studied in this thesis was the incidence of T2D. According to the International Classification of Diseases (ICD) published by the WHO, the ICD-10 code E11: Non-insulin-dependent diabetes mellitus to detect the occurrence of T2D was used. UK Biobank provided the look-up table for ICD codes on the UK Biobank website.

The primary care records were available for 45% of the UK Biobank cohort, accounting for 228,495 participants with data censored in 2017. However, this was updated and combined with data from hospital inpatient records to measure the incidence of T2D. The outcome was extracted up to June 2021. The national electronic health-related data is shown in **Table 2-3** (Bešević et al., 2022).

Table 2-3 Primary care records and hospital admissions linked data in UK Biobank

Data type	Number of participants	Collection date
Primary care records	230,000	England 1938- Scotland 1939- Wales 1948-
Hospital admissions	Whole cohort	England 1997- Scotland 1977- Wales 1999-

Source: Adapted from Bešević et al., 2022

2.5 Exposure Variables Used in This Thesis

The exposures in this thesis included grip strength, device-measured PA, dietary patterns, and obesity-related indicators assessed using different methods. Data collections for these exposures are described in detail below.

2.5.1 Grip Strength

Grip strength in the UK Biobank dataset was measured using a Jamar J00105 hydraulic hand dynamometer. Every day before the operation, staff calibrated the instrument by measuring their own hand grip and inspected the device's functions. Participants were asked to sit upright with their elbow by their side flexed at 90° so that their forearm was facing forward and resting on an armrest. The staff explained to participants how to measure hand grip. Isometric grip force was assessed from single maximal grip efforts of the right- and left sides, with every single power gripped for 3 seconds. Grip strength in the UK biobank was recorded as grams (g) (UK Biobank, 2011b).

This thesis studied grip strength in terms of absolute and relative values. Absolute values were grip strength in kg (unit received from the measurement), while relative values were grip strength in kg divided by body weight in kg. Absolute values were studied in terms of 5 kg lower grip strength and relative in terms of 0.05 kg/kg lower grip strength. The study also investigated grip strength in terms of per 1-SD increment.

2.5.2 Device-based Physical Activity Measurement

UK Biobank used Axivity AX3 wrist-worn triaxial accelerometers designed by Open Lab, Newcastle University, to collect objectively measured PA. The device was arranged to record the 3-axial acceleration data for 7-day durations at a rate of 100 Hz and a dynamic range of +-8g. It was set to begin operating at 10 a.m., two working days after mail delivery to participants (Doherty et al., 2017).

A random sample of UK Biobank participants were invited by email between February 2013 and December 2015 to wear accelerometers. Participants who agreed to join this study received letters and devices from June 2013 (Doherty et al., 2017).

Participants were asked to wear the devices shortly after receiving them on the wrist of the hand that they typically write with for seven days. Also, they were advised to wear it consistently while continuing regular daily activities and to know that the device automatically turned on and off at the prearranged time. At the end of the 7-day duration, participants were asked to send the device back to the study centres (UK Biobank, 2016, Doherty et al., 2017).

At the study centres, raw acceleration data were interpreted into PA data as summarised in Figure 2-1.

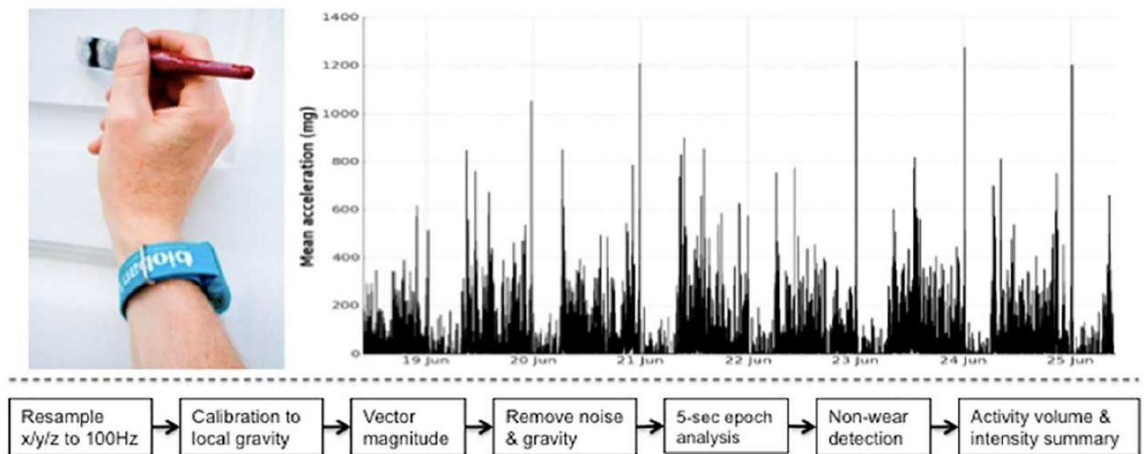


Figure 2-1 Processing approaches for the accelerometer data

Source: Figure received from Doherty et al, 2017.

Doherty et al. (UK Biobank Physical Activity Expert Working Group) reported that 236,519 participants received the invitations; of those, 106,053 (44.8%) agreed to wear the devices. However, due to lost data, the study only obtained data

from 103,712 participants. In the wear time analysis, insufficient data to calibrate were excluded from the study. For PA analysis, participants who had insufficient wear time, that is the accelerometer was worn for less than 72 hours, or who did not have acceleration data during every hour of the 24-hour cycle, were excluded. Finally, 96,600 participants (93.3%) aged 45-79 years were included in the PA analysis (Doherty et al., 2017).

Data available on the UK Biobank website (UK Biobank, 2019) was described as raw acceleration data, average acceleration by day and by hour, acceleration intensity distribution, wear time/non-wear time and duration by day and by hour, and accelerometer calibration and quality metrics (UK Biobank, 2016).

In my study, the accelerometer was studied in terms of total PA and specific intensity PA, including light PA (30-125 mg), moderate PA (125-400 mg), vigorous PA (>400 mg), and moderate-to-vigorous PA (sum of moderate PA and vigorous PA), as well as total acceleration.

2.5.3 Dietary Assessment

Dietary data were collected from UK Biobank participants using FFQ and 24-hour dietary recall. The baseline FFQ was collected from all participants between 2006 and 2010. Further collections were obtained from 20,000 participants in 2012-2013, 100,000 participants in 2014, and 60,000 participants in 2019. The 24-hour dietary recall was collected among 210,000 participants in 2011, as shown in **Table 2-2**.

2.5.3.1 Food Frequency Questionnaire

FFQ used in UK Biobank was a self-administered touchscreen questionnaire at baseline assessment (2006-2010). It included 29 questions about foods and 18 questions about alcohol (Bradbury et al., 2018). This FFQ aimed to collect the frequency of food intake from the previous year. Food groups that were asked in the FFQ comprised salad/raw vegetables, cooked vegetables, dried fruit, fresh

fruit, oily fish, other fish, beef, pork, lamb, poultry, processed meats, salt added to food, cheese, water, and tea (Bradbury et al., 2018).

Types of commonly used and quantity of consumption were asked of the following foods: spread, milk, breakfast cereal, bread, coffee and type most typically used. Questions regarding avoiding particular diets and food groups (dairy products, eggs, sugar, and wheat) were asked in the questionnaire. Also, questions relating to hot drink temperature, age last eaten any kind of meat, major dietary changes in the last five years, and variation in diet (participants who reported their diets varied often) were included in the questionnaire (Bradbury et al., 2018, UK Biobank, 2019).

2.5.3.2 24-hour Dietary Recall

A web-based diet questionnaire was developed, known as Oxford WebQ, to be used in UK Biobank and other sizeable prospective cohort studies in the UK (Liu et al., 2011). The Oxford WebQ is a 24-hour dietary recall questionnaire that is executed online, taking 10-15 minutes to complete. It was designed to collect data on the amounts of every food and drink taken during the previous 24 hours (Liu et al., 2011). The Oxford WebQ in UK Biobank provided questions asking about dietary intake of up to 206 types of foods and 32 types of beverages during the last 24 hours (Bradbury et al., 2018).

Participants who completed the Oxford WebQ questionnaire at the assessment centre at recruitment were 70,046 individuals in 2009-2010. Participants who completed the online Oxford WebQ questionnaire in four cycles between February 2011 and June 2012 included 99,904 individuals for online cycle 1, 82,646 individuals for online cycle 2, 103,136 individuals for online cycle 3, and 99,460 individuals for online cycle 4 (UK Biobank, 2012, Bradbury et al., 2018). Therefore, a total of 210,126 participants completed the 24-hour dietary recall questionnaire. Data from all cycles were included in the UK Biobank dataset.

The questions asked 14 food groups including; cold and hot beverages; alcoholic beverages; cereal; milk, eggs, and cheeses; bread, pasta, and rice; soups,

snacks, and pastries; meat and fish; vegetarian alternatives; spreads, sauces, and cooking oils; fruit and vegetables; meal type; vitamin and mineral supplements; and physical activity. Dietary information was estimated about total food weight, total energy intake, carbohydrate, protein, total fat, polyunsaturated fat, saturated fat, total sugars, fibre, iron, calcium, vitamin B6, vitamin B12, vitamin C, folate, magnesium, potassium, carotene, retinol, vitamin D, vitamin E, starch, and alcohol (UK Biobank, 2012).

It is worth noting that dietary questions included in the FFQ were assessed repeatability. Over 4 years of follow-up, 70% of participants consistently indicated adherence to the same or proximate dietary categories on key food groups, i.e. fruit, vegetables, meat, and fish. In addition, individuals were classified according to their responses to the dietary FFQ during recruitment. Within each category, the average consumption of the same food group or nutrient was determined for individuals who had completed at least one Oxford WebQ dietary assessment. The comparison indicated that the dietary touchscreen characteristics, available on the full cohort, consistently classify people based on their consumption of the primary food categories (Bradbury et al., 2018).

The current thesis used dietary data from touch screen FFQ for the primary analysis and 24-hour web-based dietary recall for supplementary results. Five types of diets, including vegetarians, fish, fish & poultry, omnivores and variations in diet (vary in diets), with the question “Does your diet vary much from week to week?”, were included in the study.

2.5.4 Body Composition and Anthropometric Assessment

This study estimated body composition in relation to the risk of T2D using both traditional and novel anthropometric measures. Standard anthropometric assessments included height, body mass, and body circumferences such as WC and HC, which are commonly used to evaluate general and central adiposity.

In addition to these conventional measures, several advanced indices were assessed to determine which may offer better predictive value for T2D risk. These indices were derived through mathematical calculations based on anthropometric data and included:

- BMI: Calculated from body mass and height.
- ABSI: Calculated based on WC, BMI, and height (Krakauer and Krakauer, 2012).
- WHR: Calculated from WC and HC.
- WHtR: Calculated from WC and height.
- HI: Calculated using HC, body mass, and height (Krakauer and Krakauer, 2016).
- ARI: Incorporating height, BMI, ABSI, and HI (Krakauer and Krakauer, 2016).

Additionally, the VAI was included as a composite measure incorporating both anthropometric variables (WC and BMI) and lipid biomarkers i.e. TG and HDL (Amato et al., 2010) to reflect adipose tissue function at the molecular level.

All data were collected using standardised protocols and trained personnel, as described in the following sections.

2.5.4.1 Height

Standing height was measured by using a Seca 202 height measure which was recommended by experts. Participants had their height measured without shoes. Staff read the measurement and subsequently input data manually into the assessment centre's IT system (UK Biobank, 2007).

2.5.4.2 Body Mass

Body mass was measured by using the Tanita BC-418 MA body composition analyser. Participants took off their shoes and heavy outerwear before placing their feet onto the footpads of the analyser. The results were automatically

downloaded to the assessment centre's IT system. The system accurately measured body weight within 0.1 kilograms (UK Biobank, 2007, UK Biobank, 2011a).

2.5.4.3 Waist Circumference

WC was measured by using a Wessex non-stretchable sprung tape measure, which has been used in extensive health investigations. WC was estimated at the umbilicus level, measured midway between the lowest rib margin and the iliac crest in a horizontal plane. Staff read the measurement and subsequently inputted data manually into the assessment centre's IT system (UK Biobank, 2007).

The cutoff point of WC follows the WHO criteria: WC > 88 cm for women and > 102 cm for men were used to define central obesity (World Health Organization, 2011).

2.5.4.4 Hip Circumference

Hip circumference was measured using a Wessex non-stretchable sprung tape measure, the same tape measure as the WC measurement, at the widest point. Staff read the measurement and subsequently inputted data manually into the assessment centre's IT system (UK Biobank, 2011a).

2.5.5 Adiposity and Body Anthropometrics

Adiposity can be assessed using various anthropometric measurements (Duren et al., 2008; Shuster et al., 2012). BMI and WC were used to represent general and central (visceral) adiposity, respectively, in the mediation analyses.

BMI was calculated as body mass in kilograms divided by height in metres squared (kg/m^2). The World Health Organization (WHO) classification was applied to define BMI categories: underweight ($<18.5 \text{ kg}/\text{m}^2$), normal weight ($18.5\text{-}24.9 \text{ kg}/\text{m}^2$), overweight ($25\text{-}29.9 \text{ kg}/\text{m}^2$), and obesity ($\geq 30 \text{ kg}/\text{m}^2$) (Weir &

Jan, 2023). Details on WC cut-off points and data collection methods are provided in earlier sections.

2.6 Covariates Used in This Thesis

Several variables were used as covariates and utilised to quantify exposures in the study. Variables that were strongly associated with T2D were chosen to be covariates. That included sociodemographic, lifestyle, health-related and adiposity-related factors. The data available for sociodemographic factors is shown in **Table 2-1**, while lifestyle, health-related, adiposity-related factors, and biomarkers are shown in **Table 2-5**.

2.6.1 Sociodemographic Factors

2.6.1.1 Age

Age was calculated from the dates of birth and baseline assessment.

2.6.1.2 Sex

Sex was self-reported by the participants at the baseline assessment.

2.6.1.3 Deprivation Index

An area-based measure of socioeconomic status was derived from the postal code of residence by using the Townsend deprivation score (TownsendPhillimore and Beattie, 1988).

2.6.1.4 Ethnicity

Ethnicity was self-reported by the participants at the baseline assessment. A question for this variable was, “What is your ethnic group?”. The choices for choosing included White, Mixed, Asian or Asian British, Black or Black British, Chinese, other ethnic group, Do not know, or Prefer not to answer. For each ethnic group, there were further questions about ethnic background. For example, if participants chose White, they were asked to select British, Irish or

any other white background (UK Biobank, 2019). The detail is shown in **Table 2-4**.

However, research categorised this variable as white, mixed, South Asian, black, Chinese and other.

Table 2-4 Ethnic groups and ethnic backgrounds in the UK Biobank cohort

Ethnic group	Ethnic background
White	British
	Irish
	Any other white background
Mixed	White and Black Caribbean
	White and Black African
	White and Asian
	Any other mixed background
Asian or Asian British	Indian
	Pakistani
	Bangladeshi
	Any other Asian background
Black or Black British	Caribbean
	African
	Any other Black background

Chinese	
Other ethnic group	

Source: Adapted from UK Biobank cohort, 2019.

2.6.1.5 Education

Education was self-reported by the participants at the baseline assessment. A question for this variable was, “Which of the following qualifications do you have? (You can select more than one)”. The choices for this question included College or University degree, A levels/AS levels or Equivalent, O levels/GCSEs or equivalent, CSEs or equivalent, NVQ or HND or HNC or equivalent, Other professional qualifications e.g. nursing, teaching, None of the above, or Prefer not to answer (UK Biobank, 2019).

2.6.2 Lifestyle Factors

2.6.2.1 Dietary Intake

Dietary intake was self-reported by the participants at the baseline assessment, which was collected by using a touch-screen FFQ (UK Biobank, 2019). Dietary factors used in this thesis included fruit and vegetables, processed meat and red meat.

2.6.2.2 Smoking Status

Smoking status was self-reported by the participants at the baseline assessment. There were a few questions about smoking but the variable used in the study summarised the participant's current and past smoking status. The variable was categorised as never, former, and current (UK Biobank, 2019).

2.6.2.3 Alcohol Intake

Alcohol intake was self-reported by the participants at the baseline assessment. A question for this variable was “About how often do you drink alcohol”. The

choices were categorised into daily or almost daily, 3-4 times a week, once or twice a week, 1-3 times a month, special occasions only, never, and Prefer not to answer (UK Biobank, 2019).

2.6.2.4 Sleep Duration

Sleep duration was self-reported by the participants at the baseline assessment. A question for this variable was “About how many hours of sleep do you get in every 24 hours? (please include naps)” (UK Biobank, 2019).

2.6.2.5 Sedentary Time

Sedentary behaviour was self-reported by the participants at the baseline assessment. This variable was derived from a discretionary screen-time variable that combined TV viewing and leisure PC screen time in hours per day (Celis-Morales et al., 2018).

2.6.2.6 Type of Physical Activity

A type of PA was self-reported by the participants at the baseline assessment. A question for this variable was “In the last 4 weeks did you spend any time doing the following? (You can select more than one answer)”. The choices included walking for pleasure (not as a means of transport), other exercises (e.g. swimming, cycling, keeping fit, bowling), strenuous sports including sports that make you sweat or breathe hard, Light do-it-yourself (DIY) (e.g. pruning, watering the lawn), heavy DIY (e.g. lawn mowing, carpentry, digging, home or car maintenance, lifting heavy objects or using heavy tools, chopping wood), none of the above, or prefer not to answer (UK Biobank, 2019).

2.6.2.7 Total Self-reported Physical Activity

PA was based on the International Physical Activity Questionnaire (IPAQ) short form, with participants reporting the frequency and duration of walking, and moderate and vigorous activity undertaken in a typical week (International Physical Activity Questionnaire, 2005). Total PA was computed as the sum of

walking, moderate and vigorous activity, measured as MET (hours/week). However, if the summary of total PA, total screen time and sleeping of an individual participant rose above 24 hours, that was an unreasonable value, it was not counted for this variable (Celis-Morales et al., 2018). Total PA <600 MET-minutes/week was defined as physical inactivity.

2.6.3 Health-related Factors

2.6.3.1 Multimorbidity

Multimorbidity was derived from participants who self-reported having chronic diseases at baseline based on 43 long-term conditions (painful conditions, hypertension, depression, asthma, atrial fibrillation, coronary heart disease, dyspepsia, diabetes, thyroid disorders, connective tissue disorders, chronic obstructive pulmonary disease, anxiety, irritable bowel syndrome, alcohol problems, other psychoactive substance abuse, treated constipation, stroke/transient ischaemic attack (TIA), chronic kidney disease, diverticular disease, peripheral vascular disease, heart failure, prostate disorders, glaucoma, epilepsy, dementia, schizophrenia/bipolar disorder, psoriasis/eczema, inflammatory bowel disease, migraine, chronic sinusitis, anorexia or bulimia, bronchiectasis, Parkinson's disease, multiple sclerosis, viral hepatitis, chronic liver disease, osteoporosis, chronic fatigue syndrome, endometriosis, Meniere's disease, pernicious anaemia, polycystic ovary, and cancer) (Jani et al., 2019). It was categorised as the number of existing morbidities.

2.6.3.2 Systolic Blood Pressure

Blood pressure measurements were collected twice by a standard automated device, placed a few seconds separate from one another. However, in cases where the standard automated instrument could not be applied, a manual sphygmomanometer was handled (UK Biobank, 2019). An average value of twice blood pressure was used in the current thesis.

2.6.3.3 Family History of Diabetes

Family history of diabetes was self-reported by the participants at the baseline assessment. Questions for this variable included “Has/did your father ever suffer from? (You can select more than one answer)”, and “Has/did your mother ever suffer from? (You can select more than one answer)”. Choices for this variable consisted of heart disease, stroke, high blood pressure, chronic bronchitis/emphysema, Alzheimer's disease/dementia, diabetes, none of the above, do not know, or prefer not to answer (UK Biobank, 2019).

2.6.4 Biomarkers

Biomarkers used included HbA1c, TG and HDL. HbA1c was used to exclude participants with a baseline HbA1c ≥ 48 mmol/mol. TG and HDL were used to calculate adiposity-related markers. Serum and packed red blood cell samples were collected at baseline by professionals following standard protocols and analysed according to standard protocols. TG was analysed using enzymatic techniques, while enzyme immuno-inhibition techniques analysed HDL (UK Biobank, 2007, Elliott and Peakman, 2008).

Table 2-5 Data available for lifestyle, health-related, and adiposity variables

Variables available at the UK Biobank	Numbers of participants with data available	Data available for individuals without diabetes at baseline	Data available for individuals with diabetes at baseline
Alcohol intake	501,018	473,094	26,360
Smoking status	501,643	473,502	26,402
Adiposity variables			
Body mass index	499,599	471,344	26,108

Waist circumference	500,357	471,971	26,220
Body fat percentage	492,110	464,651	25,375
Total physical activity	406,365	385,939	19,422
Type of physical activity	462,493	439,233	22,031
Total sedentary time	499,078	470,289	26,177
Sleep duration	498,304	470,724	26,050
Dietary variables			
Fruit and vegetable	502,535	473,502	26,402
Red meat	502,535	473,502	26,402
Processed meat	501,625	473,502	26,402
Health-related variables			
Multimorbidity	502,535	473,474	26,400
Systolic blood pressure	472,372	445,413	24,849
Haemoglobin A1c	466,530	440,214	24,308
High-density lipoprotein cholesterol	429,894	405,569	22,427
Triglycerides	469,240	442,733	24,463
Mother's history of diabetes	476,196	450,468	24,450

Father's history of diabetes	458,758	434,210	23,319
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2.7 Self-reported Medical Diagnoses

Self-reported medical diagnoses of conditions were used to exclude participants who had it at baseline. The conditions used in this present research are shown in **Table 2-6**.

Table 2-6 Chronic disease prevalences at baseline

Chronic disease	Numbers of available at baseline
Diabetes prevalence	26,402
Cancer prevalence	38,618
Heart disease prevalence (including prevalent angina, heart attack and stroke only)	29,161

2.8 Follow-up data

UK Biobank tracked the health status of participants through the linkage of national electronic health-related records (Collins, 2012, Sudlow et al., 2015). UK Biobank received permission from all participants at enrolment to access their past and future medical and other health-related data (Sudlow et al., 2015). UK Biobank followed health status from several sources, including death and cancer registries, hospital inpatient records, primary care records, and self-reporting by participants (UK Biobank, 2007, Sudlow et al., 2015).

2.8.1 Primary Care Records

Health-related information, including primary care, clinical and prescribing databases in Scotland, was linked straightforwardly via an individual's CHI number, while in England and Wales, the data was extracted from the Connecting for Health (CfH) programme, which is based on NHS Care Records Service and the Secondary Uses Service (UK Biobank, 2007). Primary care records included Read-coded data on diagnoses, prescriptions and referrals; these data were linked to UK Biobank resources (Bešević et al., 2022).

2.8.2 Hospital Inpatient Records

UK Biobank extracted participants' health events and activity information from the Scottish Morbidity Record (SMR) in Scotland and the Department of Health's Hospital Episode Statistics (HES) in England and Wales (UK Biobank, 2007). Hospital records included ICD-coded diagnoses and Office of Population Censuses and Surveys Classification of Interventions and Procedures (OPCS)-coded procedures from hospital inpatient records, including critical care; these data were linked to UK Biobank resources (Bešević et al., 2022).

2.9 Participant Withdrawal

UK Biobank informed participants that they could withdraw from the study at any time without addressing a reason and with no penalty. There were three options for withdrawal offered to the participants (UK Biobank, 2007).

1. No further contact: This meant that the UK Biobank did not contact participants anymore, but participants still allowed the UK Biobank to utilise their information and samples and other information from their health-relevant records.
2. No further access: This meant that UK Biobank did not contact participants anymore or access information from their health-relevant records in the future, but participants still allowed the UK Biobank to utilise their information and samples.

3. No further use: This meant UK Biobank would stop any activities and eradicate all the information and samples collected formerly.

UK Biobank informed the registered researchers that the withdrawn data would be removed from the dataset and that those participants would be excluded.

2.10 Ethics

The UK Biobank was approved for ethics by the NHS Northwest Multicentre Research Ethics Committee (Ref: 11/NW/0382 on 17th June 2011). Data and specimens have been exclusively employed for research that has received ethical and scientific approval. Participants' data and samples have remained confidential throughout all procedures. In 2018, the Ethics Advisory Committee (EAC) was established. The EAC has offered guidance to the UK Biobank Board and Funders concerning ethical issues that arise during the development, maintenance, and utilisation of current and forthcoming undertakings within the UK Biobank study (UK Biobank, 2019).

The current thesis was conducted using the UK Biobank resource under project application number 7155, which the University of Glasgow has an existing material transfer agreement. The PhD candidate have registered and been approved as an investigator in this project by the UK Biobank. Data access privileges include an anonymised extract of the relevant data which is encrypted and password protected. For thesis analysis, the PhD candidate worked on a password-protected personal computer that does not allow anyone else to access it. By data protection requirements, there is no direct reference to information that can identify a participant, therefore, the data from this current study are only presented as averaged results. The university ethics committee was not required to provide further ethical approval because the NHS ethical approval had already been done.

2.11 Reference Chapter 2

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Chapter 3 Associations between grip strength and incident type 2 diabetes: findings from the UK Biobank prospective cohort study

The original article of this chapter has been published in *BMJ Open Diabetes Research & Care*. The contents, style, and order of structures have been modified to conform to the standard thesis format.

Boonpor J, Parra-Soto S, Petermann-Rocha F, et al. Associations between grip strength and incident type 2 diabetes: findings from the UK Biobank prospective cohort study. *BMJ Open Diab Res Care* 2021;9:e001865. doi:10.1136/bmjdr-2020-001865.

Contributions: I developed research questions, prepared study materials, prepared the dataset and performed data analyses. I drafted the manuscript with inputs from my supervisors (CCM, SRG and FKH). I led the submission of the manuscript and responded to reviewer comments, with input and support from my supervisors.

3.1 Abstract

Introduction Grip strength has been associated with chronic diseases and mortality. However, current evidence of the association between grip strength and incident T2D is controversial. The aim of this study was to investigate the associations of absolute and relative grip strength with incident T2D and whether these associations differ by sociodemographic, lifestyle and adiposity-related factors.

Methods This was a prospective cohort study of 166,894 participants in the UK Biobank (mean age 56.5 years, 54.4% women). The outcome was T2D incidence and the exposure was grip strength, expressed in absolute (kg) and relative (kg per kg of body weight) values. The association between grip strength and T2D incidence was investigated using Cox-proportional regression

Results The median follow-up was 5.3 years (IQR: 4.7-6.1). During this time, 3,713 participants developed T2D. Lower grip strength was associated with a higher risk of T2D in both sexes. Those in the lowest quintile of absolute grip strength had a 50% higher risk in men (HR: 1.50; 95% CI: 1.30-1.73) and 25% higher risk in women (HR: 1.25; 95% CI: 1.06-1.47) compared with those in the highest quintile. For relative grip strength, risk of diabetes was more than double for men (HR: 2.22; 95% CI: 1.84-2.67) and 96% higher for women (HR: 1.96; 95% CI: 1.52-2.53) in the lowest compared with highest quintiles.

Conclusions Grip strength is associated with a higher risk of T2D incidence in both men and women independent of important confounding factors including age, deprivation, adiposity and lifestyle. However, the associations were stronger when grip strength is expressed relative to body weight, which could reflect the importance of muscle quality.

Keywords Muscle strength, Muscle quality, Type 2 diabetes mellitus

Significance of this study

What is already known about this subject?

- T2D incidence has increased worldwide.
- Lower grip strength has been associated with a higher risk of T2D and other chronic diseases.

What are the new findings?

- The association of grip strength with incident T2D differed if grip strength was expressed in absolute or relative terms.
- A 1-SD lower relative grip strength was associated with a 12% and 20% higher T2D risk in women and men, respectively.

How might these results change the focus of research or clinical practice?

- Assessing grip strength is a simple and cheap method that could be used in clinical practice to identify people who have muscle weakness and therefore have a high risk of developing T2D.

3.2 Introduction

T2D is a common but complex disease which is associated with elevated cardiovascular risk (Rawshani et al., 2017). Identifying predictors for the development of T2D as well as modifiable risk factors is, therefore, of great interest. Several lifestyle factors such as cardiorespiratory fitness (Tarp et al., 2019), PA (Aune et al., 2015) and muscle strength (Ntuk et al., 2017, Li et al., 2016, Tarp et al., 2019) have been shown to be associated with T2D incidence and involved in the aetiology of the disease.

There are several physiological reasons for muscle being important in the development of T2D. For example, skeletal muscle plays an important role in glucose disposal after meals, with around 75% of glucose disposal occurs in skeletal muscle after a meal (DeFronzo and Tripathy, 2009, Solis-Herrera et al., 2000[Updated 2021 Sep 27]). Moreover, disruption of glucose transport in skeletal muscle is enough to provoke insulin resistance in the whole body (CaspersenPowell and Christenson, 1985). Measures of muscle health are, therefore, important factors in the maintenance of metabolic health. Notably, among all the markers of muscle, strength (rather than mass) is most consistently associated with metabolic outcomes, such as insulin sensitivity.

Although there are several methods to measure muscle health, grip strength is widely used because it is a cost-effective method that has strong clinical and prognostic value for chronic diseases and mortality (Leong et al., 2015, Bohannon, 2015). For example, low levels of grip strength have been associated with a higher risk of CVDs, respiratory disease, cancer, and premature mortality in middle-aged and older adults (Celis-Morales et al., 2018b, Ho et al., 2019, Cooper et al., 2010). Grip strength is thus a practical tool for epidemiology studies outside the laboratory (CaspersenPowell and Christenson, 1985) and was used in the current thesis.

it is well established that grip strength is higher in men vs women and it peaks at around 30-40 years of age, after which it progressively declines (Dodds et al.,

2014). A large prospective study using data from the Survey of Health, Ageing and Retirement in Europe found that lower handgrip strength was independently associated with a higher risk of developing T2D among older adults. Even after adjusting for age, BMI, hypertension, smoking, and other covariates, individuals with weaker grip strength had significantly greater risk of new-onset T2 (Li et al., 2021).

A large cross-sectional analysis of 418,656 UK Biobank participants examined the relationship between grip strength and T2D prevalence across three major ethnic groups: white European, black, and South Asian adults (Ntuk et al., 2017). The study found that each 5 kg reduction in grip strength was associated with a 20-30% increase in the risk of T2D, independent of age, BMI, PA, and socioeconomic factors. This inverse association was consistent across all ethnic and sex groups, reinforcing grip strength as a robust, non-invasive marker of metabolic risk. Notably, South Asian participants had both the lowest average grip strength (by ~5-6 kg) and the highest T2D prevalence, approximately three- to fourfold higher than in white Europeans, at all levels of grip strength. The attributable risk of T2D related to low grip strength was also highest in men and women, South Asians (3.9 and 4.2 per 100, respectively), highlighting the potential utility of muscle strength as a screening tool in high-risk ethnic populations (Ntuk et al., 2017). These findings support the rationale for investigating grip strength in the risk stratification of T2D and suggest that ethnic-specific strategies may be warranted. Therefore, grip strength may serve as a useful predictor of T2D, although little research has examined associations with T2D incidence, rather than prevalence.

Although there is increasing evidence regarding the association between grip strength and T2D from prospective studies, current evidence is controversial and has some major limitations (Tarp et al., 2019, Li et al., 2016, Wander et al., 2011, Wang et al., 2019, Leong et al., 2015, Karvonen-Gutierrez et al., 2018). A recent meta-analysis conducted by Tarp *et al.*, which included 13 prospective studies (n=1,713,468 participants), reported that a 1-SD higher absolute grip strength was associated with a 13% lower risk of T2D (Tarp et al., 2019). This

study also highlighted the high heterogeneity within existing studies, differences in the number of confounding factors accounted for and a lack of sensitivity analyses to reduce the possible effect of reverse causation. In addition, as this meta-analysis was based on summary statistics rather than individual participants' data, it has limited capacity to account for confounding factors harmonised across different studies.

This study will address these limitations by using data from the UK Biobank, a large prospective cohort study. The aim of this study, therefore, was to investigate the associations between grip strength, expressed in absolute and relative units, and incident T2D and to explore whether these associations differed by key sociodemographic, lifestyle and adiposity-related factors.

3.3 Methods

Study design and population

At baseline, the UK Biobank recruited >502,000 participants between 2006 and 2010 (5.5% response rate, men and women were aged 37-73 years) from the general population (Collins, 2012). Participants attended 1 of 22 assessment centres across England, Wales, and Scotland (Sudlow et al., 2015, Palmer, 2007). At the assessment centres, participants completed an electronically signed consent, a touch screen questionnaire and physical measurements such as handgrip measurement, and collected biological samples, including blood, urine, and saliva, were collected as previously described (Palmer, 2007, Sudlow et al., 2015). Analyses for the current study were conducted in 166,894 participants of the UK Biobank cohort, who had available records from primary care, the exposure (grip strength) and covariates. Participants with prevalent diabetes and undiagnosed diabetes (n=29,765), as well as those with prevalent CVD and cancer (n=67,776) at the baseline assessment, were excluded from the study (Additional File Figure 3-1).

Outcome

Incident T2D was derived from linkage to primary care data in UK Biobank. Records were extracted for 45% of the UK Biobank cohort (228,495 participants). The end of coverage (extract date) was May 2017 for Scotland, September 2017 for Wales and August 2017 for England. Detailed linkage procedures are available at

http://biobank.ndph.ox.ac.uk/showcase/showcase/docs/primary_care_data.pdf

. Incident T2D was defined as primary care diagnosed with ICD-10 code E11. ICD codes were converted to read codes using UK Biobank's look-up table. All participants with T2D from primary care data and who were diagnosed before their UK Biobank baseline assessment visit were excluded from the analyses.

Exposure

Grip strength was measured using a Jamar J00105 hydraulic hand dynamometer. Isometric grip force was assessed from single 3-s maximal grip efforts of the right- and left-sides with participants seated upright with their elbow by their side flexed at 90° so that their forearm was facing forward and resting on an armrest. The dynamometer was adjusted to the participant's hand size. Moreover, if participants could not perform the grip strength test due to existing health issues, then these data were excluded from the analyses. The average value recorded from the right and left hand was expressed in absolute (kg) and relative units (kg of grip strength divided by kg of body weight) and used for subsequent analyses (Celis-Morales et al., 2016, Celis-Morales et al., 2018b, Ho et al., 2019).

Covariates

Sex was self-reported at baseline, age was calculated from date of birth and baseline assessment; ethnicity was self-reported at baseline and was categorised as white, South Asian, mixed, Chinese, or other. Deprivation Index, an area-based measure of socioeconomic status, was derived from the postal code of residence by using the Townsend deprivation score (Mackenbach, 1988). Education was self-reported at baseline.

Anthropometric measurements were obtained by trained personnel following standard operating procedures and using calibrated equipment (UK Biobank, 2007). Body mass was measured, without shoes and outdoor clothing, using the Tanita BC 418 body composition analyser. Height was measured, without shoes, using the wall-mounted SECA 240 height measure. BMI was calculated from body mass (in kg) divided by the square of height (in meters). The World Health Organization's criteria were used to classify BMI into categories of underweight ($<18.5 \text{ kg/m}^2$), normal weight (18.5 to 24.9 kg/m^2), overweight (25 to 29.9 kg/m^2) and obese ($\geq 30 \text{ kg/m}^2$) (World Health Organization, 1995). WC was measured midway between lowest rib margin and the iliac crest, in a horizontal plane, using a non-elastic SECA 200 tape measure. A WC >88 cm for women and >102 cm for men was used to define central obesity. Further details can be found in the UK Biobank protocol (UK Biobank, 2007).

Smoking status was categorised into never, former, and current. Fruit and vegetable, red meat, and processed meat intake were recorded by using a touch screen questionnaire asking about the reported frequency of consumption at baseline. Alcohol intake was self-reported and categorised into daily/almost daily, 3-4 times a week, once or twice a week, 1-3 times a month, special occasions only and never. Sedentary behaviour was self-reported, and a discretionary screen-time variable was derived to combine TV viewing and leisure PC screen time in hours per day (Celis-Morales et al., 2018a). PA was based on the IPAQ short form (Celis-Morales et al., 2018a), with participants reporting the frequency and duration of walking, moderate and vigorous activity undertaken in a typical week. Total PA was computed as the sum of walking, moderate and vigorous activity, measured as MET (hours/week). Total PA <600 MET-minute/week was defined as being physically inactive. Sleep duration was self-reported and categorised as short sleep <7 h/day, normal sleep 7-9 h/day and long sleep >9 h/day.

Prevalent diseases that were medically diagnosed were self-reported at baseline. Additional details about these measurements can be found in the UK Biobank online protocol (UK Biobank, 2007).

Ethical approval

The UK Biobank study was approved by the North West Multi-Centre Research Ethics Committee (Ref 11/NW/0382 on June 17, 2011), and all participants provided written informed consent to participate in the UK Biobank study. The study protocol is available online. This research has been conducted using the UK Biobank resource under application number 7155.

Statistical analyses

Cox-proportional hazard models were used to investigate the associations between grip strength (in absolute and relative units) and incident T2D with follow-up as the timeline variable. The results are reported as HRs together with 95% CIs. Analyses were conducted using a 2-year landmark period, excluding all participants with unknown T2D status at baseline ($n = 30,592$). Participants with prevalent T2D at baseline were also excluded, as the Cox regression model assumes that none of the included individuals have already experienced the outcome of interest, in this case, incident T2D.

Grip strength was treated as a continuous variable, and HRs were calculated per 5 kg decrease in absolute grip strength and per 0.05 kg/kg decrease in relative grip strength, stratified by sex. The 5 kg decrement was chosen based on prior research linking this threshold to significantly increased risks of mortality and CVD. Additionally, both absolute grip strength (measured in kg) and relative grip strength (measured in kg per kg of body weight) were standardised, with each unit corresponding to 1-SD. This standardisation enabled direct comparison of the associations for both grip strength measures using a common metric. HRs were also calculated across age- and sex-specific quintiles of both absolute and relative grip strength, using participants in the highest quintile as the reference group (cut-off points are provided in Additional File **Table S3-1**). Stratifying by age and sex is essential to account for the substantial differences in grip strength observed between men and women and different age groups.

Moderator analyses were conducted to investigate whether the association between grip strength and T2D differed by sociodemographic, lifestyle and health-related factors. Therefore, Cox-regression analyses using 5-kg and 0.05 kg/kg grip strength as exposure were stratified by age (≤ 55 vs > 55 years), deprivation (below and above the median), ethnicity (whites, South Asians and blacks), BMI (normal weight vs obesity), central obesity (normal vs central obesity), and PA (active vs inactive). An interaction term between grip strength and the moderator was fitted into the model to test whether the association between grip and T2D incidence differed by these factors.

Rate advancement periods (RAPs) were used to estimate the number of additional chronologic years that would be required to yield the equivalent risk rate of T2D incidence among individuals in the lowest quintile for handgrip strength compared to the highest quintile. The coefficient of incidence for those individuals in the lowest quintile for handgrip strength referent to individuals in the highest quintile was divided by the coefficient for incidence associated with each yearly increase in age, as described elsewhere (Discacciati et al., 2016).

Four models were conducted with an increasing number of covariates: model 0 (minimally adjusted) included age, ethnicity, deprivation index, and education. Model 1 was adjusted as in model 0 but also included smoking, fruit and vegetable intake, red meat intake, processed meat intake, alcohol intake, total sedentary time and sleep time. Model 2 (sensitivity analyses) was adjusted as in model 1 but also included BMI to investigate whether the association of grip strength and T2D was independent of overall adiposity. Similarly, Model 3 was adjusted for Model 1, but BMI was replaced with WC to investigate whether the associations were independent of central adiposity. The Pearson correlation of absolute and relative grip strength with BMI was 0.044 and -0.414, respectively. Therefore, collinearity assumptions were not violated when relative grip strength was adjusted for BMI or WC in the models.

The proportional hazard assumption was checked by tests based on Schoenfeld residuals. Statistical analyses were performed using the statistical software STATA 16 (StataCorp LP). Significance was accepted at $p < 0.05$.

3.4 Results

The analyses were conducted in 166,894 (73,100 men and 93,794 women) participants with full data available for T2D incidence, grip strength and covariates. The median follow-up period was 5.4 years (interquartile range, IQR: 4.7 to 6.1) after excluding the first two years in landmark analysis. Over the follow-up, 3,713 participants developed T2D (2,073 men and 1,640 women).

The primary cohort characteristics by grip strength quintiles are presented in **Table 3-1**. Baseline participant characteristics were stratified by quintiles to facilitate meaningful comparisons of grip strength across quintiles, ranging from the lowest to the highest. Over half of the participants were women. Individuals in the lowest grip strength quintile tended to be older (mean age: 56.1 years) and had higher socioeconomic deprivation (38.7%) compared to those in the highest quintile. Although the majority of the cohort was white, the proportion of white participants in the lowest quintile (92.1%) was slightly lower than in the higher quintiles. Conversely, the representation of ethnic minorities, including South Asians (4.5%), individuals of mixed ethnicity (1.8%), and Chinese participants (0.5%), was greater in the lowest grip strength group.

Educational attainment also varied by grip strength. Only 43.5% of participants in the lowest quintile held a college or university degree, a smaller proportion compared to those in higher grip strength categories (46.1-48.0%). Lifestyle behaviours followed a similar pattern: participants in the lowest grip quintile had higher rates of current smoking (11.3%), lower rates of former smoking (31.1%), and demonstrated generally unhealthier behaviours, including lower fruit and vegetable intake, higher alcohol consumption, reduced PA, and shorter sleep durations. Interestingly, while these individuals displayed more unhealthy

behaviours, they had a lower prevalence of overweight, or obesity (62.9%) compared to those in the highest grip quintile (69.3%).

In summary, participants with the highest levels of grip strength were more likely to be individuals with low deprivation, from a white or black ethnic background, those with college or university degree, overweight, previous smokers and normal sleepers (7-9 h/day). Those in the highest quintile of grip strength also reported a higher fruit and vegetable intake, and total PA, but also had a higher systolic blood pressure when compared with the lowest grip strength quintile.

Cohort characteristics by sex are presented in Additional File **Table S3-2** and **S3-3**. Sex-specific analyses revealed largely consistent patterns for women and men, with a few notable exceptions. Women in the lowest grip quintile had a lower prevalence of current smoking (8.4%) than their male counterparts, and in contrast to the overall trend, had a higher BMI than women in the highest quintile. Among men, those with the lowest grip strength had slightly higher educational attainment (47.7%) compared to those in the highest group (45.1%), and also reported higher rates of both current and former smoking.

Table 3-1 Cohort characteristics by quintiles of grip strength

Characteristics	Age- and sex-specific grip strength quintiles					
	Overall	High	High/Middle	Middle	Middle/Low	Low
Total participants, n	166,894	32,603	31,960	33,916	35,332	33,083
Women, n (%)	93,794 (56.2)	17,510 (53.7)	17,401 (54.5)	19,562 (57.7)	21,069 (59.6)	18,252 (55.2)
Age, years (mean, SD)	55.8 (8.1)	55 (8.4)	55.5 (8.1)	56.3 (8.0)	56.1 (7.9)	56.2 (7.8)
<i>Townsend Deprivation Index</i> , n (%)						
Lower deprivation	57,435 (34.4)	12,544 (38.5)	11,723 (36.7)	12,007 (35.4)	11,852 (33.5)	9,309 (28.1)
Middle deprivation	57,877 (34.7)	11,522 (35.3)	11,311 (35.4)	11,935 (35.2)	12,143 (34.4)	10,966 (33.2)
Higher deprivation	51,582 (30.9)	8,537 (26.2)	8,926 (27.9)	9,974 (29.4)	11,337 (32.1)	12,808 (38.7)
<i>Ethnicity</i> , n (%)						

Whites	159,677 (95.7)	31,702 (97.2)	31,035 (97.1)	32,732 (96.5)	33,738 (95.5)	30,470 (92.1)
Mixed	2,051 (1.2)	310 (1.0)	327 (1.0)	369 (1.1)	456 (1.3)	589 (1.8)
South Asians	2,950 (1.8)	139 (0.4)	224 (0.7)	417 (1.2)	671 (1.9)	1499 (4.5)
Black	1,775 (1.1)	417 (1.3)	312 (1.0)	323 (1.0)	346 (1.0)	377 (1.1)
Chinese	441 (0.3)	35 (0.1)	62 (0.2)	75 (0.2)	121 (0.3)	148 (0.5)
Education, n (%)						
College or University degree	64,082 (46.0)	13,705 (48.0)	13,010 (47.3)	13,039 (46.1)	13,011 (44.7)	11,317 (43.5)
A levels/AS levels or equivalent	18,655 (13.4)	3,861 (13.5)	3,649 (13.3)	3,746 (13.2)	3,878 (13.3)	3,521 (13.6)
O levels/GCSEs or equivalent	36,303 (26.0)	7,088 (24.8)	6,886 (25.1)	7,465 (26.4)	7,925 (27.2)	6,939 (26.7)
SEs or equivalent/NVQ or HND or HNC	20,395 (14.6)	3,929 (13.8)	3,935 (14.3)	4,036 (14.3)	4,281 (14.7)	4,214 (16.2)
Smoking status, n (%)						

Never	94,980 (56.9)	18,179 (55.8)	18,103 (56.6)	19,282 (56.9)	20,343 (57.6)	19,073 (57.7)
Previous	55,087 (33.0)	11,278 (34.6)	10,738 (33.6)	11,328 (33.4)	11,455 (32.4)	10,288 (31.1)
Current	16,827 (10.1)	3,146 (9.7)	3,119 (9.8)	3,306 (9.8)	3,534 (10)	3,722 (11.3)
<i>Diet and physical activity</i>						
Process meat intake, portion/week (mean, SD)	1.8 (1.1)	1.9 (1.0)	1.8 (1.0)	1.8 (1.0)	1.8 (1.1)	1.9 (1.1)
Red meat intake, portion/week (mean, SD)	2.1 (1.4)	2.1 (1.4)	2.1 (1.4)	2.1 (1.4)	2 (1.4)	2.1 (1.5)
Fruit and vegetable intake, g/day (mean, SD)	326.8 (191.8)	331.4 (185.6)	329.9 (190.4)	328.2 (189.0)	324.4 (188.8)	320.6 (204.4)
Alcohol intake (mean, SD)	2.9 (1.5)	2.8 (1.4)	2.8 (1.4)	2.9 (1.5)	2.9 (1.5)	3.1 (1.6)
Total Sedentary time, h/day (mean, SD)	5 (2.2)	5 (2.2)	5 (2.2)	5 (2.2)	5 (2.2)	5 (2.4)
Total physical activity, MET-hr/week (mean, SD)	2,901.6 (3,081.2)	3,050.1 (3,124.3)	2,965 (3112.8)	2,898.3 (3,046.7)	2,845.3 (3,038.4)	2,744.8 (3,078.1)
Grip strength (kg)	30.8 (11.0)	40.9 (10.7)	34.9 (8.9)	30.7 (8.2)	26.9 (7.8)	21.1 (7.9)

Grip strength per body weight (kg/kg)	0.4 (0.1)	0.5 (0.1)	0.5 (0.1)	0.4 (0.1)	0.4 (0.1)	0.3 (0.1)
Sleep categories, n (%)						
Normal (7-9 h per day)	124,481 (74.6)	25,026 (76.8)	24,227 (75.8)	25,689 (75.7)	26,204 (74.2)	23,335 (70.5)
Short sleep (<7 h per day)	39,954 (23.9)	7,262 (22.3)	7,324 (22.9)	7,812 (23.0)	8,550 (24.2)	9,006 (27.2)
Long sleep (>9 h per day)	2,459 (1.5)	3,15 (1.0)	409 (1.3)	415 (1.2)	578 (1.6)	742 (2.2)
Adiposity						
Waist circumference, cm (mean, SD)	89.2 (12.9)	90.1 (12.8)	88.9 (12.6)	88.6 (12.8)	88.4 (12.8)	90.1 (13.2)
BMI, kg/m ² (mean, SD)	27.1 (4.6)	27.5 (4.5)	27 (4.3)	27 (4.4)	27 (4.6)	27.4 (4.9)
BMI category						
Underweight (<18.5 kg/m ²)	877 (0.5)	90 (0.3)	113 (0.4)	175 (0.5)	235 (0.7)	264 (0.8)
Normal (18.5-24.9 kg/m ²)	56,665 (34.0)	9,943 (30.5)	11,002 (34.4)	12,033 (35.5)	12,662 (35.8)	11,025 (33.3)

Overweight (25-29.9 kg/m ²)	72,190 (43.3)	14,786 (45.4)	14,245 (44.6)	14,652 (43.2)	14,834 (42.0)	13,673 (41.3)
Obese (\geq 30.0 kg/m ²)	37,162 (22.3)	7,784 (23.9)	6,600 (20.7)	7,056 (20.8)	7,601 (21.5)	8,121 (24.6)

Data are presented as mean and standard deviation (SD) for continuous variables and as frequency and percentage (%) for categorical variables. A/AS level, Advanced/Advanced Subsidiary level; BMI, body mass index; GCSE, General Certificate of Secondary Education; HNC, Higher National Certificate; HND, Higher National Diploma; MET, metabolic equivalent task; NVQ, National Vocational Qualification; O level, Ordinary level; SE, Secondary Education.

As shown in **Figure 3-1**, lower grip strength was associated with a higher risk of incident T2D for men and women with the associations stronger when grip strength was expressed in relative units (kg per kg of body weight). In the minimally adjusted model (Model 0), 5-kg lower grip strength was associated with an 8% higher T2D risk for both men and women and a 0.05 kg/kg lower relative grip strength was associated with a 10% and 15% higher risk of T2D for men and women, respectively (**Figure 3-2**). The magnitude and direction of the associations were similar when the analyses were adjusted for lifestyle factors (Model 1). However, when the analyses were further adjusted for BMI or WC, the associations were attenuated, although remained statistically significant. The risk of T2D for the fully adjusted model (Model 3) was 4% and 6% higher per 5-kg lower grip strength in women and men, respectively, and per 0.05 kg/kg lower relative grip strength the risk of T2D was 3% higher for both men and women (**Figure 3-1**).

When grip strength was expressed per 1-SD lower grip strength the risk observed for the minimally adjusted model was higher for relative grip strength (77% and 92% per 1-SD lower grip for men and women, respectively) compared to absolute grip strength (14% and 21% per 1-SD lower grip for men and women, respectively). However, when the analyses were fully adjusted (Model 3, adjusted by WC instead of BMI), differences in T2D risk within absolute and relative grip strength were smaller. A 1-SD lower absolute grip strength was associated with an 11% higher risk for both men and women; and a 1-SD lower relative grip strength was associated with a 12% and 20% higher T2D risk in women and men, respectively (**Figure 3-1**).

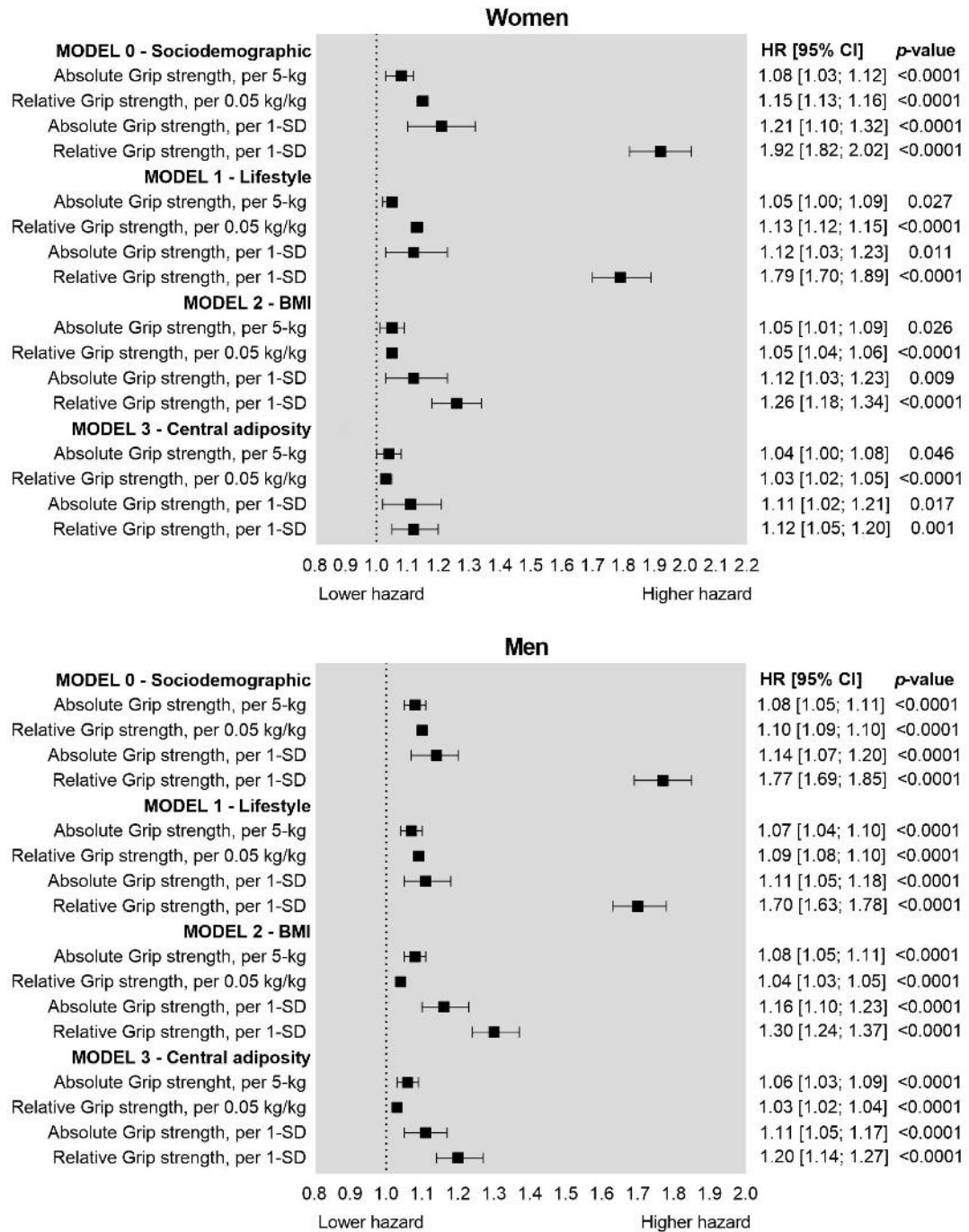


Figure 3-1 Associations between grip strength and type 2 diabetes incidence in women and men

Data are presented as hazard ratios (HRs) and 95% confidence intervals (CIs). HRs were estimated for absolute units (per 5-kg lower grip strength), relative units (0.05 kg/kg of body weight), and per 1-standard deviation (SD) lower grip strength. Model 0 was adjusted for age, deprivation, ethnicity and education; Model 1 was adjusted for all covariates included

in Model 0 plus lifestyle variables (smoking, fruit and vegetable, red meat intake, processed meat, alcohol intake, total sedentary time and sleep time); and Model 2 was adjusted for all covariates included in Model 0 and 1 plus BMI categories. Model 3 was like model 2 but BMI was replaced for waist circumference. All analyses were conducted using 2-years landmark analyses and excluding participants with comorbidities at baseline (type 1 and type 2 diabetes, unknown diabetes, cardiovascular diseases and cancer). For absolute grip strength, 1-SD was equivalent to 6.15 and 8.70 kg for women and men, respectively. For relative grip strength, 1-SD was equivalent to 0.10 and 0.11 kg per kg of body weight for women and men, respectively. BMI, body mass index.

The associations between age- and sex-specific quintiles of absolute and relative grip strength are presented in **Figure 3-2**. For the minimally adjusted models (Model 0), there were clear differences in T2D risk between absolute and relative quintiles of grip strength. One quintile lower absolute grip strength was associated with an 8% and 7% higher risk of T2D in men and women, respectively. However, the T2D risk per 1-quintile lower relative grip strength was 50% and 61% higher for men and women, respectively (**Figure 3-2**). The magnitude of associations remained similar when analyses were adjusted for lifestyle factors (Model 1) but were considerably attenuated when the analyses were adjusted for BMI or WC (Models 2 and 3). For the fully adjusted model (Model 3), the diabetes risk per 1-quintile lower absolute grip strength was 4% and 7% higher for women and men, respectively. However, the risk per 1-quintile lower relative grip strength was 11% and 15% higher in women and men, respectively.

The RAP analysis revealed that individuals with the lowest grip strength (quintile 1) will experience the same diabetes incidence rate as those among the highest fifth for grip strength who were 23.0 years (95% CI: 20.7-27.5) and 34.5 (95% CI: 35.2-34.0) years older, for women and men, respectively. The RAP estimates for each quintile of relative grip strength compared to those in the highest fifth of grip are presented in Additional File **Table S3-4**.

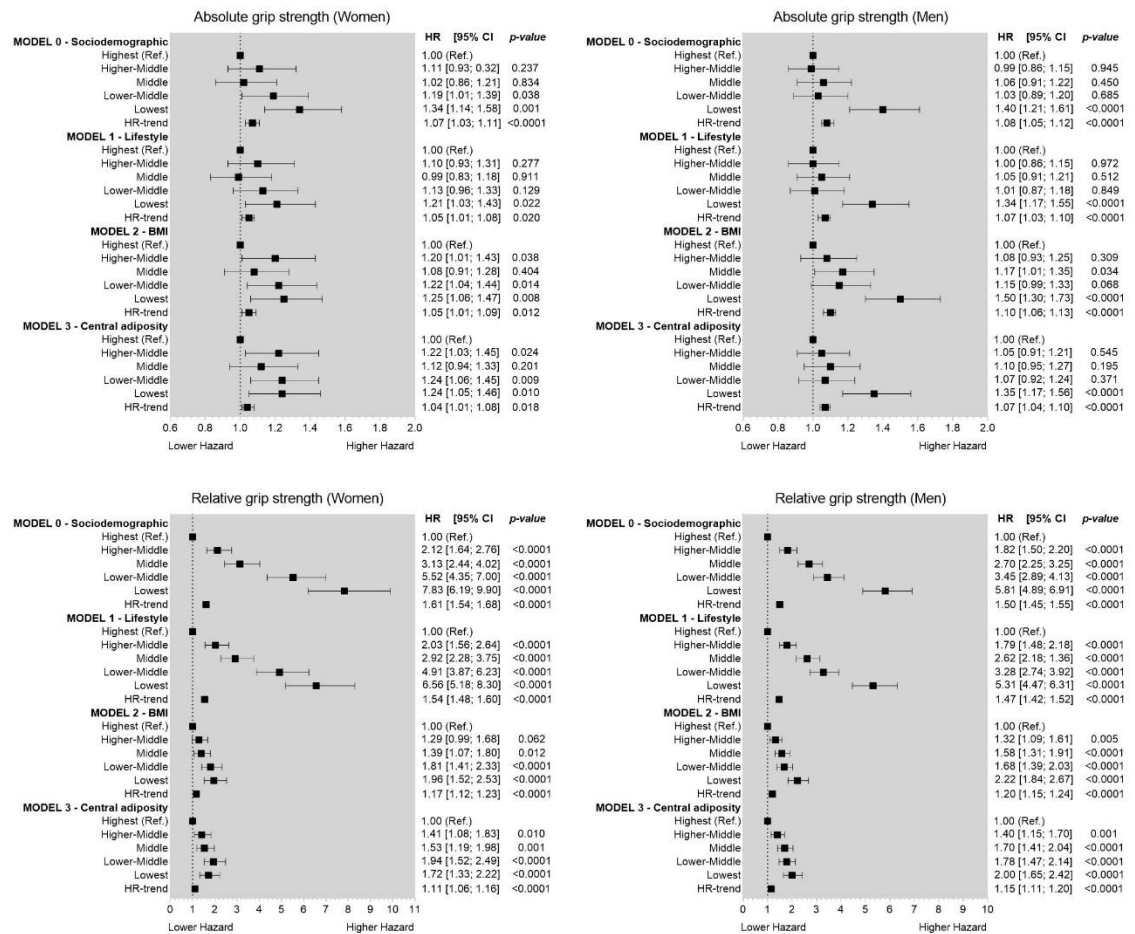


Figure 3-2 Association of age- and sex-specific quintiles of grip strength with type 2 diabetes incidence for men and women

Data are presented as hazard ratios (HRs) and 95% confidence intervals (CIs). HRs were estimated for absolute (expressed in kg) and relative (expressed per kg of grip per kg of body weight) quintiles of grip strength. The reference group was those in the highest quintile for grip strength. Model 0 was adjusted for age, deprivation, ethnicity and education; Model 1 was adjusted for all covariates included in Model 0 plus lifestyle variables (smoking, fruit and vegetable, red meat intake, processed meat, alcohol intake, total sedentary time and sleep time); and Model 2 was adjusted for all covariates included in Model 0 and 1 plus BMI categories. Model 3 was like model 2 but BMI was replaced for waist circumference. All analyses were conducted using 2-years landmark analyses and excluding participants with comorbidities at baseline (type 1 and type 2 diabetes, unknown diabetes, cardiovascular diseases and cancer). BMI, body mass index.

Figure 3-3 shows the associations between grip strength and T2D risk stratified by sociodemographic, lifestyle and adiposity levels. For absolute grip strength, 1-SD lower grip strength was associated with a 24% higher risk in individuals ≤ 55 years compared to a 13% higher risk of T2D observed in individuals aged > 55 (p -interaction=0.033). No significant differences were observed for any other moderator when absolute grip strength was used as exposure. However, the risk of T2D per 1-SD lower relative grip strength was different within age groups and ethnicity (**Figure 3-3**). T2D risk was 39% higher per 1-SD lower relative grip strength in individuals aged ≤ 55 compared to a 23% higher risk observed in individuals aged > 55 (p -interaction < 0.0001). The association of relative grip strength and T2D also differed by ethnicity (p -interaction=0.005). White European participants had the highest T2D risk (29% per 1-SD lower relative grip strength) compared to South Asians (16%), however, no associations were observed for individuals of a black ethnic background (**Figure 3-3**).

For adiposity, higher T2D risk was observed for individuals with normal weight (19%) versus those with obesity, who had an 8% higher T2D risk per 1-SD lower absolute grip strength. Similar results were observed for central obesity per 1-SD increment on absolute grip strength, those with normal WC had a 22% higher T2D risk compared with 10% observed for those centrally obese (**Figure 3-3**). However, when grip strength was expressed in relative terms, no differences were observed between normal-weight individuals and individuals with obesity (**Figure 3-3**).

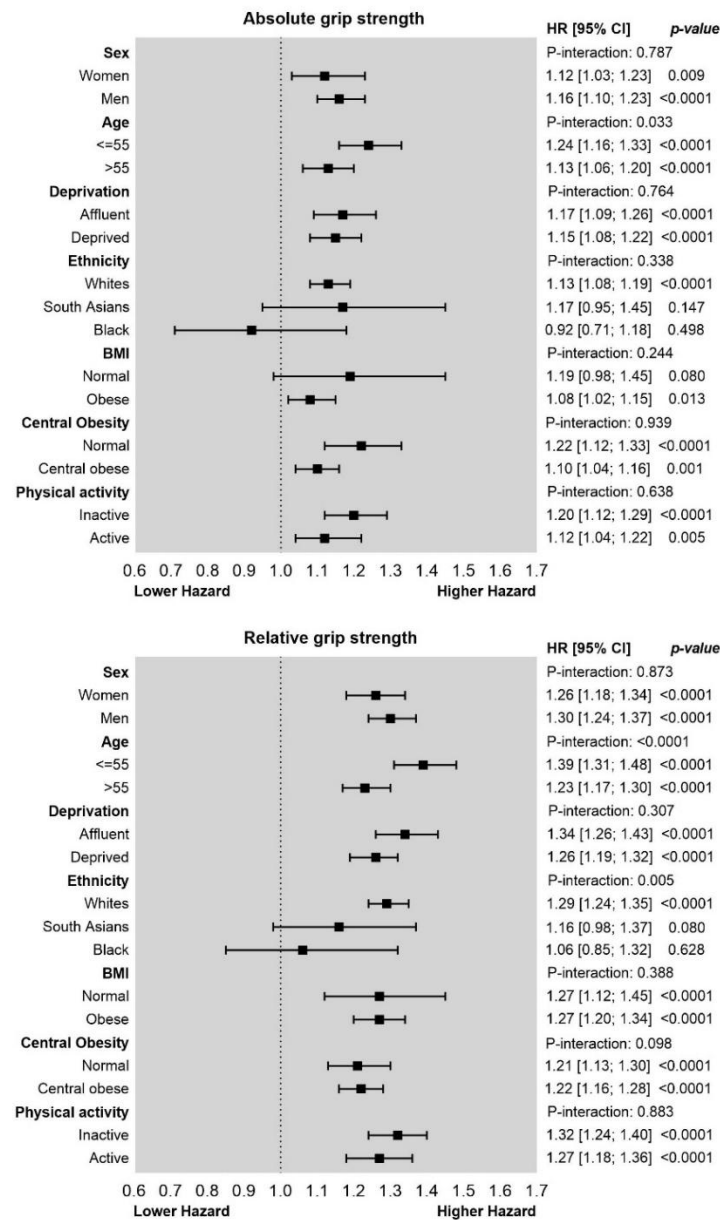


Figure 3-3 Association of grip strength with type 2 diabetes incidence by socio-demographics, lifestyle and adiposity

Data are presented as hazard ratios and 95% confidence intervals (CIs) per 1-standard deviation (SD) lower grip strength expressed in absolute and relative units. Analyses were adjusted for sex, age, deprivation, ethnicity, education, lifestyle variables (smoking, fruit and vegetable intake, red meat intake, processed meat intake, alcohol intake, total sedentary time and sleep time) and BMI, except when the covariate was used as the moderator in the analyses. 1-SD grip strength was equivalent to 11.0 kg for absolute grip and to 0.12 kg per kg of body weight for relative grip strength. BMI, body mass index.

3.5 Discussion

The main finding of this study is that lower grip strength was associated with a higher incidence of T2D in both men and women, with the association appearing stronger among men, independent of anthropometric measurements, diet, and other measures of PA. However, the association differed if grip strength was expressed in absolute or relative, i.e. in relation to body weight. These findings have important public health relevance as grip strength is easy to use, quick to conduct, cheap (Buckner et al., 2018) and it is the simplest measurement of muscle function assessment in clinical practice (Roberts et al., 2011, Celis-Morales et al., 2018b). Lower grip strength was found to have a stronger dose-response association with risk of T2D when expressed relative to body weight, whereas for absolute grip strength only those in the lower fifth were at higher risk. Therefore, relative grip strength may be a practical method to identify people who have muscle weakness, who are at high risk of developing T2D (Brown et al., 2020).

Comparison with other studies

These findings partially agree with existing evidence regarding the association of muscle strength and T2D risk (Wang et al., 2019, Leong et al., 2015, Karvonen-Gutierrez et al., 2018, Larsen et al., 2016, Tarp et al., 2019). A recent meta-analysis conducted in 39,233 incident T2D cases and 1,713,468 non-diabetic participants from 13 studies reported that 1-SD higher absolute grip strength is associated with a 24% lower risk of T2D when the analyses were not adjusted for adiposity (mainly BMI), however, the association was attenuated but remained significant when the analyses were adjusted for adiposity (13% lower risk of T2D per 1-SD higher grip strength) (Tarp et al., 2019). This study also observed that the magnitude of the associations was higher when grip strength was normalised by body weight (relative grip strength), similar to the finding observed in this current study. However, some of the limitations highlighted by this meta-analysis were the high heterogeneity within studies as well as the lack of approaches to reduce the effect of reverse causation (Tarp et al., 2019).

Furthermore, this meta-analysis also reported that not all studies included reported a protective effect, with some of them reporting a detrimental association (Li et al., 2016, Lee et al., 2018).

This agrees with other international studies such as the PURE, which was undertaken across 17 countries including 139,691 adults of whom 2,939 (2.1%) developed T2D over a median of 4.0 years follow-up, reported no significant association between grip strength and T2D, although a trend was evident (HR: 1.03 per 5-kg lower grip strength (95% CI: 0.99-1.06) (Leong et al., 2015). This borderline association could be explained by the diversity of the PURE cohort, as grip strength was substantially different between low (30.2 kg), middle (37.3 kg) and high (38.1 kg) income countries, especially for men. Moreover, the analyses conducted by the PURE study did not stratify by sex, which is surprising due to the large differences in grip strength between men and women (Leong et al., 2015). Another study conducted in the Michigan site of the Study of Women's Health study, which included 424 participants (60% black, 40% white) and who were followed up for 16 years, reported that a 0.1 unit increment in relative grip strength (kg of grip strength divided by kg of body weight) was associated with a 19% lower risk of incident T2D after adjustment for age, race/ethnicity, economic strain, smoking, menopause status, hormone use, PA and WHR. This study also reported that when the associations were stratified by ethnicity, for each 0.1 increment in relative grip strength, there was a 54% lower hazard of incident T2D among white but not black women (Karvonen-Gutierrez et al., 2018). This agrees with the present findings where grip strength was associated with incident T2D in white but not black participants. However, it is also likely that the lack of association is explained by the low number of participants of black ethnicity included in this present study (n=1,775). Therefore, future studies with longer follow-up and a larger representation of non-white ethnic groups are needed.

The current study corroborates some of the findings reported from previous studies (Wang et al., 2019, Leong et al., 2015, Karvonen-Gutierrez et al., 2018) and extends them by being able to explore these associations stratified by sex in

a large prospective cohort study. Moreover, this study also provides novel evidence on whether the association between grip strength and incident T2D differ by sociodemographic and lifestyle factors. Previous studies have reported that the magnitude of associations between some risk factors such as adiposity and grip strength with diabetes risk differs by ethnic groups (Mulwijk et al., 2019, Ntuk et al., 2017, Ferguson et al., 2018). Although some of the mechanisms suggested for adiposity are linked to higher levels of ectopic fat in non-white ethnic groups, especially South Asians, mechanisms for grip strength have not been elucidated yet.

Ethnicity, strength and type 2 diabetes risk

There was no evidence of interaction between absolute grip strength and T2D risk when stratified by ethnicity. In contrast, when grip strength was accounted for by body weight, the difference in risk of T2D was observed. However, this study did not find an association of grip strength with T2D risk among South Asians and the black population for both absolute and relative units, which is likely due to the lack of power, as these populations are underrepresented in the UK Biobank. This finding contrasts with previous cross-sectional studies, which may be due to important methodological differences. The previous study using UK Biobank data by Ntuk et al. (2017) applied logistic regression to examine the likelihood of individuals with T2D presenting with low grip strength, focusing on cross-sectional associations in prevalent cases. By contrast, the present study employed a prospective design to assess whether lower baseline grip strength was associated with an increased risk of incident T2D. These key differences in study design, temporal orientation, and analytical strategy should be considered when interpreting and comparing findings, as they limit the direct comparability of results.

Consequently, it is important to acknowledge that South Asian and black individuals are underrepresented in the UK Biobank cohort, a limitation resulting from the original recruitment strategy rather than a decision made in the present study. Given this constraint, adjusting for ethnicity in the statistical

models was considered the most appropriate approach to partially address this imbalance and account for its potential confounding effects.

Significance and clinical relevance

In studies with large sample sizes, such as the UK Biobank, statistically significant differences between groups, such as those related to sociodemographic factors and other variables, often do not reflect clinically meaningful differences. This is an important consideration, as statistical significance alone does not imply clinical relevance. For example, while the average age difference between participants in the lowest and highest grip strength quintiles may be statistically significant (e.g., 1.5 years), such a small difference is unlikely to be clinically important. Therefore, results should be interpreted with caution. However, HRs are less affected by this issue, as they estimate the relative risk associated with an exposure.

The HR quantifies the effect size by indicating the relative risk of an outcome, in this case, T2D, associated with a specific exposure, i.e. grip strength. Evidence from previous research suggested that even a 5-kg lower in grip strength was associated with approximately a 15% increased risk of all-cause mortality (Celis-Morales et al., 2018b). The critical point is to assess whether such differences also have meaningful clinical implications. In the current study, although some differences in relative grip strength per 1-SD increment between groups may appear numerically small, around 0.12 kg per kg of body weight, they were statistically significantly associated with a 12% higher risk of T2D in women and a 20% higher risk in men. Therefore, those indicated that what may appear to be a modest numerical difference in strength can, in fact, carry important clinical consequences.

Age, body weight, strength and T2D risk

The association between low grip strength and risk of T2D was stronger in individuals aged ≤ 55 years, and white people. The higher risk of T2D observed in individuals aged < 55 years could be attributable to health-related factors, as

below the age of 55 years, the decline in grip strength is relatively modest, with this decline becoming more rapid after 55 years. Having a low grip strength at age <55 years is, therefore, likely to be indicative of future poor health outcomes and is thus could explain why a stronger association between T2D and grip strength was observed in individuals aged <55 years.

Risk differences among normal weight and individuals with obesity were only observed for absolute grip strength but not for relative strength, suggesting that the ratio between strength and body mass plays a role, as we know that individuals with higher body weight tend to have higher levels of grip strength compared with those who have lower body weight. Therefore, although individuals could be classified as normal weight, their levels of strength put them at higher risk of T2D. However, the association between grip strength and T2D did not differ by sex, deprivation or PA levels. This is particularly of interest as people with lower socioeconomic status were also more vulnerable to risk factors (Foster et al., 2018).

Clinical implications

These findings have important clinical implications. Previous studies have suggested that grip strength is a strong predictor of cardiovascular risk and premature mortality (Welsh et al., 2020, Celis-Morales et al., 2018b). However, evidence regarding the predictive ability of grip strength for T2D is limited. A recent study conducted in 5,108 participants aged 20-80 years from the National Health and Nutrition Examination Survey (NHANES) has derived new grip strength cut-off points that could be used as a screening tool for diabetes risk in apparently healthy adults (Brown et al., 2020). However, future studies are needed to formally assess whether grip strength improves the prediction ability of the current risk score for T2D. Moreover, this current study has provided evidence that T2D incidence rates for those with the lowest levels of relative grip strength are equivalent to someone in the highest quintile of grip strength but who were 23.0 and 34.5 years older, for women and men, respectively.

Strengths and limitations

This present study has several notable strengths. First, the large sample size provided by the UK Biobank allowed the study to robustly examine the association between grip strength and risk of T2D, including potential interactions with key sociodemographic and lifestyle-related factors. The breadth of covariate data available also enabled comprehensive adjustment for a wide range of potential confounders, enhancing the internal validity of these findings.

Another strength lies in the simplicity, cost-effectiveness, and feasibility of grip strength assessment using handheld dynamometers. These devices are easy to use, non-invasive, and require minimal training, making them highly suitable for widespread implementation in both research and clinical settings. This enhances the potential translational value of these findings for early identification of individuals at risk of T2D based on muscle strength assessments.

However, the study is not without limitations. One key limitation is related to statistical power in stratified analyses. While the overall sample size was large, subgroup analyses, particularly by ethnicity, were underpowered due to the small number of participants from South Asian and black backgrounds. This limited the study's ability to draw precise conclusions for these groups, as reflected in wider confidence intervals and greater uncertainty in risk estimates. Future studies with more diverse and balanced ethnic representation are needed to clarify the association between grip strength and risk of T2D across ethnic subgroups.

Another limitation is the representativeness of the UK Biobank cohort. Participants tended to be healthier, more affluent, and less ethnically diverse than the general UK population, introducing a "healthy volunteer" selection bias. Although this affects the generalisability of prevalence estimates, previous research suggested that exposure-disease associations, such as those examined in this study, remain largely valid and informative (Fry et al., 2017).

The reverse causation was considered. Reverse causation is a well-recognised source of bias in observational research, arising when the direction of the association between exposure and outcome is misinterpreted. In such instances, the outcome may influence the exposure, rather than the exposure being a causal factor for the outcome. This misinterpretation underscores the importance of using methods that reduce the influence of reverse causation, such as excluding early cases through landmark analyses, conducting sensitivity analyses, or complementing findings with evidence from longitudinal and Mendelian randomisation studies (Sattar and Preiss, 2017).

Even with comprehensive measurement of risk factors and comorbidities, the potential for reverse causation cannot be fully eliminated, particularly due to the influence of subclinical or undiagnosed diseases. This concern is especially relevant in epidemiological studies examining lifestyle behaviours, such as sedentary activity and adiposity. For example, body weight loss can begin long before a formal clinical diagnosis is made and may reflect early signs of an underlying illness. Such changes in body composition can precede mortality by several years, as shown in studies by Sattar and Preiss (2017) and Kushner et al. (2020), highlighting the potential for reverse causation to confound observed associations (Sattar and Preiss, 2017, Kushner et al., 2020).

To address this issue, the current study employed several strategies to minimise the impact of reverse causation. Participants with major chronic diseases at baseline, including CVD, cancer, type 1 and type 2 diabetes, and elevated HbA1c, were excluded. In addition, individuals who developed T2D within the first two years of follow-up were also excluded through a landmark analysis approach. These measures aimed to reduce the influence of undiagnosed or subclinical illness on baseline grip strength, thereby strengthening the temporal validity of the observed associations. While this approach reduces the likelihood of reverse causation, it may not eliminate it entirely. A longer exclusion period (e.g., 5-10 years) would offer stronger protection against reverse causation, but this was not possible due to the relatively short follow-up duration of the UK Biobank cohort.

Adiposity and reverse causation

However, reverse causation related to adiposity remains a consideration in the interpretation of these findings. Notably, participants with the lowest grip strength, who were at higher risk of developing T2D, were more often in the underweight or normal-weight categories, compared to those with higher grip strength. This seemingly paradoxical finding may be explained by the presence of other adverse health behaviours and conditions. For instance, individuals in the lowest strength category were more likely to be current smokers, consume an unhealthy diet, drink alcohol at higher levels, report lower PA, and have shorter sleep durations. These characteristics may contribute to lower or normal BMI values at baseline, despite underlying health deterioration. As such, the relationship between low grip strength and higher T2D risk in these participants may reflect an interplay of early-stage health decline and behavioural risk factors rather than a straightforward protective effect of lower body weight.

A recent and increasingly applied epidemiological technique for addressing reverse causation and unmeasured confounding is Mendelian Randomisation (MR).

Mendelian randomisation

Mendelian randomisation uses genetic variants as instrumental variables to assess whether an observed association between a risk factor (exposure) and an outcome is consistent with a causal effect (EmdinKhera and Kathiresan, 2017, Smith and Ebrahim, 2003). This method capitalises on the principle that germline genetic variants are randomly allocated at conception and remain fixed throughout life. As such, they are generally independent of lifestyle and environmental confounders that often bias traditional observational analyses (Smith and Ebrahim, 2003, Richmond and Davey Smith, 2022).

A key concept underpinning MR is gene-environment equivalence, which suggests that a change in phenotype, whether driven by genetic variation or environmental exposure, should result in similar downstream effects on the

outcome. This assumption supports the validity of MR in inferring causal relationships between modifiable risk factors (such as adiposity or grip strength) and health outcomes (Richmond and Davey Smith, 2022).

In the causal inference framework, MR functions as a type of instrumental variable (IV) analysis, where genetic variants act as proxies for modifiable exposures. For an MR analysis to be valid, three key assumptions must be satisfied:

- The genetic variant is robustly associated with the exposure of interest (grip strength).
- The genetic variant is not associated with confounding variables, whether measured or unmeasured.
- The genetic variant affects the outcome (incidence of T2D) only through its effect on the exposure and not through any alternative pathway (i.e., no horizontal pleiotropy).

These assumptions are often illustrated using a directed acyclic graph (DAG), as shown in **Figure 3-4**, which visually represents the proposed causal pathway from the genetic variant to the outcome via the exposure of interest.

MR thus provides a valuable tool for strengthening causal inference in epidemiology, particularly in studies where traditional observational designs are vulnerable to biases such as reverse causation and residual confounding.

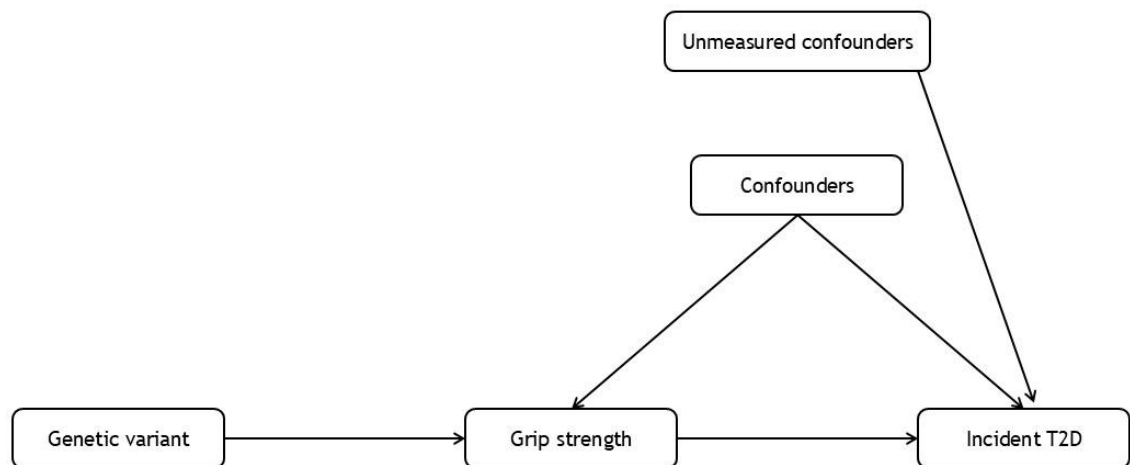


Figure 3-4 A directed acyclic graph for Mendelian randomisation

Grip strength is associated with the incidence of type 2 diabetes (T2D). Typically, the association is confounded by other factors, while unmeasured confounders may also influence the incidence of T2D. A genetic variant is associated with grip strength, independent of confounders, whether measured or unmeasured. The genetic variant affects the incidence of T2D only through its effect on grip strength and not through any alternative pathway.

Source: Adapted from Richmond and Davey Smith (2022)

As previously mentioned, the current study is a prospective cohort study, which allows for the observation of associations over time but does not permit firm conclusions regarding causality between grip strength and the risk of T2D. However, MR studies using UK Biobank data have provided valuable insights into potential causal relationships by leveraging genetic variants as instrumental variables.

A study led by Willems et al. (2017) conducted a large-scale genome-wide association study (GWAS), using UK Biobank data, identified multiple genetic loci associated with hand grip strength, shedding light on the biological underpinnings of muscular fitness. The study revealed 64 genome-wide significant loci, implicating genes involved in skeletal muscle structure, central nervous system function, and cell adhesion. They also investigate whether

genetically predicted levels of sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulphate (DHEA-S), insulin, and insulin-like growth factor-I (IGF-I) were associated with grip strength. Instrumental variables were derived from genome-wide significant single-nucleotide variants (SNVs) associated with SHBG, DHEA-S, and IGF-I levels. The MR analyses provided no evidence for a causal association between SHBG, DHEA-S, or IGF-I and grip strength. In contrast, there was some indication of a potential causal effect of insulin resistance and fasting insulin levels on grip strength, as supported by inverse-variance weighted and median-weighted MR estimates. However, the substantial heterogeneity observed in the inverse-variance weighted results necessitates cautious interpretation (Willems et al., 2017).

One such MR study by Tikkanen et al. (2018) demonstrated that genetic variants were associated with muscular strength and further identified substantial genetic correlations with 78 traits, many of which were cardiometabolic in nature, including blood pressure, lipid profiles, and metabolic biomarkers. However, the study did not report results specifically for T2D (Tikkanen et al., 2018).

Therefore, future studies should utilise the MR study to investigate the relationship between grip strength and incident T2D.

3.6 Conclusions

Individuals with lower relative grip strength exhibited substantially higher T2D risk across multiple analytical approaches, including continuous, quintile-based, and standard deviation-based analyses. Notably, the RAP analysis revealed that individuals in the lowest quintile of grip strength experience T2D incidence rates equivalent to those who are more than two to three decades older but in the highest quintile of grip strength, highlighting the powerful prognostic value of muscular strength as a biomarker of metabolic health.

Stratified analyses further indicated that the association between grip strength and T2D was more pronounced in younger adults (≤ 55 years) and among white European participants, though caution is warranted when interpreting subgroup analyses due to limited representation of ethnic minorities in the UK Biobank.

From a clinical and public health perspective, these findings are particularly relevant. Grip strength assessment is quick, inexpensive, non-invasive, and easily implementable in both research and clinical settings. Handgrip dynamometry can be integrated into routine health assessments in primary care or community health programs as a feasible screening tool for identifying individuals at elevated risk of T2D. The stronger and more consistent associations observed for relative grip strength support its use as a more informative metric than absolute grip strength, particularly for early risk stratification and potential intervention targeting.

Although causal inference is limited due to the observational nature of the study, the findings contribute to a growing body of evidence linking muscular strength to metabolic health. Complementary evidence from MRs suggests a potential causal relationship between muscle strength and improved insulin sensitivity, as well as reduced risk of T2D. Future research should investigate the mechanisms underlying this association and assess whether interventions targeting muscular strength, such as resistance training, can serve as effective strategies for T2D prevention.

3.7 Reference Chapter 3

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3.8 Additional File Chapter 3

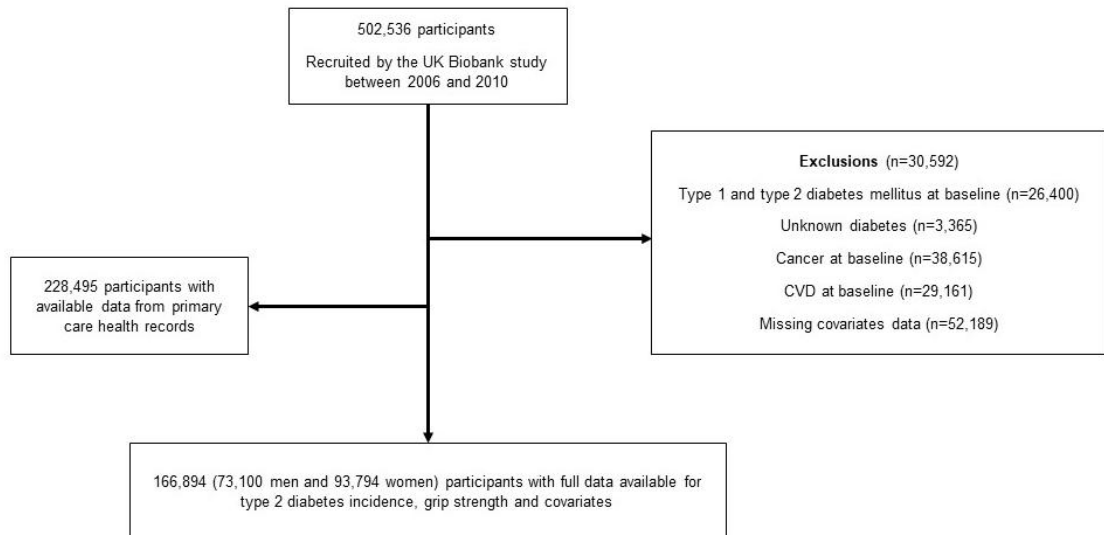


Figure S3-1 Flowchart of participants throughout the study

Table S3-1 Cut-off point for absolute and relative grip strength quintiles

		Absolute grip strength (kg)				
Sex	Age group	Low	Middle/Low	Middle	High/Middle	Highest
Women	<56 years	<20.5	20.5 - 24	24.5 - 27	27.5 - 30.5	>30.5
	56 to 65 years	<18	18 - 21	21.5 - 24	24.5 - 27	>27.5
	>65 years	<16.5	16.5 - 19	19.5 - 22	22.5 - 25	>25
Men	<56 years	<35	35.5 - 40	40.5 - 44	44.5 - 49	>49
	56 to 65 years	<32	32 - 36.5	37 - 40.5	41 - 45	>45
	>65 years	<29	29 - 34	34.5 - 38	38.5 - 42	>42.5
		Relative grip strength (kg/kg)				
Women	<56 years	<0.275	0.276 - 0.337	0.338 - 0.391	0.392 - 0.456	>0.456
	56 to 65 years	<0.238	0.238 - 0.293	0.294 - 0.341	0.342 - 0.399	>0.399
	>65 years	<0.219	0.219 - 0.272	0.273 - 0.317	0.318 - 0.370	>0.370
Men	<56 years	>0.395	0.395 - 0.463	0.464 - 0.521	0.522 - 0.588	>0.588
	56 to 65 years	>0.364	0.364 - 0.428	0.429 - 0.483	0.484 - 0.547	>0.547
	>65 years	>0.343	0.343 - 0.404	0.405 - 0.457	0.458 - 0.519	>0.519

Data are presented as kg for absolute grip strength and as kg by kg of body weight for relative grip strength.

Table S3-2 Cohort characteristics by quintiles of grip strength in women

Characteristics	Grip strength quintiles					
	Overall	High	High/Middle	Middle	Middle/Low	Low
Women, n (%)	93,794	19,313	16,440	18,320	22,176	17,545
Age (mean, SD)	55.8 (8.0)	51.6 (7.5)	54.5 (7.8)	56.1 (7.8)	57.8 (7.4)	59 (7.2)
<i>Townsend Deprivation Index</i> , n (%)						
Lower deprivation	32,033 (34.2)	6,944 (36)	5,979 (36.4)	6,436 (35.1)	7,504 (33.8)	5,170 (29.5)
Middle deprivation	32,773 (34.9)	6,778 (35.1)	5,750 (35.0)	6,425 (35.1)	7,814 (35.2)	6,006 (34.2)
Higher deprivation	28,988 (30.9)	5,591 (29.0)	4,711 (28.7)	5,459 (29.8)	6,858 (30.9)	6,369 (36.3)
<i>Ethnicity</i> , n (%)						
Whites	89,757 (95.7)	18,593 (96.3)	15,866 (96.5)	17,636 (96.3)	21,284 (96)	16,378 (93.4)

Mixed	1,258 (1.3)	261 (1.4)	220 (1.3)	233 (1.3)	267 (1.2)	277 (1.6)
South Asians	1,450 (1.6)	98 (0.5)	130 (0.8)	201 (1.1)	353 (1.6)	668 (3.8)
Black	1,045 (1.1)	315 (1.6)	186 (1.1)	192 (1.1)	198 (0.9)	154 (0.9)
Chinese	284 (0.3)	46 (0.2)	38 (0.2)	58 (0.3)	74 (0.3)	68 (0.4)
Education, n (%)						
College or University degree	35,117 (45.1)	8,803 (49.6)	6,725 (46.9)	6,883 (44.9)	7,509 (42.4)	5,197 (40.6)
A levels/AS levels or equivalent	11,047 (14.2)	2,628 (14.8)	2,150 (15.0)	2,141 (14)	2,421 (13.7)	1,707 (13.3)
O levels/GCSEs or equivalent	22,361 (28.7)	4,455 (25.1)	3,837 (26.7)	4,452 (29)	5,519 (31.2)	4,098 (32.0)
SEs or equivalent/NVQ or HND or HNC	9,424 (12.1)	1,860 (10.5)	1,643 (11.5)	1,852 (12.1)	2,263 (12.8)	1,806 (14.1)
Smoking status, n (%)						
Never	57,048 (60.8)	11,663 (60.4)	10,025 (61)	11,149 (60.9)	13,540 (61.1)	10,671 (60.8)

Previous	28,669 (30.6)	5,809 (30.1)	4,983 (30.3)	5,638 (30.8)	6,874 (31.0)	5,365 (30.6)
Current	8,077 (8.6)	1,841 (9.5)	1,432 (8.7)	1,533 (8.4)	1,762 (8.0)	1,509 (8.6)
<i>Diet and physical activity</i>						
Process meat intake, portion/week (mean, SD)	1.6 (1.0)	1.6 (1.0)	1.6 (1.0)	1.6 (1.0)	1.6 (1.0)	1.6 (1.0)
Red meat intake, portion/week (mean, SD)	2.0 (1.4)	2.0 (1.4)	1.9 (1.3)	2 (1.3)	2.0 (1.3)	2.0 (1.4)
Fruit and vegetable intake, g/day (mean, SD)	348.4 (188.3)	344.5 (187.5)	348.5 (186.8)	349.7 (189.3)	348.1 (180.3)	351.5 (199.4)
Alcohol intake (mean, SD)	3.1 (1.5)	3.0 (1.4)	3.0 (1.5)	3.1 (1.5)	3.2 (1.5)	3.4 (1.6)
Total Sedentary time, h/day (mean, SD)	4.7 (2.0)	4.6 (2.0)	4.6 (1.9)	4.7 (2.0)	4.7 (2.0)	4.8 (2.1)
Total physical activity, MET-hr/week (mean, SD)	2,664.5 (2,743.0)	2,749.4 (2,743.1)	2,688 (2,761.3)	2,656.2 (2,737.8)	2,628.1 (2,730.1)	2,597.2 (2,744.8)

Grip strength (kg)	23.6 (6.2)	31.9 (3)	26.9 (0.9)	23.9 (0.9)	20.5 (1.1)	14.7 (3.3)
Grip strength per body weight (kg/kg)	0.3 (0.1)	0.5 (0.1)	0.4 (0.1)	0.4 (0.1)	0.3 (0.1)	0.2 (0.1)
Sleep categories, n (%)						
Normal (7-9 h per day)	70,230 (74.9)	15,086 (78.1)	12,611 (76.7)	13,769 (75.2)	16,431 (74.1)	12,333 (70.3)
Short sleep (<7 h per day)	22,019 (23.5)	4,019 (20.8)	3,611 (22)	4,296 (23.5)	5,326 (24)	4,767 (27.2)
Long sleep (>9 h per day)	1,545 (1.7)	208 (1.1)	218 (1.3)	255 (1.4)	419 (1.9)	445 (2.5)
Adiposity						
Waist circumference, cm (mean, SD)	83.9 (11.9)	83.5 (11.9)	83.0 (11.6)	83.4 (11.6)	84.0 (11.9)	85.5 (12.4)
BMI, kg/m ² (mean, SD)	26.9 (4.9)	26.8 (5)	26.5 (4.8)	26.7 (4.8)	26.8 (4.9)	27.4 (5.2)
BMI category						
Underweight (<18.5 kg/m ²)	702 (0.8)	93 (0.5)	126 (0.8)	134 (0.7)	182 (0.8)	167 (1.0)

Normal (18.5-24.9 kg/m ²)	37,368 (39.8)	7,968 (41.3)	6,983 (42.5)	7,499 (40.9)	8,800 (39.7)	6,118 (34.9)
Overweight (25-29.9 kg/m ²)	35,145 (37.5)	7,054 (36.5)	6,140 (37.4)	6,921 (37.8)	8,319 (37.5)	6,711 (38.3)
Obese (\geq 30.0 kg/m ²)	20,579 (21.9)	4,198 (21.7)	3,191 (19.4)	3,766 (20.6)	4,875 (22)	4,549 (25.9)

Data are presented as mean and SD for continuous variables and as frequency and % for categorical variables. BMI: body mass index, SD: standard deviation, MET: metabolic equivalent task

Table S3-3 Cohort characteristics by quintiles of grip strength in men

Characteristics	Grip strength quintiles					
	Overall	High	High/Middle	Middle	Middle/Low	Low
Participants, n (%)	73,100	14,436	16,483	14,979	14,075	13,127
Age, years (mean, SD)	55.8 (8.2)	52.3 (7.8)	54.9 (8.0)	56.4 (8.0)	57.5 (8.0)	58.6 (7.8)
<i>Townsend Deprivation Index</i> , n (%)						
Lower deprivation	25,402 (34.8)	5,547 (38.4)	6,107 (37.1)	5,277 (35.2)	4,714 (33.5)	3,757 (28.6)
Middle deprivation	25,104 (34.3)	5,083 (35.2)	5,747 (34.9)	5,208 (34.8)	4,796 (34.1)	4,270 (32.5)
Higher deprivation	22,594 (30.9)	3,806 (26.4)	4,629 (28.1)	4,494 (30.0)	4,565 (32.4)	5,100 (38.9)
<i>Ethnicity</i> , n (%)						
Whites	69,920 (95.7)	13,982 (96.9)	15,975 (96.9)	14,429 (96.3)	13,407 (95.3)	12,127 (92.4)

Mixed	793 (1.1)	127 (0.9)	162 (1.0)	143 (1.0)	161 (1.1)	200 (1.5)
South Asians	1,500 (2.1)	103 (0.7)	173 (1.1)	259 (1.7)	342 (2.4)	623 (4.8)
Black	730 (1.0)	209 (1.5)	151 (0.9)	118 (0.8)	123 (0.9)	129 (1.0)
Chinese	157 (0.2)	15 (0.1)	22 (0.1)	30 (0.2)	42 (0.3)	48 (0.4)
Education, n (%)						
College or University degree	28,965 (47.1)	5,850 (45.1)	6,740 (47.0)	6,039 (48.0)	5,511 (48.0)	4,825 (47.7)
A levels/AS levels or equivalent	7,608 (12.4)	1,586 (12.2)	1,760 (12.3)	1,530 (12.2)	1,421 (12.4)	1,311 (13.0)
O levels/GCSEs or equivalent	13,942 (22.7)	3,048 (23.5)	3,203 (22.4)	2,807 (22.3)	2,593 (22.6)	2,291 (22.6)
SEs or equivalent/NVQ or HND or HNC	10,971 (17.8)	2,484 (19.2)	2,624 (18.3)	2,205 (17.5)	1,962 (17.1)	1,696 (16.8)
Smoking status, n (%)						
Never	37,932 (51.9)	7,833 (54.3)	8,654 (52.5)	7,689 (51.3)	7,095 (50.4)	6,661 (50.7)

Previous	26,418 (36.1)	4,881 (33.8)	5,921 (35.9)	5,543 (37.0)	5,276 (37.5)	4,797 (36.5)
Current	8,750 (12.0)	1,722 (11.9)	1,908 (11.6)	1,747 (11.7)	1,704 (12.1)	1,669 (12.7)
<i>Diet and physical activity</i>						
Process meat intake, portion/week (mean, SD)	2.2 (1.0)	2.2 (1.0)	2.2 (1.0)	2.2 (1.0)	2.2 (1.0)	2.2 (1.1)
Red meat intake, portion/week (mean, SD)	2.2 (1.5)	2.3 (1.4)	2.2 (1.4)	2.2 (1.5)	2.2 (1.5)	2.2 (1.6)
Fruit and vegetable intake, g/day (mean, SD)	299.2 (192.6)	299.9 (183.9)	300.1 (190.0)	300.9 (189.7)	298 (193.4)	296.8 (206.9)
Alcohol intake (mean, SD)	2.6 (1.4)	2.5 (1.3)	2.5 (1.3)	2.5 (1.4)	2.6 (1.4)	2.8 (1.5)
Total Sedentary time, h/day (mean, SD)	5.4 (2.4)	5.5 (2.5)	5.4 (2.4)	5.4 (2.4)	5.4 (2.4)	5.4 (2.5)
Total physical activity, MET-hr/week (mean, SD)	3,198.1 (3,435.1)	3,367 (3,536.7)	3,282.7 (3,467.6)	3,197.4 (3,374.6)	3,118.8 (3,351.8)	2,981.1 (3,421.8)
Grip strength (kg)	40.1 (8.7)	52.3 (4.4)	44.3 (1.6)	39.5 (1.2)	35.0 (1.4)	27.5 (4.5)
Grip strength per body weight (kg/kg)	0.5 (0.1)	0.6 (0.1)	0.5 (0.1)	0.5 (0.1)	0.4 (0.1)	0.3 (0.1)

Sleep categories, n (%)						
Normal (7-9 h per day)	54,251 (74.2)	10,871 (75.3)	12,364 (75.0)	11,199 (74.8)	10,450 (74.3)	9,367 (71.4)
Short sleep (<7 h per day)	17,935 (24.5)	3,463 (24.0)	3,962 (24.0)	3,601 (24.0)	3,426 (24.3)	3,483 (26.5)
Long sleep (>9 h per day)	914 (1.3)	102 (0.7)	157 (1.0)	179 (1.2)	199 (1.4)	277 (2.1)
Adiposity						
Waist circumference, cm (mean, SD)	96 (10.7)	96.5 (10.3)	95.7 (10.4)	95.6 (10.7)	95.7 (10.8)	96.4 (11.3)
BMI, kg/m ² (mean, SD)	27.5 (4.0)	28.1 (3.9)	27.5 (3.8)	27.4 (3.9)	27.3 (4.0)	27.4 (4.3)
BMI category						
Underweight (<18.5 kg/m ²)	175 (0.2)	8 (0.1)	16 (0.1)	31 (0.2)	37 (0.3)	83 (0.6)
Normal (18.5-24.9 kg/m ²)	19,297 (26.4)	2,967 (20.6)	4,222 (25.6)	4,141 (27.7)	4,134 (29.4)	3,833 (29.2)
Overweight (25-29.9 kg/m ²)	37,045 (50.7)	7,706 (53.4)	8,591 (52.1)	7,624 (50.9)	6,924 (49.2)	6,200 (47.2)

Obese (≥ 30.0 kg/m ²)	16,583 (22.7)	3,755 (26.0)	3,654 (22.2)	3,183 (21.3)	2,980 (21.2)	3,011 (22.9)
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Data are presented as mean and standard deviation (SD) for continuous variables and as frequency and % for categorical variables. BMI: body mass index, SD: standard deviation, MET: metabolic equivalent task

Table S3-4 Advance Rate Period (RAP) for incidence type 2 diabetes in men and women by quintiles of relative handgrip strength

<i>RAP for T2D Incidence (95% CI)</i>		
	Women	Men
Highest (Ref.)	Reference	Reference
Higher-Middle	8.6 (-0.7; 15.4)	12.1 (5.0; 16.5)
Middle	11.3 (3.6; 17.4)	19.8 (15.6; 22.4)
Middle-Lower	20.4 (17.0; 25.2)	22.4 (19.1;24.4)
Lowest	23.0 (20.7; 27.5)	34.5 (35.2; 34.0)

Estimated based on RR shown in Figure 2 for model 2. T2D: type 2 diabetes

Chapter 4 Dose-response relationship between device-measured physical activity and incident type 2 diabetes: findings from the UK Biobank prospective cohort study

The original article of this chapter has been published in BMC Medicine. The contents, style, and order of structures have been modified to conform to the standard thesis format.

Boonpor, J., Parra-Soto, S., Petermann-Rocha, F. et al. Dose-response relationship between device-measured physical activity and incident type 2 diabetes: findings from the UK Biobank prospective cohort study. *BMC Med* 21, 191 (2023). <https://doi.org/10.1186/s12916-023-02851-5>.

Contributions: I developed research questions, prepared study materials, prepared the dataset and performed data analyses. I drafted the manuscript with inputs from my supervisors (CCM, SRG and FKH). I led the submission of the manuscript and responded to reviewer comments, with input and support from my supervisors.

4.1 Abstract

Introduction Most studies investigating the association between PA and the risk of T2D are derived from self-reported questionnaires, with limited evidence using device-based measurements. Therefore, this study aimed to investigate a dose-response relationship between device-measured PA and incident T2D.

Methods This prospective cohort study included 40,431 participants of the UK Biobank. Wrist-worn accelerometers were used to estimate total, light, MPA, VPA and MVPA. The associations between PA and incident T2D were analysed using Cox-proportional hazard models. The mediating role of BMI was tested under a causal counterfactual framework.

Results The median follow-up period was 6.3 years (IQR: 5.7 - 6.8), with 591 participants developing T2D. Compared to those achieving <150 min/week of MPA, people achieving 150 - 300, 300 - 600 and >600 min/week were at 49% (95% CI; 62%-32%), 62% (95% CI; 71%-50%) and 71% (95% CI; 80%-59%) lower risk of T2D, respectively. For VPA, compared to those achieving <25 min/week, individuals achieving 25-50, 50-75 and >75 min/week were at 38% (95% CI; 48%-33%), 48% (95% CI; 64%-23%) and 64% (95% CI; 78%-42%) lower T2D risk, respectively. Twelve per cent and 20% of the associations between vigorous and moderate PA and T2D were mediated by lower BMI, respectively.

Conclusions PA has clear dose-dependent relationships with a lower risk of T2D. The present findings support the current aerobic PA recommendations but suggest that additional PA beyond the recommendations is associated with even greater risk reduction.

Keywords Accelerometer, Obesity, Physical activity, Type 2 diabetes mellitus

4.2 Introduction

T2D is a common condition, with a growing prevalence worldwide (Federation, 2019, Saeedi et al., 2019), which is associated with an increased risk of numerous adverse health outcomes, such as neuropathy, nephropathy, retinopathy and CVD (Federation, 2019, Saeedi et al., 2019). T2D is associated with numerous adverse health outcomes, including CVD, nephropathy, neuropathy, and retinopathy, all of which contribute to increased morbidity and premature mortality. Identifying modifiable risk factors for the development of T2D is therefore crucial for targeting high-risk individuals and developing effective prevention strategies.

While obesity is a well-established risk factor for T2D (Lean et al., 2018), other modifiable factors related to PA, including cardiorespiratory fitness (CRF) and muscular strength, are also independently associated with T2D (Tarp et al., 2019, Al-Ozairi et al., 2021, Boonpor et al., 2021). PA is defined as any bodily movement produced by skeletal muscles that results in energy expenditure. It encompasses a range of intensities and types, from light-intensity movements (such as casual walking) to MVPA, including brisk walking, running, or resistance training **Figure 4-1**.

Cardiorespiratory fitness reflects the ability of the cardiovascular and respiratory systems to deliver oxygen to working muscles during sustained PA and is often considered a powerful marker of metabolic health. Muscular strength, on the other hand, refers to the maximal force a muscle or muscle group can generate and plays a vital role in glucose uptake and insulin sensitivity through skeletal muscle mass and function. Both CRF and muscular strength are influenced by PA, but also by genetic, hormonal, and behavioural factors (**Figure 4-1**). Importantly, regular participation in PA can acutely and chronically improve insulin sensitivity and glycaemic control (Bird and Hawley, 2016),

supporting its inclusion in both the prevention and management of T2D (Pan et al., 1997).

The 2020 WHO Guidelines on Physical Activity and Sedentary Behaviour recommend that adults accumulate at least 150-300 minutes of moderate-intensity or 75-150 minutes of vigorous-intensity aerobic PA per week (or an equivalent combination of both), as well as engage in muscle-strengthening activities involving all major muscle groups on two or more days per week (Bull et al., 2020). These recommendations are based primarily on evidence linking PA with a wide range of health benefits, including reduced risk of T2D. However, it remains unclear whether these thresholds, derived mostly from self-reported data, are optimal when PA is measured more precisely.

To date, most of the evidence linking PA with T2D risk has relied on self-reported questionnaires (Celis-Morales et al., 2012). These methods are prone to recall and social desirability bias, leading to exposure misclassification and likely underestimation of the true strength of associations (Smith et al., 2016). In contrast, device-based measurements, such as accelerometers, offer greater accuracy in capturing the full range of daily activities across intensities, including light activity and sedentary time (Dempsey et al., 2022). This enables a more nuanced understanding of dose-response relationships and supports the development of more precise and actionable guidelines.

Recent evidence in all-cause mortality research has shown that risk reduction estimates based on device-measured PA are nearly double those obtained through self-report (Ekelund et al., 2019), underscoring the importance of using objective measures in chronic disease epidemiology. However, only a few studies have explored the association between device-measured PA and incident T2D, and those that have were conducted in relatively small populations ($n < 8000$), often using pedometers that cannot distinguish between PA intensities (Califf et al., 2008, Sternfeld et al., 2019, Garduno et al., 2022).

To date, only two studies (Chen et al., 2020, Sternfeld et al., 2019) have examined the association between accelerometer-measured PA and incident T2D in middle-aged adults. However, these studies focused exclusively on MVPA, failing to examine the potential protective role of light-intensity activity. Furthermore, they did not assess whether current WHO PA guidelines are supported by device-based evidence in the context of T2D prevention. As light-intensity PA has recently been suggested to confer metabolic benefits, particularly in sedentary populations, this represents a critical evidence gap.

In summary, current evidence linking PA to T2D risk is limited by:

- A reliance on self-reported PA, which is susceptible to bias and measurement error.
- A lack of large-scale, prospective studies using device-based PA assessments capable of capturing intensity-specific activity.
- Insufficient attention to light-intensity PA, despite emerging evidence of its health benefits.
- Limited evidence evaluating the appropriateness of current PA guidelines in relation to T2D prevention using objective data.

These limitations have important implications for both clinical practice and public health policy. Without accurate quantification of PA levels across intensities, recommendations may lack the specificity needed for effective risk stratification and targeted interventions. This study addresses these gaps by using accelerometer-derived PA data from a large, well-characterised cohort to investigate the full spectrum of PA intensities and their associations with incident T2D.

Therefore, the aim of this study was to investigate the dose-response relationship between accelerometer-measured PA at varying intensities (light, moderate, vigorous) and the risk of incident T2D in middle-aged adults. In

addition, the study examined whether current WHO PA guidelines are supported by device-based data in relation to T2D prevention.

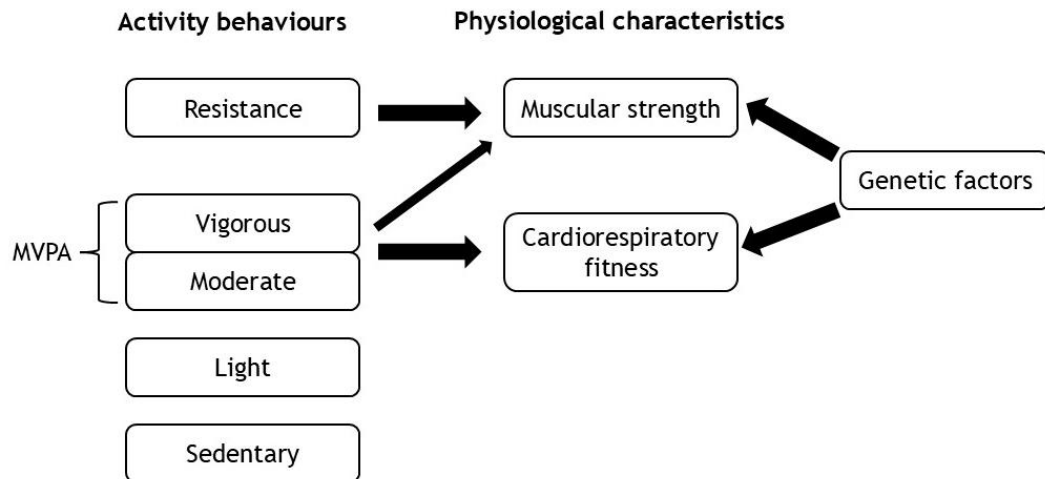


Figure 4-1 Interaction among activity behaviours, genetics, muscular strength and cardiorespiratory fitness

Source: Adapted from Gill (2022)

4.3 Methods

Study design and population

UK Biobank recruited over 500,000 participants between 2006 and 2010 (5.5% response rate) from the general population (Collins, 2012). At the baseline assessment (between 2006 and 2010) participants attended one of 22 assessment centres across Scotland, England and Wales (Sudlow et al., 2015, Palmer, 2007). Participants completed electronic consent and touch screen questionnaires and had physical measurements taken, and biological samples collected, as described elsewhere (Palmer, 2007, Sudlow et al., 2015). Device-based PA was assessed in 96,519 participants between 2013 and 2015. Therefore the end date

of the accelerometer wear time was used as the start date for the Cox-regression analysis which means that T2D cases diagnosed before this date were excluded. Participants with prevalent type 1, type 2 diabetes (n=1,534) or undiagnosed diabetes (HbA1c \geq 48 mmol/mol) (n=206) at the baseline assessment as well as 132 missing relevant covariates were also excluded (Additional File **Figure S4-1**). After applying these exclusions 40,431 participants had data available on device-measured PA, incident T2D, and relevant covariates. More information about the UK Biobank protocol can be found online (<http://www.ukbiobank.ac.uk>).

Ethical approval

The UK Biobank study was approved by the North West Multi-Centre Research Ethics Committee (Ref 11/NW/0382 on June 17, 2011) and all participants provided written informed consent to participate in the UK Biobank study. The study protocol is available online. This research has been conducted using the UK Biobank resource under application number 7155.

Exposure

Axivity AX3 wrist-worn triaxial accelerometers were used to collect objectively measured PA (Doherty et al., 2017). The device was worn on the dominant wrist over a period of 7 days at 100 Hz. Of the 103,681 participants who agreed to wear accelerometers, 7,162 were excluded due to insufficient wear time (<72 hours wear), missing data, or poor device calibration, resulting in 96,519 participants being eligible for inclusion in the analyses. However, only 40,431 participants with data available for device-measured PA, diabetes incidence and covariates were included in the current study (Additional File **Figure S4-1**). More details about data collection and processing can be found elsewhere (Doherty et al., 2017).

The average vector magnitude in mg was used to estimate the total volume of PA. Minutes per week (min/week) of light, moderate and vigorous PA were determined from the time spent at 30-125 mg, 125-400 mg, and >400 mg of acceleration, respectively. These thresholds were derived previously by other groups and validated (White et al., 2019, Strain et al., 2020). Then, those data were multiplied by the time spent for each magnitude category. In accordance with current PA recommendations (Bull et al., 2020), the following categories for MPA (<150, 150-299, 300-599 and \geq 600 min/week) and VPA (<25, 25-49, 50-74 and \geq 75 min/week) were derived. MVPA was estimated from the sum of MPA and (VPA*2), which is used to calculate 'equivalent' hours/week as specified in MVPA guidelines (Scholes and Mindell, 2020), and expressed in minutes per week. This is because the intensity from vigorous PA is at least twice that of moderate PA. All that data was summarised as the total volume of PA.

MET is a physiological metric that quantifies the intensity of PA and is a common approach used in epidemiological research and public health recommendations. One MET is defined as the volume of oxygen utilised at rest, quantified as 3.5 ml O₂ per kg of body weight per minute (1.2 kcal/minute for a 70 kg person). The MET idea was a straightforward, practical, and comprehensible method of quantifying the energy expenditure of PA as a multiple of resting metabolic rates (JettéSidney and Blümchen, 1990). Therefore, 1-MET represents the energy equivalent expended by an individual while sitting at rest. For example, an activity with 3-METs intensity (Light PA) means people are expending three times the energy compared to a state of sitting at rest. Activities with an intensity of 1.5 to 3 METs are generally classified as light intensity, while activities with an intensity of 3 to <6 METs are classified as moderate intensity, and those with an intensity of >6 METs are classified as vigorous intensity. Total PA and MVPA were also studied in terms of intensity-weighted domains of PA, expressed as the total METs minutes per week, which accounts for both intensity and duration. For example, an activity with a moderate intensity of 150 minutes

per week (unweighted intensity) is equal to an activity at 600 METs minutes per week (150 minutes x 4 METs for moderate intensity; weighted intensity).

Total PA was derived from the sum of light (assumed on average 3 METs), moderate (average 4 METs) and vigorous PA (average 8 METs) and expressed as MET-minutes per week. As the intensity-weighted domains of PA could produce imprecise risk estimates MVPA and total PA were also presented as unweighted minutes per week and as total acceleration counts for total PA.

Outcome

Prevalent type 1 and type 2 diabetes was ascertained from self-report and from HbA1c concentrations $\geq 6.5\%$ at baseline (undiagnosed diabetes). Incident T2D was ascertained from linkage to primary care records and hospital inpatient records. Records were available up to March 2021 and detailed procedures can be found in the UK Biobank online resource (<http://www.ukbiobank.ac.uk/>). Participants with at least one new record of T2D, from either primary care or hospital inpatient data, were defined as having incident T2D. Records of T2D at primary and secondary diagnosis were defined as ICD-10 code E11 or equivalent READ codes, mapped using UK Biobank's look-up table (<https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=41270>).

Covariates

The covariates included were assessed at the baseline assessment visit (between 2006 and 2010). Age was calculated from dates of birth and baseline assessment date; ethnicity was self-reported and categorised as white, South Asian, black or other/mixed backgrounds. The deprivation index, an area-based measure of socioeconomic status, was derived from the postal code of residence using the Townsend deprivation score (TownsendPhillimore and Beattie, 1988). Education achievement was self-reported at baseline. Alcohol intake was self-reported and

categorised as daily or almost daily, 3-4 times a week, once or twice a week, 1-3 times a month, special occasions only and never. Smoking status was self-reported as never, former, or current smoker. BMI was measured at baseline and it was calculated as body mass (in kilograms; kg) divided by the square of height (in meters; m), and the WHO criteria were applied to categorise participants into underweight (BMI <18.5 kg/m²), normal (18.5-24.9 kg/m²), overweight (25.0-29.9 kg/m²) and obese (30.0 kg/m²) (W. H. O. Consultation on Obesity and WHO, 2000). WC was measured midway between the lowest rib margin and the iliac crest, in a horizontal plane, using a non-elastic SECA 200 tape measure. WC ≥88 cm for women and ≥102 cm for men was used to define central obesity. Additional details about these measurements can be found in the UK Biobank online protocol (UK Biobank, 2007).

Statistical analyses

Continuous variables were expressed as means and SD, and categorical variables as frequencies and percentages by categories of total PA. Cox-proportional hazard models were used to investigate the associations between PA domains and incident T2D, with years of follow-up as the timeline variable. The end date of the accelerometer wearing time was used as the start of the follow-up. The results were reported as HRs together with 95% CIs. Incident cases, total person-year per 10,000 participants and incident rate per 100,000 person-year were also estimated. The analyses included participants who had accelerometer, primary care data and hospital inpatient records available but excluded those with prevalent type 1, type 2 (n=1,534) or undiagnosed diabetes (HbA1c ≥6.5%) (n=206) at baseline assessment.

The study used categorised variables and nonlinear analyses to investigate the associations of total PA and intensity-specific PA domains with incident T2D. Firstly, PA exposures were fitted into the model as categories of moderate and vigorous PA and MVPA. Next, nonlinear associations between PA domains and

incident T2D were investigated using penalised cubic splines fitted in Cox proportional hazard models. The penalised spline is a variation of the basis spline, which is not as sensitive to knot numbers and placements as restricted cubic splines (Govindarajulu et al., 2009). Nonlinearity in exposure-outcome relationships was tested by likelihood ratio tests comparing models with PA splines and models with linear PA terms. The proportional hazard assumption was checked using Schoenfeld residuals. A two-years landmark analysis was applied to minimise reverse causation.

The association between PA and incident T2D was adjusted for covariates measured at the baseline assessment (2006-2010). These covariates were age, sex, deprivation index, ethnicity, education, smoking status, and alcohol intake. These covariates are likely confounders (i.e. common causes for PA and T2D) and thus were the main model. The study conducted a sensitivity analysis by mutually adjusting the PA intensities (light, moderate and vigorous). In addition, BMI categories were also included as a covariate in a sensitivity analysis model. This model was only used for examining the non-linear association between PA and T2D as BMI is a likely mediator. The joint association between moderate and vigorous PA was created by using the risk matrix. Another sensitivity spline analysis was conducted using time spent on total PA and MVPA without weighting for intensity as those might not be precise.

As BMI is likely to mediate PA and T2D risk, the analysis performed a causal counterfactual framework analysis (Tingley et al., 2014). Adjusting for all the confounders included in the main model, T2D was regressed by PA and BMI (outcome model); and BMI was regressed by PA (mediator model). The outcome and mediator models were then combined to compute the natural indirect effect (NIE) and total effect (TE) for each participant, which was then averaged. Quasi-Bayesian estimation with 1,000 iterations was used to estimate the 95% CI and p-values of the NIE and TE. Mediation proportion was calculated as NIE / TE .

Sensitivity analysis for mediation was conducted by using WC (normal vs central obesity) instead of BMI.

RAPs (BrennerGefeller and Greenland, 1993) were used to estimate the number of additional chronologic years that would be required to yield the equivalent risk rate of incident T2D among individuals who reported the lowest PA compared to those who reported higher levels of PA, as described elsewhere (Discacciati et al., 2016).

Preventable fractions for the study population (PFP) (Shield et al., 2016) were calculated to estimate the proportions of all incident T2D cases that could have been prevented if the individuals in different PA categories were as active as the most active group, assuming that the associations were causal.

Statistical analyses were performed using the statistical software STATA 17 (StataCorp LP) and R v4.0.2. P-values <0.05 were regarded as statistically significant.

4.4 Results

Of the 502,458 participants who were enrolled in UK Biobank, 40,431 participants with data available for accelerometry-measured PA, T2D and covariates were included in this study (Additional File **Figure S4-1**). The median follow-up period was 6.3 years (IQR: 5.7-6.8). Over the follow-up period, 591 participants were diagnosed with T2D (245 women and 346 men).

Table 4-1 presents the general characteristics of the participants, categorised by total PA quartiles. Compared to those in the highest quartile of total PA, individuals with the lowest total PA were older and had similar educational qualifications, but higher area deprivation. They had higher BMI and WC and were more likely to be current smokers but never drink alcohol.

Table 4-1 Cohort characteristics by total physical activity quartile

Characteristics	Lowest	Low-Middle	Middle-High	Highest
Women	4,534 (46.3)	5,723 (56.0)	6,269 (61.4)	6,755 (66.2)
Men	5,263 (53.7)	4,502 (44.0)	3,935 (38.6)	3,450 (33.8)
Age, years (mean, SD)	57.4 ± 7.7	56.3 ± 7.8	55.7 ± 7.7	54.8 ± 7.7
Ethnicity, n (%)				
White	9,548 (98.7)	9,967 (98.7)	9,967 (98.8)	9,900 (98.5)
South Asian	82 (0.9)	81 (0.8)	72 (0.7)	90 (0.9)
Black	41 (0.4)	54 (0.5)	46 (0.5)	60 (0.6)
Education qualifications, n (%)				
College or University degree	4,705 (53.9)	5,134 (55.0)	5,014 (53.4)	4,707 (50.5)
A levels/AS levels or equivalent	1,222 (14.0)	1,261 (13.5)	1,377 (14.7)	1,275 (13.7)
O levels/GCSEs or equivalent	1,874 (21.5)	2,036 (21.8)	2,108 (22.5)	2,298 (24.6)
CSEs or equivalent/NVQ or HND or HNC	935 (10.7)	905 (9.7)	887 (9.5)	1,050 (11.3)
Townsend Deprivation Index, n (%)				

Lower deprivation	3,534 (36.1)	3,870 (37.9)	4,003 (39.2)	3,860 (37.8)
Middle deprivation	3,394 (34.6)	3,660 (35.8)	3,619 (35.5)	3,577 (35.1)
Higher deprivation	2,869 (29.3)	2,695 (26.4)	2,582 (25.3)	2,768 (27.1)
Alcohol intake, n (%)				
Daily or almost daily	2,112 (21.6)	2,304 (22.5)	2,314 (22.7)	2,279 (22.3)
3-4 times a week	2,394 (24.4)	2,773 (27.1)	2,815 (27.6)	2,743 (26.9)
Once or twice a week	2,503 (25.6)	2,602 (25.5)	2,636 (25.8)	2,544 (24.9)
1-3 times a month	1,188 (12.1)	1,128 (11.0)	1,047 (10.3)	1,073 (10.5)
Special occasions only	992 (10.1)	923 (9.0)	851 (8.3)	969 (9.5)
Never	608 (6.2)	495 (4.8)	541 (5.3)	597 (5.9)
Smoking status, n (%)				
Never	5,368 (54.9)	5,958 (58.4)	6,005 (58.9)	6,061 (59.5)
Previous	3,551 (36.3)	3,609 (35.4)	3,577 (35.1)	3,498 (34.4)
Current	855 (8.8)	638 (6.3)	612 (6.0)	620 (6.1)
Physical activity				
Total physical activity, min/day	263.3 ± 38.8	338.7 ± 15.6	392.2 ± 16.3	476.4 ± 47.4

Light physical activity, min/day	220.1 ± 33.9	275.2 ± 24.3	312.1 ± 27.8	366.1 ± 42.8
Moderate physical activity, min/day	40.8 ± 18.2	59.6 ± 19.9	75.1 ± 23.2	103.1 ± 34.6
Vigorous physical activity, min/day	2.3 ± 3.7	3.9 ± 5.2	5.1 ± 6.2	7.2 ± 7.8
MVPA, METs/min/week	1,273.9 ± 616.8	1,886.2 ± 705.4	2,388.9 ± 831.6	3,292.0 ± 1206.5
Adiposity				
BMI, kg/m ² (mean, SD)	27.9 ± 4.8	26.7 ± 4.2	26.1 ± 4.1	25.4 ± 3.9
Waist circumference, cm (mean, SD)	92.3 ± 12.8	88.2 ± 12.1	86.1 ± 11.9	83.7 ± 11.7
BMI category, n (%)				
Underweight (<18.5 kg/m ²)	32 (0.3)	40 (0.4)	53 (0.5)	80 (0.8)
Normal (18.5-24.9 kg/m ²)	2,751 (28.1)	3,818 (37.3)	4,437 (43.5)	5,108 (50.1)
Overweight (25-29.9 kg/m ²)	4,321 (44.1)	4,469 (43.7)	4,187 (41.0)	3,828 (37.5)
Obese (≥ 30.0 kg/m ²)	2,693 (27.5)	1,898 (18.6)	1,527 (15.0)	1,189 (11.7)

Data are presented as mean and standard deviation (SD) for continuous variables and as frequency and percentage (%) for categorical variables. A levels/AS levels, advanced/advanced subsidiary levels; BMI Body mass index, CSE certificate of secondary

education, GCSE General certificate of secondary education, HNC Higher national certificate, HND Higher national diploma, MET Metabolic equivalent, NVQ National vocational qualification, O levels, Ordinary levels, PA Physical activity

The associations between PA domains and incident T2D adjusted for sociodemographic and lifestyle factors (main model) are presented in **Table 4-2** and **Figure 4-1**. Compared to participants who performed <150 min/week of moderate PA, those who performed between 150-299, 300-599 and ≥ 600 min/week had a 49%, 62% and 71% lower risk of incident T2D (**Table 4-2**). The splines for moderate PA showed that T2D risk decreased sharply with increasing moderate PA up to the level of 300 min/week, with risk reduction levelling off thereafter (**Figure 4-1**). For vigorous PA, the results suggest a 38%, 48% and 64% lower risk of incident T2D for people achieving 25-49, 50-74, and ≥ 75 min/week, respectively, compared to those achieving <25 min/week (**Table 4-2**). The splines for vigorous PA showed that the risk of incident T2D appears to lower sharply with greater vigorous PA up to 75 min/week, plateaued between 75 and 150 min/week, then reduced further above 150 min/week (**Figure 4-1**). For light PA, the lowest risk was observed around 1500 min/week, then plateaued thereafter (**Figure 4-1**). The dose-response relationships for both total PA expressed in MET-min/week and MVPA expressed in minutes/week were similar, with the risk of incident T2D decreasing sharply up to the level of 3000 MET-min/week for total PA and 400 minutes/week of MVPA, respectively, with risk reduction levelling off thereafter.

Table 4-2 Risk and the preventable fraction of incident type 2 diabetes by categories of moderate and vigorous PA

	Prevalence in the study sample (%)	Incident cases	Total person-years (10,000)	Incident rate per 100,000 person-years	HR (95% CI)	Rate Advancement Period ^b (95% CI)	Preventable Fractions for the Population ^a	
							% (95% CI)	Cumulative % (95% CI)
MPA, min/week								
0 to <150	3.45	67	0.8	86.8	1.00 (Reference)	Reference	6.18 (4.95; 7.23)	6.18 (4.99; 7.25)
150 to <300	17.29	155	4.0	38.4	0.51 (0.38; 0.68)	16.2 (7.2; 32.7)	9.67 (6.25; 13.42)	15.85 (12.08; 19.43)
300 to <600	51.88	274	12.3	22.3	0.38 (0.29; 0.50)	23.9 (13.0; 41.9)	11.97 (3.89; 21.75)	27.82 (20.89; 36.35)
≥600	27.38	78	6.6	11.9	0.29 (0.20; 0.41)	29.8 (16.7; 54.5)	Reference	Reference

VPA, min/week								
0 to <25	60.05	455	14.1	32.3	1.00 (Reference)	Reference	47.42 (41.17; 55.51)	47.42 (40.68; 55.25)
25 to <50	18.80	68	4.5	15.2	0.62 (0.52; 0.77)	11.5 (4.9; 22.1)	6.01 (2.12; 10.23)	53.43 (47.92; 61.61)
50 to <75	11.09	32	2.7	12.1	0.52 (0.36; 0.77)	15.7 (4.9; 34.6)	2.26 (-0.44; 5.07)	55.69 (50.34; 62.72)
≥75	10.06	19	2.4	7.8	0.36 (0.22; 0.58)	24.6 (10.2; 51.2)	Reference	Reference
MVPA, min/week								
0 to <150	3.12	61	0.7	84.2	1.00 (Reference)	Reference	6.97 (6.09-7.73)	6.97 (6.09-7.73)
150 to <300	14.11	148	3.6	41.1	0.57 (0.42-0.78)	13.5 (4.6; 29.4)	14.56 (12.50-16.45)	21.53 (19.31-23.70)
300 to <600	45.59	268	11.5	23.3	0.36 (0.27-0.49)	24.5 (13.3; 44.3)	20.23 (15.65-25.32)	41.76 (38.30-45.76)
≥600	37.18	97	7.8	12.4	0.21 (0.15-0.29)	37.6 (23.2; 64.2)	Reference	Reference

MPA and VPA were mutually adjusted. All analyses were adjusted for age, sex, deprivation, education, ethnicity, alcohol intake and smoking status. Body mass index (model 2) was not adjusted as this is a likely mediator as confirmed in the mediation analysis. MVPA is the sum of time spent on MPA and VPA \times 2.

HR Hazard ratio, MPA Moderate-intensity PA, MVPA Moderate to vigorous-intensity PA, PA Physical activity, VPA Vigorous-intensity PA.

^aPreventable fractions estimated the fractions of all incident type 2 diabetes in the study population that could have been prevented if the individuals in those PA categories were as active as the reference group.

^b Rate advancement period was conducted to estimate the number of additional chronologic years that would be required to yield the equivalent risk rate of type 2 diabetes incidence among individuals who reported the higher PA compared to those who reported the lowest PA.

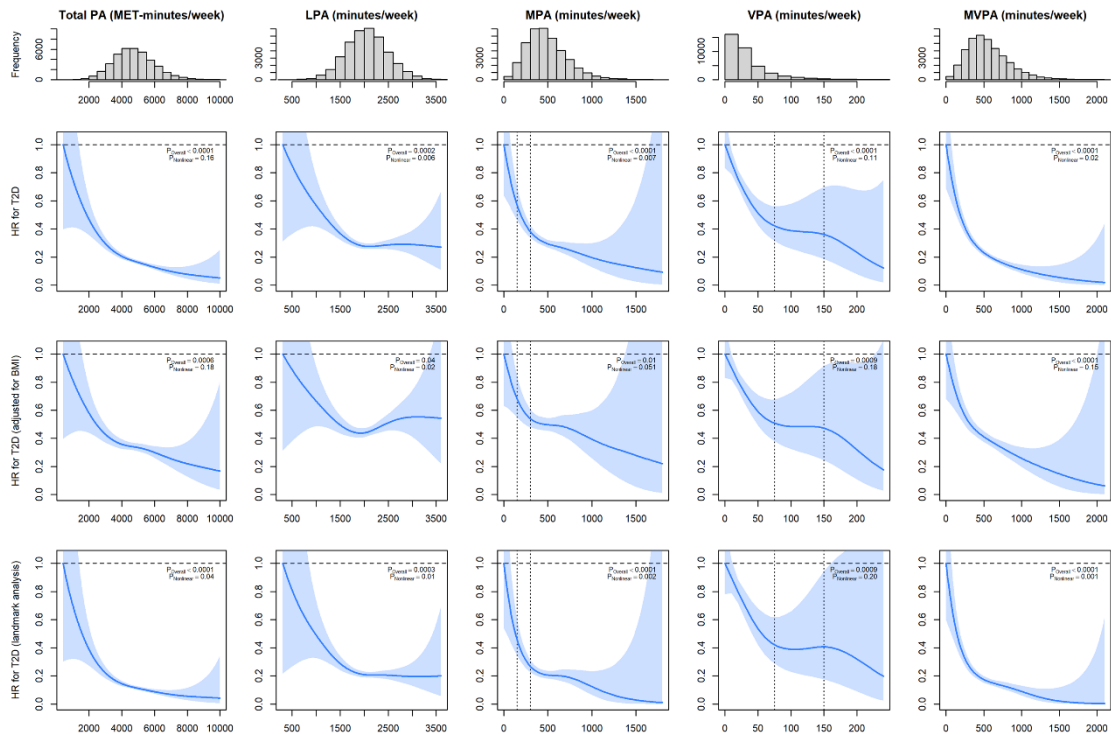


Figure 4-1 Non-penalised cubic splines for the association between physical activity domains and incident type 2 diabetes.

Data are presented as hazard ratios (HRs) and 95% confidence intervals (CIs). The top row of the panel was adjusted for age, sex, deprivation, education, ethnicity, alcohol intake and smoking status. The second row was additionally adjusted for body mass index (BMI). The bottom row was adjusted for the same covariates as the middle row but include a 2-year landmark analysis. Vertical dotted lines represent the current PA recommendations for moderate and vigorous PA. LPA, light physical activity; MPA, moderate physical activity; MVPA, moderate-vigorous physical activity; PA, physical activity; T2D, type 2 diabetes; VPA, vigorous physical activity. MVPA is the sum of time spent on MPA and VPA \times 2.

Sensitivity analyses applying a two-year landmark did not alter these associations (**Figure 4-1**). However, when the analysis for MVPA was adjusted for BMI, the shape of the association with incident T2D became linear (**Figure 4-1**). When light, moderate and vigorous PA were mutually adjusted, the shape of associations remained similar (Additional File **Figure S4-2**). However, when BMI

was added as a covariate, the magnitude of associations was slightly attenuated but remained significant (**Figure 4-1**). Using unweighted PA variables resulted in similar findings (Additional File **Figure S4-3**).

Mediation analyses showed that BMI explained up to 23.6%, 19.6% and 12.5% of the associations of total PA, moderate PA and vigorous PA with incident T2D. There was no evidence to support BMI mediating the associations between light PA and T2D (Additional File **Table S4-1**). Similar results were found for WC (as a sensitivity analysis) but WC mediated the associations of total PA with incident T2D at ~ 9%, as shown in Additional File **Table S4-1**.

A risk matrix for the joint associations between moderate and vigorous PA is presented in **Figure 4-2**. Undertaking a lower amount of moderate (<150 min/week) but more than 75 min/week of vigorous PA was associated with a 71% lower risk of incident T2D. Similarly, a 71% lower risk of incident T2D was observed for those doing little vigorous PA (<25 min/week) but high amounts of moderate PA (>600 min/week) (**Figure 4-2**). The lowest (92%) risk was observed in those participants doing >600 and >75 min/week of moderate and vigorous PA, respectively, compared to the least active (<150 and 25 min/week of moderate and vigorous PA) (**Figure 4-2**).

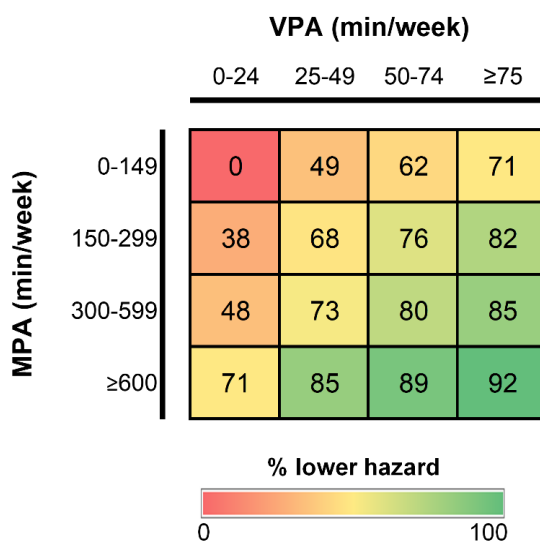


Figure 4-2 Risk matrix for the joint association of MPA and VPA with incident type 2 diabetes.

Estimated in Cox regression adjusted for age, sex, deprivation, education, ethnicity, alcohol intake and smoking status. The numbers presented are the associated reduction in hazard (%) compared with the least active group, based on the hazard ratios shown in Table 2. MPA, moderate physical activity; VPA, vigorous physical activity.

The proportions of T2D cases that increased PA could have prevented are presented in Table 4-2. Assuming causality, 7% of incident T2D cases in the study population could have been prevented if all participants had met current aerobic PA recommendations of 150 to 300 minutes/week of MVPA, and 41.8% could have been prevented if participants had undertaken 600 minutes/week of MVPA. The rate advancement period analysis revealed that people who do not meet the current PA guidelines (<150 min/week of MVPA) would experience the equivalent T2D risk rate as those who met the recommendation (150-300 min/week) 13.5 years earlier. Compared to those who undertook twice the

current PA recommendation (≥ 600 min/week of MVPA), people who achieved less than 150 min/week experienced a similar T2D risk rate 37.6 years earlier (Table 4-2).

4.5 Discussion

Objectively measured PA - whether of light, moderate or vigorous intensity - had a protective association with the development of T2D, with less than one-fifth of the association explained by the reduction of BMI due to PA. These findings reinforced the importance of individuals meeting current aerobic PA recommendations (150-300 min/week of MVPA) in that adherence to the recommendations would delay T2D by 13.5 years, and could prevent 7% of T2D cases. Indeed, low doses of MVPA were associated with rapid declines in the risk of T2D. However, the results also suggested that going beyond current recommendations could produce much greater benefits, even beyond reductions in BMI. The dose-response relationship was observed across the full range of moderate and vigorous PA; with no observable plateau. For example, 41.8% of T2D cases potentially be prevented if people perform ≥ 600 equivalent minutes/week of MVPA.

Although there is a large amount of evidence based on self-reported PA that supports an inverse association between PA and T2D risk (Kyu et al., 2016), there is very limited evidence from studies using device-measured PA. To date, only two small-scale studies have been conducted using accelerometer-measured PA (Sternfeld et al., 2019, Chen et al., 2020), while another three studies have been based on step count using pedometers in older adults (Garduno et al., 2022, Ballin et al., 2020, Califf et al., 2008). The Hispanic Community Health Study (Chen et al., 2020), which included 7,280 adults aged between 18 and 74 years and who were followed up for six years (871 T2D incident cases) reported that MVPA, measured using an Actical accelerometer, was inversely and nonlinearly associated with lower T2D risk. Compared to the lowest quartile for

MVPA, a similarly lower risk was observed for those in the 2nd, 3rd and 4th (highest) quartile of MVPA, with HRs ranging from 0.76 to 0.67. The authors reported that T2D decreased sharply with increasing MVPA up to a level of 30 min/day, but no further benefits were observed beyond this point. Another study assessing the association between PA, measured by Actigraph accelerometers, and T2D risk was the Coronary Artery Risk Development in Young Adults (CARDIA) study. This study included 2,291 adults aged between 38 and 50 years who were followed up for 5 to 10 years (147 participants developed T2D). The authors reported 45% and 30% lower T2D for those in the highest compared to the lowest PA tertile (Sternfeld et al., 2019), for men and women, respectively. Although these studies partially agree with the current findings, the association with other PA domains such as light or total PA was not investigated. In addition, none of these studies investigated whether current aerobic PA recommendations were associated with lower T2D risk, as the study reported in the current study. Furthermore, the authors simply adjusted for BMI rather than estimate how much of the association between PA and T2D risk was explained by baseline BMI, which is something the analyses were able to do in the current study.

Other studies have also investigated the association between step count as a proxy of overall PA, and T2D risk; however, most, but not all, of them have been conducted in older adults (Sternfeld et al., 2019, Chen et al., 2020, Garduno et al., 2022, Califf et al., 2008, Ballin et al., 2020). Although these studies cannot be compared directly to the present findings due to the different approaches to measuring the exposure, the findings are consistent, showing that a higher number of steps is associated with a lower risk of incident T2D. The OPACH study conducted on 3,279 older women (mean age 78.9 years) followed-up for 6.9 years (395 developed diabetes) reported that total steps per day were linearly associated with lower T2D risk. However, when intensity was estimated, only moderate-intensity, not light-intensity steps, was associated with a lower risk of T2D (HR: 0.86 per 2,000 steps increment, 95% CI 0.74 - 1.00) (Garduno et al., 2022). Other studies reporting similar findings are the Nateglinide and Valsartan

in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial. This study reported that the risk of T2D was 6% lower per 2,000 steps/day, without accounting for intensity (Califf et al., 2008). Similarly, the Healthy Ageing Initiative study (HAI), which included 3,055 community-dwelling 70-year-old participants (52% women), who were followed up for 2.6 years (81 developed T2D), reported a nonlinear inverse association between steps and risk of T2D. A steeper decline in the risk of T2D was observed from a lower daily step count until around 6,000 steps/day, without accounting for intensity (Ballin et al., 2020).

The present study meaningfully extends this literature (Aune et al., 2015) by showing that lower baseline BMI only partially mediates the association between PA and T2D risk. Therefore, the association between PA and the reduction of T2D risk is likely due to the variety of other mechanisms through which PA improves glycaemic control (Yang et al., 2019, Sgrò et al., 2021, Al-Ozairi et al., 2021, Reiner et al., 2013, Rod K. Dishman et al., March 2021). Previous data showing the benefits of PA for glycaemic control provides strong support for the association between PA and T2D being causal in nature, but this should be confirmed in appropriately designed trials.

These present findings are of important public health relevance as they provide strong evidence using device-measured PA that current recommendations for MVPA are effective for T2D risk prevention but that higher PA levels are associated with even greater benefits. The study demonstrated that adherence to the recommendations delays the onset of T2D and prevents some cases. This has important economic implications given that the global cost of T2D is on target to almost double to \$2.5 trillion by 2030 (Bommer et al., 2018). Moreover, this present study also provides evidence that T2D risk estimates derived from previous self-reported PA studies have underestimated the true magnitude of the associations between PA and T2D risk. A meta-analysis of 28 prospective cohort studies estimated that self-reported PA was associated with

26% lower T2D risk (95% CI; 20%-31%) among those who achieved 150 min/week of moderate PA relative to inactive individuals. Achieving twice this amount of PA was associated with a risk reduction of 36% (95% CI; 27%-46%) (Smith et al., 2016). These risk estimates were weaker than the ones reported in the current study, where individuals meeting moderate PA recommendations had a 49% lower risk of T2D, while those achieving twice this amount had a 62% lower risk. The differences may be attributable to recall bias when questionnaires are used, but there is also a possibility that this could be explained by the algorithms used to quantify PA. As questionnaires used in previous studies recorded data on PA only if it was performed in 10-minute bouts, which is no longer required on the latest PA guidelines (Bull et al., 2020) and therefore, it was not applied in the current analysis of these accelerometric data.

The strengths of the present study include the large number of participants, which allowed us to explore the dose-response relationship between PA and T2D risk. An extensive list of confounders, in comparison to previous studies, was also considered. The current study used accelerometers to measure PA. This is a substantial advantage over much of the existing literature as it overcomes the limitations related to recall bias and misclassification from PA questionnaires.

A previous systematic review of patterns of accelerometer-measured PA and health outcomes in adults pointed out that engaging in PA at higher intensities may yield greater health advantages compared to engagement at lower intensities (Brady et al., 2022). The findings also suggested the persistent challenges in this study area, including the variability in accelerometer data management and analysis protocol, such as threshold setting, along with inconsistencies in the categories of bout duration, frequency and intensity. In addition, the lack of adjustments for mutual adjustment for the effects of all other components or the absence of adjustments for a total volume of PA (The product of duration, intensity and frequency over a given time) in most studies restricts the ability to determine whether the patterns of activity accumulation

(combination of different bouts, intensities and frequencies) are as significant as the overall volume of PA in promoting health advantages for adults (Brady et al., 2022).

However, this current study provides some evidence to close the gap, contributing novel insights into the strength of associations when accelerometer-measured PA levels exceed the WHO-recommended thresholds, particularly for T2D risk, with limited previous data to support this evidence. However, clinical settings need to confirm the benefit of patterns or the overall volume of PA. Another insight is about mutual adjustments in the analysis. The current study has made mutual adjustments in the analyses of MPA, VPA, and MVPA. This is likely to conclude the findings that the benefits associated with each intensity level are independent of those derived from other intensity levels. Interestingly, when mutual adjustment for light PA (Additional File **Figure S4-2**), the trend of the association was similar to the trend after adjusting for BMI (**Figure 4-1**). This is probably because light PA was confounded with other intensities or adiposity. Further study should confirm these findings.

However, the present study is not exempt from limitations. All the covariates in this study were measured earlier than the measurement of PA, therefore, some of them could change between the baseline assessment and the date when the device-based PA was measured. The UK Biobank is not representative of the general population of the UK, including sociodemographic, physical, lifestyle and health-related characteristics. Effect size estimates are still generalisable to the broader population; but estimates of cases avoided may be an underestimate of the true figure in the general population due to UK Biobank participants having a healthier lifestyle (Fry et al., 2017, Celis-Morales et al., 2017). In addition, the findings reported in this current study could not be generalised to non-white ethnic groups as more than 95% of the participants were white Europeans. We also should consider the health-promoting effect of physical activity assessment by accelerometer, which could influence the PA behaviours of participants.

Although BMI was used as a proxy of adiposity in this present study, other markers such as body fat may explain a higher proportion of the mediation. Reverse causation is another potential limitation of this study, but the study attempted to mitigate this risk by conducting a 2-year landmark analysis excluding participants who were recorded as developing diabetes within the first 2 years of follow-up. Additionally, the analysis was conducted to examine correlations between baseline BMI and measurements taken at three subsequent time points during the follow-up period (between 2006 and 2019). The correlation across all these time points was very high ($r \geq 0.89$), suggesting that BMI has been pretty stable during the follow-up. Although the study could not rule out reverse causation, the high correlation of BMI across different time points suggested that the bias coming from when BMI was measured may not have a strong bias effect on the mediation analysis (Additional File **Table S4-2**).

However, it is important to know that the current PA guidelines offer general recommendations that do not differentiate based on sex or sociodemographic factors. Therefore, this present study did not stratify by sex or sociodemographic factors in order to explore if device-based PA measurement offers more precise data than self-report records. In addition, accurate data records enable individuals to monitor their real-time and actual activities effectively. Thus, further study should be conducted to examine the association based on sex or sociodemographic factors.

The interpretation of these findings should be cautious about participant characteristic biases, such as being more likely to be older, women, and living in less socioeconomically deprived areas compared to nonparticipants. Notably, the likelihood of developing T2D appeared to differ according to individual health status and various lifestyle factors. For example, a study on walking and adiposity among UK Biobank participants found that individuals with a slow pace were associated with a higher risk of T2D when compared to those with a fast pace. Nevertheless, individuals who engaged in brisk walking continued to

exhibit an elevated risk of T2D if they were classified as overweight or obese (Boonpor et al., 2023). Therefore, further studies focusing on sociodemographic factors, lifestyles, health conditions, PA patterns and volumes using device-based PA measurements are warranted to inform the development of potential PA recommendations.

Future research should explore: a) stratified analyses by sex, ethnicity, and sociodemographic factors to refine PA recommendations for specific subgroups; b) the clinical utility of light-intensity PA, which has been underexamined yet shows promising associations with reduced T2D risk; c) whether patterns of PA accumulation (e.g., bout duration, timing, or frequency) offer added predictive value beyond total volume; d) the development of clinically validated thresholds for PA intensity and volume, based on device-measured data, to guide preventive care.

By addressing these areas, future work can further bridge the gap between observational findings and practical, individualised recommendations for T2D prevention.

4.6 Conclusions

This study provides strong, novel evidence that higher levels of PA, measured objectively using accelerometer, are significantly and independently associated with a lower risk of developing T2D. Notably, this protective association was observed across all intensities of PA, including light, moderate, and vigorous activity, and persisted even after accounting for adiposity. Importantly, less than one-fifth of the protective effect of PA was explained by changes in BMI, underscoring the presence of additional metabolic mechanisms through which PA reduces T2D risk.

These findings demonstrate that adherence to current WHO aerobic PA recommendations (≥ 150 minutes/week of MVPA) is associated with substantial reductions in T2D risk, including an estimated 13.5-year delay in disease onset and prevention of up to 7% of T2D cases. However, the benefits do not plateau at these levels: much larger risk reductions, up to 42% of preventable cases, were observed at higher activity volumes (e.g., ≥ 600 minutes/week of MVPA), providing compelling evidence to support more ambitious PA goals where feasible.

In contrast to previous studies based largely on self-reported data, this study highlights that device-based PA assessments capture a much stronger association with T2D risk. This has important implications for both research methodology and clinical practice. The magnitude of risk reduction observed in this study exceeds that previously reported using questionnaires, likely due to reduced measurement error and the inclusion of short-duration and light-intensity activities that are often underreported. These results call into question the accuracy of current estimates derived from self-report and support a shift toward more widespread use of wearable technologies for PA assessment in both research and healthcare settings.

From a clinical perspective, the findings suggest that objective monitoring of PA could be a valuable tool in personalised risk assessment and behavioural counselling for T2D prevention. Given the growing accessibility of accelerometers and other wearable devices, integrating objective PA monitoring into routine clinical care may help identify individuals not only at risk due to inactivity but also those who would benefit most from specific intensities or volumes of activity. Moreover, this study offers support for updating and refining PA guidelines to reflect dose-response relationships and potentially encourage greater-than-minimum PA targets, particularly for individuals at high risk.

Public health strategies should consider these findings when designing interventions and policies aimed at preventing T2D. Emphasising the benefits of even modest increases in PA, while promoting higher PA targets where feasible, could lead to substantial population-level reductions in T2D burden. Furthermore, the results highlight the need for targeted strategies that consider sociodemographic and lifestyle variations, as the health benefits of PA may differ across population groups.

4.7 Reference Chapter 4

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4.8 Additional File Chapter 4

Table S4-1 Mediation analysis between physical activity and incident type 2 diabetes by body mass index and waist circumference

Type of physical activity	Mediation via BMI		Mediation via WC	
	% of mediation	P-value	% of mediation	P-value
Light PA	6.0	0.260	2.4	0.330
Moderate PA	19.6	<0.001	20.0	<0.001
Vigorous PA	12.5	<0.001	12.5	<0.001
Total PA	23.6	<0.001	9.4	0.004

The analyses were adjusted for age, sex, deprivation, education, ethnicity, alcohol intake, and smoking status. BMI: body mass index; WC: waist circumference; PA: physical activity

Table S4-2 Pearson correlation coefficients for body mass index at four times points

	Baseline assessment in 2006 N=499,305	Second assessment in 2012 N=20,296	Third assessment in 2014 N=49,720	Fourth assessment visit 2019 N=5,270
Initial assessment	1.00	-	-	-
First repeat assessment	0.93	1.00	-	-
Imaging visit	0.89	0.94	1.00	-
First repeat imaging	0.90	0.89	0.94	1.00

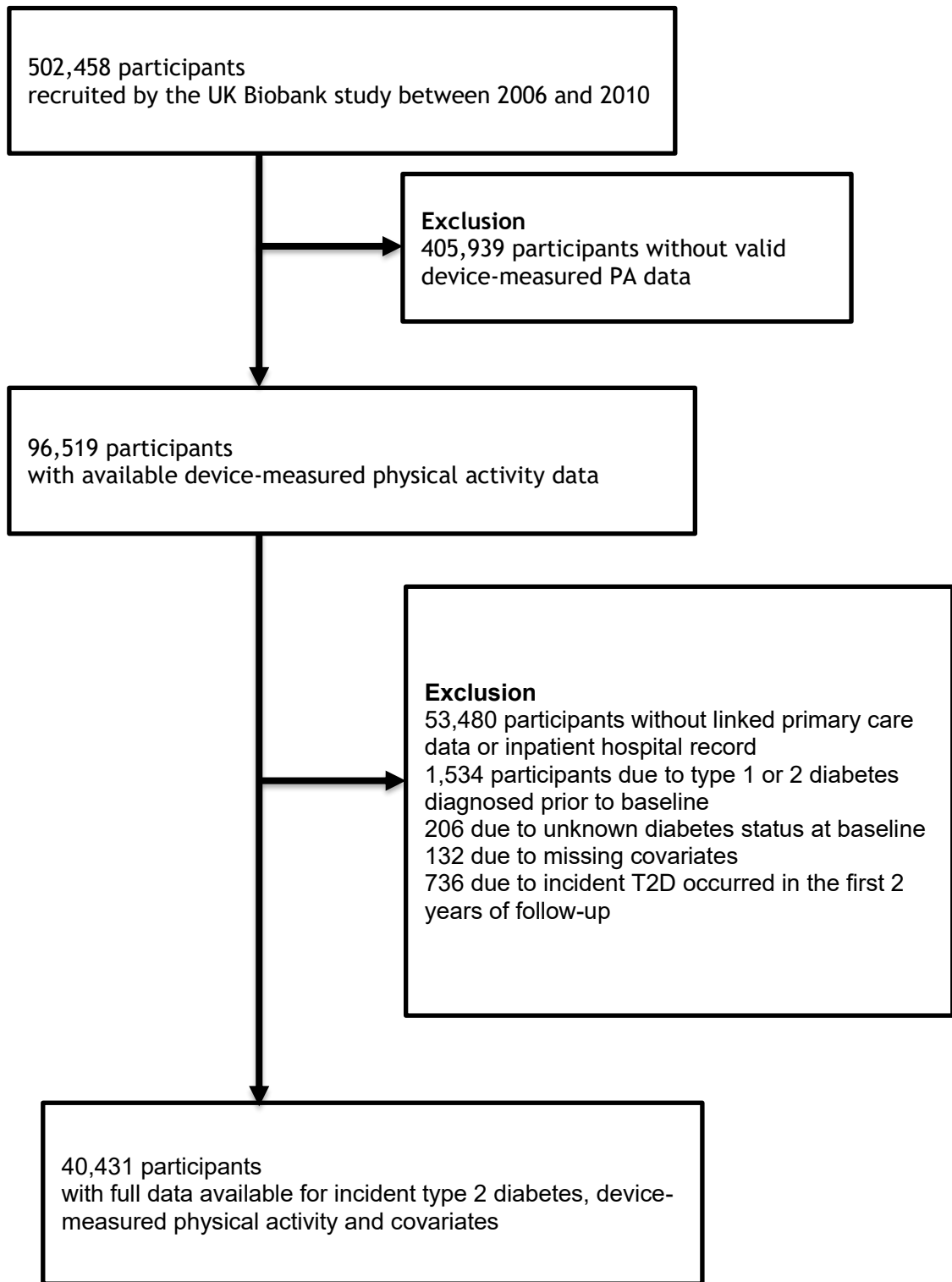


Figure S4-1 Flowchart of participants

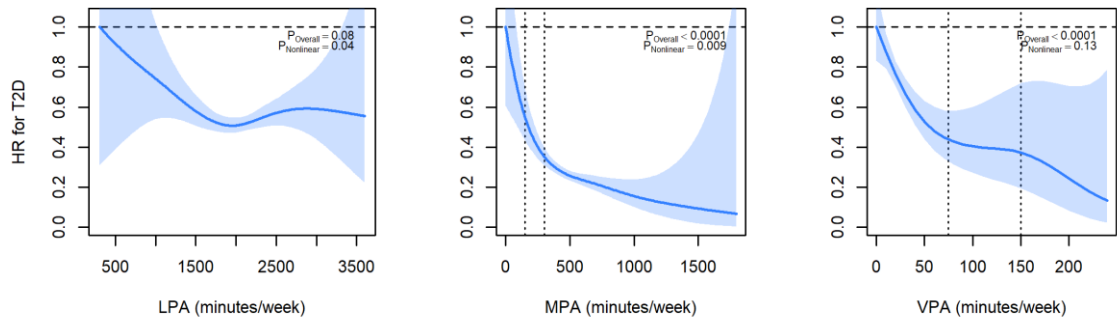


Figure S4-2 Non-linear association between physical activity domains and incident type 2 diabetes using mutually adjusted physical activity domains.

Data are presented as hazard ratios (HRs) and their 95% CIs. The analysis was adjusted for age, sex, deprivation, education, ethnicity, alcohol intake, and smoking status. LPA: light physical activity; MPA: moderate physical activity; MVPA: moderate-vigorous physical activity; PA: physical activity; T2D: type 2 diabetes; VPA: vigorous physical activity

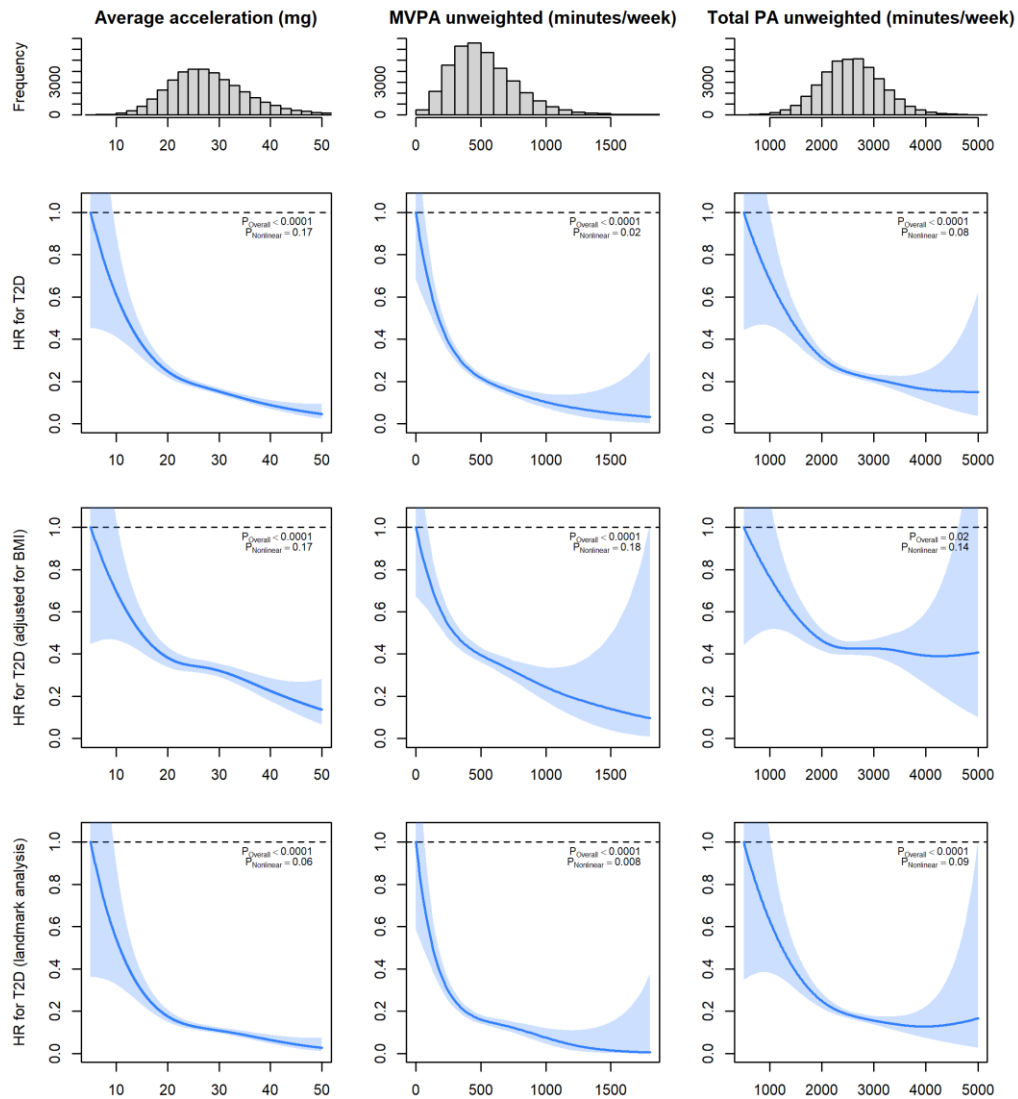


Figure S4-3 Non-linear association between unweighted physical activity domains and incident type 2 diabetes.

Data are presented as hazard ratios (HRs) and their 95% CIs. The analysis was adjusted for age, sex, deprivation, education, ethnicity, alcohol intake, and smoking status. MVPA: moderate-vigorous physical activity; PA: physical activity; T2D: type 2 diabetes

Chapter 5 Types of diet, obesity, and incident type 2 diabetes: findings from the UK Biobank prospective cohort study

The original article of this chapter has been in *Diabetes, Obesity and Metabolism*. The contents, style, and order of structures have been modified to conform to the standard thesis format.

Boonpor, J, Petermann-Rocha, F, Parra-Soto, S, et al. Types of diet, obesity, and incident type 2 diabetes: Findings from the UK Biobank prospective cohort study. *Diabetes Obes Metab*. 2022; 24(7): 1351-1359. doi:10.1111/dom.14711.

Contributions: I developed research questions, prepared study materials, prepared the dataset and performed data analyses. I drafted the manuscript with inputs from my supervisors (CCM, SRG and FKH). I led the submission of the manuscript and responded to reviewer comments, with input and support from my supervisors.

5.1 Abstract

Introduction Current evidence on the associations between alternative (e.g. fish and vegetarian) diets and incident T2D is elusive. This study aimed to investigate the associations between types of diet and incident T2D and whether adiposity mediated these associations.

Methods 203,790 participants from the UK Biobank (mean age 55.2 years; 55.8% women) without diabetes at baseline were included in this prospective study. Using the dietary intake data self-reported at baseline, participants were categorised as vegetarians (n=3,237), fish eaters (n=4,405), fish & poultry eaters (n=2,217), omnivores (n=178,004) and varied diets (n=15,927). The association between type of diet and incident T2D was investigated using Cox-proportional hazards models with a 2-year landmark analysis. The mediation role of adiposity was tested under a counterfactual framework.

Results After excluding the first two years of follow-up, the median follow-up was 5.4 (IQR: 4.8-6.3) years, during which 5,067 (2.5%) participants were diagnosed with T2D. After adjusting for lifestyle factors, fish eaters (HR 0.52: 95% CI; 0.39-0.69) and fish & poultry eaters (HR 0.62: 95% CI; 0.45-0.88) had a lower risk of incident T2D compared with omnivores. The association for vegetarians was not significant. Varied diets had a higher risk of T2D. Obesity partially mediated the association of fish (30.6%), fish & poultry (49.8%) and varied (55.2%) diets.

Conclusions Fish and fish & poultry eaters were at a lower risk of incident T2D than meat eaters, partially attributable to lower obesity risk.

Keywords Fish, Lacto-ovo diet, Meat, Poultry, Type 2 diabetes, Vegetarian

5.2 Introduction

Around 9.3% of the world's adult population are estimated to have diabetes (International Diabetes Federation, 2019), and this figure is predicted to rise to 10.9% by 2045 (Saeedi et al., 2019). T2D accounts for the majority of diabetes (Forouhi and Wareham, 2014), for example, in the UK, the number of people with diabetes will reach over 5 million by 2025, of whom 90% will have T2D (Diabetes UK, 2019). Lifestyle modifications play a key role in T2D prevention and management. An unhealthy diet, including high consumption of red meat and processed meat, sugar-sweetened beverages and refined grains, has been suggested as a driving factor for the growing incidence of T2D (ZhengLey and Hu, 2018). Conversely, diets rich in whole grains, dairy, vegetables, fruits, legumes, fish and poultry are suggested to be protective against the development of T2D (JannaschKröger and Schulze, 2017, Schwingshackl et al., 2017).

Current WHO guidelines emphasise the importance of a healthy diet in preventing all forms of malnutrition and reducing the risk of major NCDs, including T2D. A healthy diet includes a variety of nutrient-rich foods such as fruits, vegetables, legumes, nuts, and whole grains, with a recommended daily intake of at least 400 grams of fruits and vegetables (excluding starchy root crops). Free sugars should account for <10% of total energy intake, ideally below 5%, while total fat intake should not exceed 30%, with a preference for unsaturated fats over saturated and trans fats. Saturated fats should be limited to <10% and trans fats to <1% of total energy intake, with the goal of eliminating industrially produced trans fats. Sodium intake should be restricted to <5 grams per day, with all salt iodised to prevent iodine deficiency (World Health Organization, 2020).

According to the evidence-based assessment of the nutritional recommendations for prevention, management and remission of T2D, the findings from various health organisations such as the ADA and Diabetes UK, revealed that dietary

patterns associated with reduced risk of T2D typically involve regular consumption of vegetables, fruits, legumes, whole grains and cereal fibre, nuts and dairy products such as yoghurt. Conversely, habitual intake of processed and unprocessed red meats, refined grains, and sugar-sweetened beverages is associated with an increased risk of T2D. These findings support a dietary approach that emphasises the promotion of specific protective foods and the limitation of harmful ones, challenging the conventional notion that everything in moderation is universally appropriate (Forouhi, 2023).

However, the association between meat-based diets and T2D is equivocal (Kurotani et al., 2013, JannaschKröger and Schulze, 2017, Schwingshackl et al., 2017, Yang et al., 2020, Du et al., 2020). For instance, a recent meta-analysis of 28 prospective cohort studies indicated that red meat, processed meat, total meat, poultry and fish consumption were associated with a higher risk of T2D (Yang et al., 2020). Conversely, several prospective cohort studies reported that poultry intake was not associated with T2D risk (Kurotani et al., 2013, Du et al., 2020), particularly when adjusted for intake of other meats (Du et al., 2020). The association between fish intake and T2D risk was also inconsistent (Patel et al., 2012, Zhang et al., 2019), possibly depending on geographical differences (Wallin et al., 2012, Xun and He, 2012). Furthermore, it has not been shown whether, and to what extent, diets containing no red meat (e.g. fish only and poultry and fish) are associated with T2D risk.

Several studies have investigated the association between a vegetarian diet and risk of incident T2D. Generally, vegetarians had lower T2D risk, but the associations were attenuated following adjustment for BMI (Lee and Park, 2017, Olfert and Wattick, 2018). Therefore, it has been hypothesised that these diets, which are often lower in calories, could help with body weight management and therefore reduce T2D risk indirectly (Qian et al., 2019a); however, this hypothesis has not been empirically studied. To explore this further, the present study used data from UK Biobank to investigate the associations between

vegetarian, fish, poultry, meat and varied diets and incident T2D, as well as any mediation via adiposity in a large prospective cohort study.

5.3 Methods

Study design and population

The UK Biobank recruited approximately 502,000 men and women aged 37-73 years from the general population between 2006 and 2010 (5.5% response rate) (Collins, 2012). Participants attended one of 22 assessment centres across England, Wales, and Scotland (Sudlow et al., 2015, Palmer, 2007). At the assessment centres, participants completed an electronically signed consent form, a touch screen questionnaire and physical measurements, as previously described (Palmer, 2007, Sudlow et al., 2015). Individuals with missing data for any dietary variables were excluded (n=14,121; 2.8%). Vegans (no consumption of milk, cheese, fish, poultry or red meat) were excluded as the sample size was not sufficient for a separate category (n=57; 0.01%) (Petermann-Rocha et al., 2021) (Additional File **Figure S5-1**). Among 488,309 participants with available dietary data, 264,611 (54.2%) were further excluded because there were no linked primary care data to ascertain T2D. The lack of linkage is due to the electronic record system used in their general practice and should be unrelated to the exposure or outcome. Of the remaining 223,698 participants, 12,206 (5.5%) were excluded because they had prevalent type 1 or type 2 diabetes (either self-reported or in previous primary care record) and 1,549 (0.7%) because they had undiagnosed diabetes ($HbA1c \geq 48$ mmol/mol) at baseline, as well as 5,037 (2.3%) relevant covariates and 1,116 (0.5%) of any incident T2D occurring in the first two years of the follow-up period (Additional File **Figure S5-1**). Therefore, the study population comprised 203,790 UK Biobank participants.

Ethical Approval

The UK Biobank study was approved by the North West Multi-Centre Research Ethics Committee (Ref 11/NW/0382 on June 17, 2011) and all participants provided their written informed consent to participation. The study protocol is available online (<http://www.ukbiobank.ac.uk/>). This research has been conducted using the UK Biobank resource under application number 7155.

Outcome

Incident T2D was ascertained from prospective linkage to primary care records data. Primary care, instead of hospitalisation, data were used in this study because in the UK most T2D were diagnosed and managed in the primary care setting. Primary care records were available up to May 2017 for Scotland, September 2017 for Wales and August 2017 for England. Detailed linkage procedures are available at

http://biobank.ndph.ox.ac.uk/showcase/showcase/docs/primary_care_data.pdf

. The READ codes used in primary care were converted into ICD-10 codes using UK Biobank's look-up table, and we defined incident T2D as an ICD-10 code E11.

Exposure

At recruitment, participants were asked to complete a food frequency questionnaire on the touch-screen to collect the frequency of consumption of cheese, milk, fish (oily and non-oily), poultry and red meat (beef, pork, lamb and processed red meat) over the previous year. In this study, all food items were dichotomised into consumed or not consumed as this study focus on alternative diets such as vegetarian and pescatarian diets.

Participants were categorised into five types of diets: 1) vegetarians, 2) fish eaters, 3) fish & poultry eaters, 4) omnivorous eaters and 5) varied diets. Vegetarian participants were defined as those who reported consumption of cheese, milk, but not fish, poultry or red meat, i.e. lacto-ovo-vegetarians. Fish

eaters were those who reported consumption of cheese, milk and fish but not poultry or red meat. Fish & poultry eaters were those who reported consumption of cheese, milk, fish and poultry, but not red meat. Dietary patterns were defined based on self-reported consumption of major animal-derived foods (cheese, milk, fish, poultry, and red meat) from the baseline touchscreen questionnaire. Participants who consumed all listed animal products were classified as omnivores. There were 15,927 (7.8%) participants who reported that their diets varied often and were categorised in a separate group.

Additionally, the study included dietary information that was derived by using the Oxford WebQ (www.ceu.ox.ac.uk/research/oxford-webq), a web-based 24-hour recall questionnaire (Ho et al., 2020), to supplement the dietary information of participants (Table 5-2). The Oxford WebQ is only available to a small proportion of participants and therefore was not used to derive the primary diet variables in this study.

Covariates

Sex was self-reported at baseline, and age was calculated from dates of birth and baseline assessment. Deprivation Index, an area-based measure of socioeconomic status, was derived from the postcode of residence using the Townsend Deprivation score (Roberts et al., 2011). Anthropometric measurements were obtained by trained personnel following standard operating procedures and using calibrated equipment. Body mass was weighted, without shoes and outdoor clothing, using the Tanita BC 418 body composition analyser. Height was measured, without shoes, using the wall-mounted SECA 240 height measure. Smoking status was self-reported as never, former, and current. Alcohol intake was self-reported as daily or almost daily, 3-4 times a week, once or twice a week, 1-3 times a month, special occasions only and never. Sedentary behaviour was self-reported and defined as discretionary screen-time, combining TV viewing and leisure PC screen time in hours per day (Fry et al., 2017). It was

classified by tertile into low, middle and high. Type of PA was self-reported in relation to five groups: walking for pleasure, other exercises (e.g. swimming, cycling), strenuous sports, light DIY (e.g. pruning, watering the lawn) and heavy DIY (e.g. weeding, lawn mowing, carpentry and digging). Sleep duration was self-reported and categorised as short <7 h/day, normal 7-9 h/day and long >9 h/day. BMI was calculated from body weight (in kilograms) divided by the square of height (in meters). The World Health Organization's criteria were used to classify BMI into underweight (<18.5 kg/m²), normal weight (18.5 to 24.9 kg/m²), overweight (25 to 29.9 kg/m²) and obese (≥30 kg/m²). WC was measured midway between the lowest rib margin and the iliac crest, in a horizontal plane, using a non-elastic SECA 200 tape measure. Central obesity was defined as WC>88 cm for women and >102 cm for men. Additional details about these measurements can be found in the UK Biobank online protocol (UK Biobank, 2007).

Statistical Analyses

Categorical variables are summarised as frequencies and percentages and continuous variables as means and SD. Cox-proportional hazard models were used to investigate the associations between types of diet (vegetarians, fish eaters, fish & poultry eaters, omnivores and varied diets) and incident T2D. Omnivores were treated as the referent group. The results were reported as HRs together with 95% CIs. The analyses excluded all participants with prevalent diabetes (type 1 or type 2 diabetes) or undiagnosed diabetes at baseline. To minimise reverse causation, all participants who developed incident T2D in the first two years of follow-up (two-year landmark) were also excluded.

The main analyses were adjusted for potential confounding factors: age, sex, deprivation, alcohol intake, smoking status, total sedentary time, sleep time, type of PA and adiposity (BMI and WC). These covariates were included incrementally: Model 0 was an unadjusted model. Model 1 (sociodemographics) was adjusted for age, sex and deprivation. Model 2 (lifestyle) was adjusted for

all covariates included in model 1 plus alcohol intake, smoking status, total sedentary time, sleep time and type of PA. Model 3 (BMI) adjusted for all covariates included in model 2 plus BMI. Model 4 (WC) was the same as model 3, except BMI was replaced by WC.

The mediation role of BMI was formally tested under a causal counterfactual framework (Tingley et al., 2014). g-formula (VanderWeele and Tchetgen Tchetgen, 2017) approach was the mediation role of obesity in the association between diet and T2D, adjusting for all the confounders included in Model 2. Assuming causality after adjusted for the confounders, the TE of diet on T2D was decomposed as natural direct effect (NDE) and NIE, where the latter indicates the effect that was mediated through obesity. Proportion of mediation was calculated to quantify how much of the association between diet and T2D could be attributed to obesity. Nonparametric bootstrap with 500 replications was used to estimate 95% CI and p-values. Analysis was repeated replacing obesity by central obesity.

The proportional hazard assumption was tested by Schoenfeld residuals. Statistical analyses were performed using the statistical software packages STATA 16 (StataCorp LP) and R v4.0.2 with the CMAverse package (Shi et al., 2021). P-values <0.05 were regarded as statistically significant.

5.4 Results

Among the 203,790 (55.8% women) participants, omnivores were the largest group (87.3%), while fish & poultry eaters were the smallest (1.1%). After excluding the first two years, the median follow-up period was 5.4 years (IQR: 4.8-6.3). Over the follow-up period, 5,067 (2.5%) participants were diagnosed with incident T2D (2,147 women and 2,920 men).

The primary cohort characteristics of participants by types of diet are presented in **Table 5-1**. Vegetarians were younger, more deprived, and less likely to smoke. Fish & poultry eaters were more physically active. Participants with varied diet were the most likely to be obese, followed by omnivores, fish & poultry eaters, vegetarians, then fish eaters. The cohort characteristics by sex are presented in Additional File **Tables S5-1 and S5-2**. In terms of energy and nutrient intake, as shown in **Table 5-2**, fish & poultry eaters had lower total energy intake (1,970 kilocalories (kcal)/day). Participants with varied diet and omnivores had lower total carbohydrate (CHO) (46% and 47% of total energy (TE)) but higher total fat (32% of TE) intake. Sugar intake was higher in fish & poultry eaters and lower in omnivores.

Table 5-1 Cohort characteristics of participants by types of diet n= 203,790

Characteristics	Vegetarians	Fish eaters	Fish & poultry eaters	Omnivores	Varied diet
Participants, n (%)	3,237 (1.6)	4,405 (2.2)	2,217 (1.1)	178,004 (87.3)	15,927 (7.8)
Sociodemographic					
Age (years), mean (SD)	52.8 (7.9)	54.1 (8.0)	56.4 (8.2)	56.5 (8.1)	56.0 (8.1)
Townsend Deprivation Index, n (%)					
Lower deprivation	867 (26.8)	1,295 (29.4)	634 (28.6)	62,039 (34.9)	4,907 (30.8)
Middle deprivation	1,059 (32.7)	1,551 (35.2)	781 (35.2)	61,297 (34.4)	5,224 (32.8)
Higher deprivation	1,311 (40.5)	1,559 (35.4)	802 (36.2)	54,668 (30.7)	5,796 (36.4)
Ethnicity, n (%)					
Whites	2,685 (83.3)	4,155 (94.8)	2,052 (92.7)	171,599 (96.6)	14,945 (94.3)
South Asians	487 (15.1)	126 (2.9)	88 (4.0)	2,142 (1.2)	373 (2.4)

Black	9 (0.3)	40 (0.9)	31 (1.4)	1,544 (0.9)	226 (1.4)
Chinese	4 (0.1)	6 (0.1)	1 (0.1)	430 (0.2)	45 (0.3)
Mixed	37 (1.2)	54 (1.2)	42 (1.9)	1,856 (1.1)	267 (1.7)
Education, n (%)					
College or University degree	1,804 (61.1)	2,608 (63.8)	949 (51.1)	66,623 (45.6)	5,750 (44.6)
A/AS levels or equivalent	394 (13.3)	535 (13.1)	257 (13.8)	19,678 (13.5)	1,655 (12.8)
O levels/GCSEs or equivalent	524 (17.7)	686 (16.8)	417 (22.5)	38,522 (26.4)	3,345 (25.9)
SEs or equivalent/NVQ or HND or HNC	233 (7.9)	256 (6.3)	234 (12.6)	21,333 (14.6)	2,158 (16.7)
Lifestyle					
Smoking status, n (%)					

Never	2,085 (64.4)	2,563 (58.2)	1,325 (59.8)	99,378 (55.8)	8,142 (51.1)
Previous	940 (29.0)	1,548 (35.1)	732 (33.0)	60,705 (34.1)	5,457 (34.3)
Current	212 (6.6)	294 (6.7)	160 (7.2)	17,921 (10.1)	2,328 (14.6)
Sleep categories, n (%)					
Short sleep (<7 h per day)	895 (27.7)	1055 (24.0)	594 (26.8)	42,214 (23.7)	11,189 (70.3)
Normal (7-9 h per day)	2,296 (70.9)	3,292 (74.7)	1,573 (71.0)	132,960 (74.7)	4,411 (27.7)
Long sleep (>9 h per day)	46 (1.4)	58 (1.3)	50 (2.3)	2,830 (1.6)	327 (2.1)
Types of physical activity, n (%)					
Walking for pleasure	2,382 (78.4)	3,506 (82.4)	1,657 (79.2)	1285,68 (76.8)	11,218 (76.1)
Other exercises: swimming, cycling,	383 (12.6)	502 (11.8)	280 (13.4)	21,487 (12.8)	1,870 (12.7)

Strenuous sports	29 (1.0)	38 (0.9)	15 (0.7)	1,406 (0.8)	86 (0.6)
Light DIY: pruning, watering the lawn	203 (6.7)	163 (3.8)	108 (5.2)	11,526 (6.9)	1,135 (7.7)
Heavy DIY: weeding, lawn mowing, carp	41 (1.4)	45 (1.1)	33 (1.6)	4,404 (2.6)	438 (3.0)
Sedentary time, n (%)					
Low	1,962 (60.6)	2,673 (60.7)	1,260 (56.8)	80,192 (45.1)	7,038 (44.2)
Middle	817 (25.2)	1,159 (26.3)	616 (27.8)	62,176 (34.9)	5,230 (32.8)
High	458 (14.2)	573 (13.0)	341 (15.4)	35,636 (20.0)	3,659 (23.0)
Adiposity					
WC, cm (mean, SD)	84.6 (12.5)	82.7 (11.8)	82.46 (12.2)	89.5 (12.8)	91.7 (13.3)
BMI, kg/m ² (mean, SD)	25.6 (4.5)	25.1 (4.1)	25.39 (4.4)	27.2 (4.5)	28.3 (5.0)

BMI category, n (%)					
Underweight (<18.5 kg/m ²)	50 (1.5)	76 (1.7)	39 (1.8)	802 (0.5)	59 (0.4)
Normal (18.5-24.9 kg/m ²)	1,579 (48.8)	2,360 (53.6)	1,130 (51.0)	58,542 (32.9)	4,117 (25.9)
Overweight (25-29.9 kg/m ²)	1,164 (36.0)	1,482 (33.6)	741 (33.4)	78,244 (44.0)	6,809 (42.8)
Obese (≥30.0 kg/m ²)	444 (13.7)	487 (11.1)	307 (13.9)	40,416 (22.7)	4,942 (31.0)

Data are presented as mean and standard deviation (SD) for continuous variables, and as frequency and percentage (%) for categorical variables. Sedentary time was classified into three tertiles: low, middle, and high. Abbreviations: A/AS level, Advanced/Advanced Subsidiary level; BMI, body mass index; GCSE, General Certificate of Secondary Education; HNC, Higher National Certificate; HND, Higher National Diploma; NVQ, National Vocational Qualification; O level, Ordinary level; SE, Secondary Education; PA, physical activity; WC, waist circumference.

Table 5-2 Dietary intake by types of diet

Dietary intake	Data available*	Vegetarians	Fish eaters	Fish & poultry eaters	Omnivores	Varied diet
Food frequency						
Red meat, portion/week	203,790	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	2.2 (1.4)	2.2 (1.5)
Poultry, times/week	203,751	0.0 (0.0)	0.0 (0.0)	2.1 (0.9)	2.4 (0.8)	2.3 (0.9)
Non-oily fish, time/week	203,089	0.0 (0.0)	2.0 (0.9)	2.0 (0.9)	1.8 (0.7)	1.8 (0.8)
Oily fish, times/week	202,873	0.0 (0.0)	2.0 (1.0)	2.0 (1.1)	1.6 (0.9)	1.7 (0.9)
Fruits and vegetables, portions/day	203,790	5.0 (2.8)	5.1 (2.7)	5.3 (3.1)	4.0 (2.3)	4.2 (2.6)
Cheese, time/week	201,363	3.1 (1.2)	3.0 (1.1)	2.4 (1.3)	2.5 (1.1)	2.5 (1.0)
Alcohol intake, times/week	203,790	3.5 (1.7)	3.0 (1.6)	3.5 (1.6)	2.9 (1.5)	2.9 (1.5)

Type of milk (n, %)	203,712					
Full cream	13,878	241 (7.5)	211 (4.8)	76 (3.4)	12,051 (6.8)	1,299 (8.2)
Semi-skimmed	134,466	1,719 (53.1)	2,447 (55.6)	1,174 (53.0)	118,936 (66.8)	10,190 (64.0)
Skimmed	40,885	637 (19.7)	957 (21.7)	598 (27.0)	35,689 (20.1)	3,004 (18.9)
Soya	6,673	450 (13.9)	482 (10.9)	214 (9.7)	4,922 (2.8)	605 (3.8)
Other types of milk	2,101	47 (1.5)	79 (1.8)	41 (1.9)	1,699 (1.0)	235 (1.5)
Never/rarely	5,709	142 (4.4)	229 (5.2)	114 (5.1)	4,644 (2.6)	580 (3.6)
24-hour dietary recall **						
TE, kcal/day	86,723	2,080.8 (719.7)	2,090.3 (649.3)	1,970.1 (690.0)	2,120.8 (636.6)	2,128.4 (705.5)
Total CHO, % of TE	86,721	52.0 (7.9)	50.3 (8.0)	50.0 (8.8)	47.1 (8.0)	46.4 (8.6)

Sugar, % of TE	86,721	24.3 (7.5)	24.0 (7.0)	24.9 (7.9)	22.6 (6.9)	22.2 (7.4)
Starch, % of TE	86,721	25.2 (6.6)	23.8 (6.4)	22.7 (6.9)	22.7 (6.1)	22.2 (6.4)
Fibre, g/day	86,723	20.7 (8.1)	19.4 (7.1)	18.5 (7.7)	16.2 (6.4)	16.1 (7.1)
Total fat, % of TE	86,721	31.9 (7.0)	31.6 (6.8)	30.7 (7.4)	32.0 (6.6)	32.3 (6.9)
Saturated fat, % of TE	86,721	12.1 (3.6)	11.8 (3.4)	11.3 (3.6)	12.4 (3.3)	12.5 (3.5)
Polyunsaturated fat, % of TE	86,721	6.2 (2.4)	6.2 (2.3)	6.1 (2.3)	5.8 (2.2)	5.8 (2.2)
Total protein, % of TE	86,721	12.5 (2.3)	13.5 (2.8)	15.2 (3.5)	15.7 (3.6)	15.6 (3.8)
Alcohol, % of TE	86,721	3.6 (5.4)	4.6 (5.8)	4.1 (6.3)	5.2 (6.5)	5.7 (7.0)

Data are presented as mean and standard deviation (SD). For type of milk, data are presented as frequency and percentage (%).

Abbreviations: CHO, carbohydrate; TE, total energy intake.

* Data available for diet in the dataset. The analysis was conducted using 2-year landmark analyses and excluding participants with type 1 diabetes, type 2 diabetes or unknown diabetes at baseline.

**** 24-hour dietary recall data were collected according to the intake of the previous day using questions such as: 'Did you eat any fish yesterday?' The data were not included in the primary data set due to a small sample size.**

Figure 5-1 shows the associations between types of diet and incident T2D. In the sociodemographic model (Model 1), fish eaters (HR: 0.48; 95% CI: 0.36-0.64) and fish & poultry eaters (HR: 0.66; 95% CI: 0.47-0.93) had lower risk of T2D compared to omnivores. Those with varied diet had a higher risk of T2D (HR: 1.27; 95% CI: 1.15-1.39) than omnivores. However, there was no association with vegetarian diets (HR: 0.95; 95% CI: 0.74-1.21). The magnitude of the associations with fish eaters (HR: 0.52; 95% CI: 0.39-0.69), fish & poultry eaters (HR: 0.62; 95% CI: 0.45-0.88), and participants with varied diets (HR: 1.21; 95% CI: 1.11-1.33) remained similar when the models were additionally adjusted for lifestyle factors (Model 2). Further adjustment for BMI (Model 3) or WC (Model 4) attenuated the associations, and only fish eaters remained associated with incident T2D (HR: 0.69; 95% CI: 0.51-0.92 and HR: 0.68; 95% CI: 0.51-0.91, respectively).

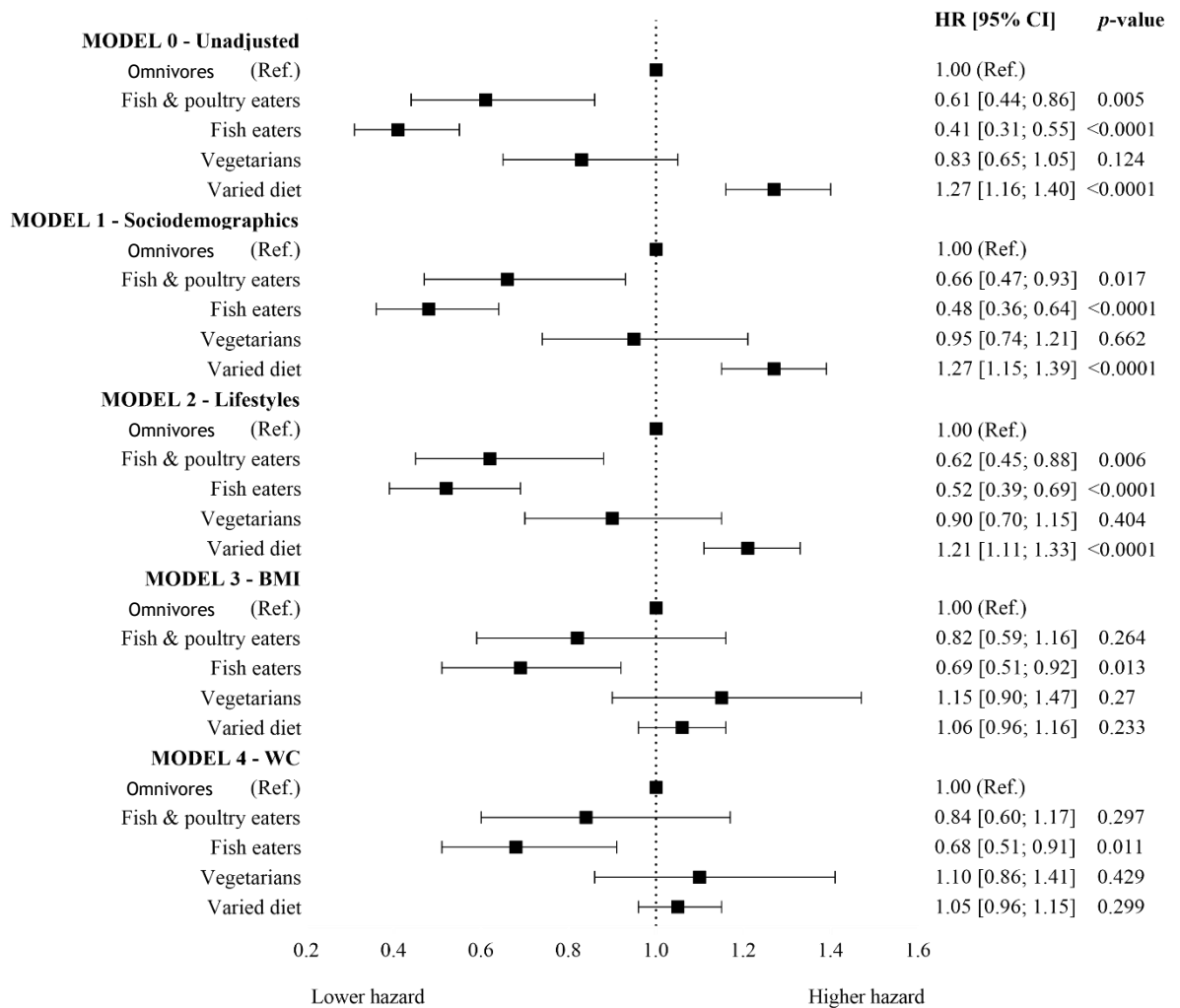


Figure 5-1 Association between types of diet and incidence of type 2 diabetes.

Data are presented as hazard ratios (HRs) and 95% confidence intervals (CIs). Omnivores served as a reference group (Ref.). Model 0 was the unadjusted model. Model 1 (sociodemographic) was adjusted for age, sex and deprivation; model 2 (lifestyle) was adjusted for all covariates included in model 1 plus lifestyle variables (alcohol, smoking, sedentary time, sleep time and type of physical activity); model 3 (body mass index [BMI]) was adjusted for all covariates included in model 2 plus BMI; and model 4 (waist circumference [WC]) was adjusted for all covariates included in model 2 plus WC. All analyses were conducted using 2-year landmark analyses and excluding participants with type 1 diabetes, type 2 diabetes or unknown diabetes at baseline.

Formal mediation analysis was conducted on adiposity. As shown in **Table 5-3**, General obesity was a partial mediator for fish and fish & poultry diets, accounting for 49.8% and 30.6% of their lower risk of T2D, respectively. Similarly, central obesity partially mediated the associations between fish and fish & poultry diets and incident T2D, as shown in **Table 5-3**. Similarly, general and central obesity mediated 55.2% and 52.9% of the elevated risk of participants with varied diet.

Table 5-3 Mediation analysis between types of diet and type 2 diabetes via adiposity

	Mediation via obesity	Mediation via central obesity
Fish and poultry diet		
TE	0.71 (0.52-0.92)	0.72 (0.52-0.91)
NDE	0.85 (0.62-1.11)	0.89 (0.66-1.13)
NIE	0.83 (0.80-0.86)	0.81 (0.78-0.83)
Proportion mediated (%)	49.8 (20.0-100.0)	61.4 (25.4-100.0)
Fish diet		
TE	0.56 (0.43-0.67)	0.58 (0.45-0.72)
NDE	0.70 (0.53-0.87)	0.69 (0.54-0.86)
NIE	0.81 (0.79-0.83)	0.83 (0.81-0.85)

Proportion mediated (%)	30.6 (16.9-56.0)	28.2 (16.3-51.1)
Varied diet		
TE	1.27 (1.18-1.39)	1.28 (1.17-1.38)
NDE	1.12 (1.03-1.22)	1.13 (1.04-1.22)
NIE	1.13 (1.12-1.15)	1.13 (1.11-1.14)
Proportion mediated (%)	55.2 (42.4-78.6)	52.9 (41.5-77.9)

Note: The analyses were adjusted for age, sex, deprivation, alcohol intake, smoking status, total sedentary time, sleep time and type of physical activity (Model 2). All analyses were conducted using 2-year landmark analyses and excluding participants with type 1 diabetes, type 2 diabetes or unknown diabetes at baseline. Data are presented as hazard ratios (HRs) and 95% confidence intervals (CIs) except for proportion mediated. Obesity defined as BMI \geq 30 kg/m²; central obesity defined as WC $>$ 88 cm for women and $>$ 102 cm for men. Abbreviations: BMI, body mass index; NDE, natural direct effect; NIE, natural indirect effect; WC, waist circumference.

5.5 Discussion

In this large prospective cohort study, the findings showed that fish and fish & poultry diets were associated with lower risk of T2D compared to omnivores, independent of sociodemographic and lifestyle factors. Obesity was attributed to half of the association of fish and poultry diets and a third of that of fish diets. Vegetarian diets were not associated with a lower risk of T2D. These findings provide important information for dietary guidelines for T2D, reinforcing regular fish consumption while limiting red and processed meat intake, as well as explaining the potential mechanisms underlying these diets.

Comparison with other studies

The previous existing evidence on this topic was inconsistent. The European Prospective Investigation into Cancer and Nutrition Oxford (EPIC-Oxford) study of 45,314 participants with a mean follow-up of 17.6 years demonstrated an association of fish eaters, low meat eaters and vegetarians with lower risk of T2D compared to regular meat eaters (Papier et al., 2019). They reported that after adjusting for sociodemographic and lifestyle factors, fish eaters (HR: 0.47; 95% CI: 0.38-0.59), low meat eaters (HR: 0.63; 95% CI: 0.54-0.75) and vegetarians (HR: 0.63; 95% CI: 0.54-0.74) were at lower risk of T2D (Papier et al., 2019). Similarly, the present findings found that fish eaters were at approximately 50% lower risk of T2D (HR: 0.52; 95% CI: 0.39-0.69). All these HRs estimates for all types of diet were attenuated but remained significant after adjusting for BMI in the EPIC-Oxford study (Papier et al., 2019). In contrast, the study only observed an independent association for fish eaters.

A prospective cohort study conducted in Japan investigated the associations between consumption of total meat, total red meat, unprocessed red meat, processed red meat and poultry and T2D risk among women and men. They found that the highest quartile of total meat, total red meat and unprocessed red meat intake had 36% (HR: 1.36; 95% CI: 1.07-1.73), 48% (HR: 1.48; 95% CI: 1.15-1.90) and 42% (HR: 1.42; 95% CI: 1.12-1.81) higher risk of T2D, respectively, among men compared to the lowest quartile after adjusting for lifestyle factors and BMI (Kurotani et al., 2013). However, they did not find a significant association with poultry intake among men, nor between any diet type and T2D risk among women (Kurotani et al., 2013). More recently, a study in China concluded that increased consumptions of fish and red meat of 50 g/day were associated with a 6% (HR: 1.06; 95% CI: 1.00-1.13) and 11% (HR: 1.11; 95% CI: 1.04-1.20) higher risk of T2D, respectively, after adjusting for sociodemographic and lifestyle factors and adiposity, but no significant association was found for poultry eaters (Du et al., 2020). It is interesting to note that a recent study

conducted on UK Biobank found that individuals who reported <1 serving/week, weekly, and \geq two servings/week of oily fish had a 16% (HR: 0.84; 95% CI: 0.78-0.91), 22% (HR: 0.78; 95% CI: 0.72-0.85) and 22% (HR: 0.78; 95% CI: 0.71-0.86) lower risk of T2D, respectively, compared to no consumption, but found no association between non-oily fish intake and incident T2D (Chen et al., 2021).

Evidence on the substitution of meat with fish or poultry supports these findings. A Danish study reported that substitution of total red meat with fish was associated with a 4% lower risk of T2D (HR: 0.96; 95% CI: 0.94-0.99), replacing processed red meat with fish produced a 6% lower risk (HR: 0.94; 95% CI: 0.91-0.97), and replacing processed red meat with poultry produced a 4% lower risk (HR: 0.96; 95% CI: 0.93-0.99) after adjusting for overall food pattern (Ibsen et al., 2019).

Controversial findings regarding vegetarians

This study found no association between lacto-ovo-vegetarian diets and T2D, in contrast to previous studies. The Adventist Health Study-2 found that lacto-ovo vegetarians (OR: 0.62; 95% CI: 0.50-0.76), vegans (OR: 0.38; 95% CI: 0.24-0.62) and semi-vegetarians (OR: 0.49; 95% CI: 0.31-0.76) were at a lower risk of T2D compared to all other non-vegetarian diets after adjusting for a similar set of confounders to those included in this study (Tonstad et al., 2013). Similarly, findings from the EPIC-Oxford study reported a significantly lower incidence of T2D among vegetarians, particularly lacto-ovo vegetarians, compared with omnivores (Appleby and Key, 2016). In addition, a study that excluded participants who had T2D, fasting blood glucose \geq 7.0 mmol/L, cancer, coronary heart disease and stroke at baseline reported that vegetarians and converted vegetarians (individuals who became vegetarians within 5 years) had a 35% and 53% lower risk of T2D, respectively, compared to non-vegetarians, after adjusting for gender, age, education, family history of diabetes, PA, use of lipid-lowering medications, follow-up methods and baseline BMI (Chiu et al., 2018).

The main reason that could explain the difference in findings would be the dietary quality differences between those studies and the UK Biobank. Not all vegetarian diets confer uniform benefits. Evidence suggests that the protective effect depends on the overall quality of the diet. A systematic review and meta-analysis of prospective cohort studies found that the inverse association between plant-based dietary patterns and a reduced risk of T2D in adults was more pronounced when the dietary patterns emphasised healthful plant-derived foods, including fruits, vegetables, whole grains, legumes, and nuts (Qian et al., 2019b).

However, in the current study, vegetarians did not consistently exhibit higher dietary quality, despite reporting greater intakes of certain plant foods (Petermann-Rocha et al., 2023). Notably, vegetarians reported higher consumption of fruits, vegetables, and soy products compared to omnivores. However, they also reported consuming less healthy diets, such as cheese and whole cream milk, more than omnivores. Based on 24-hour dietary recalls, vegetarians reported greater intakes of total carbohydrates, sugar, starch, and PUFA. Interestingly, both vegetarians and omnivores had similar total energy intake and saturated fat consumption. These suggest that, despite dietary differences, vegetarians in this current study may not necessarily have a higher overall dietary quality. This highlights the importance of considering overall dietary quality rather than dietary patterns alone.

Specifically, the inconsistent results regarding vegetarian diets may also be related to participants' total energy intake and macro- and micronutrient patterns, which warrant further study. However, such analyses could not be conducted in the current study due to limitations in the available data. It should also be noted that HRs across different Cox models might not be meaningfully compared as HRs are dependent on the adjustment variables (non-collapsibility) (MartinussenVansteelandt and Andersen, 2020). Additionally, socio-demographic

differences in deprivation between vegetarians and omnivores in this study warrant further study (Lusk and Norwood, 2016).

Adiposity as a mediator

Qian et al., found that the association between plant-based diets and T2D risk was considerably attenuated when adjusting for BMI (Qian et al., 2019a). This current study meaningfully extends the literature by showing that adiposity, as indicated by BMI and WC, was indeed a mediator for fish diets. These findings echo a study on health diet pattern and T2D risk finding adiposity was a sizable mediator (Xu et al., 2022). Further studies should explore other potential mediators, such as blood pressure and lipid profile.

Dietary patterns and methodology

Dietary intake is a complex, multilayered exposure encompassing nutrients, individual foods, eating occasions, and overall dietary patterns (**Figure 5-2**). Each level and its interactions play a distinct role in shaping health outcomes and offer unique insights into contemporary nutritional issues. The concept of dietary patterns has evolved over time, resulting in various definitions in the literature. More recently, the terminology has shifted to focus on “food patterns” or “food-based dietary patterns,” with less emphasis on nutrients (McNaughton, 2020). This is primarily due to the fact that people do not consume nutrients but food items, and they also tend to consume groups of food together, rather than picking a single food item in isolation.

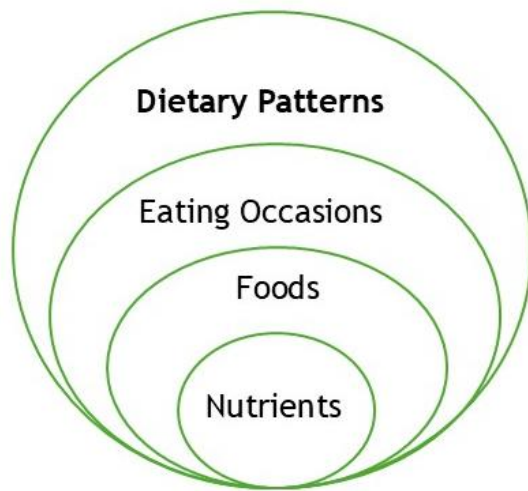


Figure 5-2 Dietary intake represents a hierarchical exposure involving multiple levels, ranging from nutrients and individual foods to eating occasions and overall dietary patterns.

Source: Adapted from McNaughton (2020)

Dietary patterns are frequently defined in operational terms, meaning they are characterised based on the specific methods used to measure or assess them. In this study, dietary patterns were defined operationally using data from both FFQs and 24-hour dietary recalls within the UK Biobank cohort. While such methods are valuable for capturing habitual intake, it is essential to recognise that dietary pattern research is conceptually designed to reflect the complexity of the entire diet, rather than focusing on isolated foods or nutrients. Operational definitions based on current assessment tools are widely used; however, an over-reliance on these may constrain methodological advancements that better capture the dynamic and integrated nature of dietary behaviours. It is also because the FFQ (food items) and 24-hour recall (food items and nutrients) do not represent how people eat and the number of variables involved poses difficulty in using them directly.

Within the literature, two major methodological approaches are commonly employed: data-driven (**a posteriori**) and investigator-defined (**a priori**) methods. Each yields composite measures of dietary behaviour but reflects different conceptual perspectives (McNaughton, 2020). Investigator-defined approaches, including selective diets and scores or indices, involve dietary patterns that are pre-specified by researchers because the dietary components and structure are predetermined. This method enables other researchers to replicate the criteria precisely, enhancing comparability across studies (Krebs-SmithSubar and Reedy, 2015). In line with the objectives of this study, the methodological choice was guided by the need to assess population-level dietary patterns in a standardised and reproducible manner, while accounting for practical limitations in dietary data collection.

Dietary assessment biases

It is well known that dietary data reported by questionnaires are prone to bias, such as over- or underreporting. Dietary underreporting refers to the systematic underestimation of food and energy intake in self-reported dietary assessment tools, such as FFQs, 24-hour dietary recalls, and food diaries. To account for potential dietary underreporting, energy intake data were assessed for plausibility based on established cut-off criteria. Participants with implausibly low or high energy intake relative to estimated energy requirements were excluded or flagged in sensitivity analyses, thereby reducing the impact of misreporting on the observed associations. Following UK Biobank protocols for 24 dietary recalls, participants with implausible energy intake values, specifically those reporting intakes outside the sex-specific plausible range (e.g., men: <3,347 kJ/days or >17,573 kJ/days or <800 kcal/days or >4,200 kcal/days); women: <2,092 kJ/days or >14,644 kJ/days or <600 kcal/days or >3,500 kcal/days) (Perez-Cornago et al., 2021). These individuals were excluded from analyses to mitigate bias caused by energy under- or over-reporting, thereby improving the validity of dietary intake estimates.

However, it is important to consider that the apparent inconsistencies in dietary quality among vegetarians, as well as the unexpected findings in some food group associations, may be partly attributed to dietary underreporting. Underreporting is particularly common among individuals with overweight or obesity, or those consuming foods perceived as unhealthy. In the UK Biobank, established protocols were used to identify and minimise the impact of implausible energy intakes; however, residual underreporting cannot be ruled out. This may have resulted in the underestimation of energy-dense or socially undesirable foods (e.g., snacks) and overreporting of healthier items (e.g., fruits, vegetables), thus distorting the true dietary profile. Consequently, this measurement error may have attenuated associations or contributed to unexpected findings, particularly in subgroups such as self-identified vegetarians whose reported diets may not accurately reflect actual intake. Therefore, caution is warranted in interpreting the associations between individual food groups and T2D risk, and future studies using objective dietary biomarkers are needed to validate these findings. In addition, the present study did not adjust for total energy intake due to data limitations. Therefore, future studies addressing this limitation are warranted.

Meat, fish, poultry and vegetarians with a possible mechanism of type 2 diabetes

Meat consumption, particularly red and processed meats, has been consistently associated with an increased risk of T2D. This may be explained by several mechanisms, including the high content of saturated fats and haem iron, which can impair insulin sensitivity and promote oxidative stress (Pan et al., 2011, Bao et al., 2012). Additionally, processing methods may introduce harmful compounds such as nitrates and advanced glycation end products (AGEs), which contribute to systemic inflammation and metabolic dysfunction (Aune Ursin and Veierød, 2009, Pan et al., 2011). Diets high in meat are also typically lower in fibre-rich plant foods, which have protective effects against diabetes.

Furthermore, animal-based diets may alter the gut microbiome in ways that promote inflammation and insulin resistance (David et al., 2014).

Fish and poultry are considered healthier protein sources in relation to T2D risk, primarily due to their lower content of saturated fat, haem iron, and harmful compounds associated with processed and red meats (De Smet, 2012). Notably, this present study showed that fish diets were associated with lower T2D risk partly because these diets were associated with lower BMI and WC. However, there was still a substantial proportion of the association unexplained. Because fish is a major dietary source of PUFA, it is possible that PUFA intake is a mechanism between fish-based diet and T2D. A systematic review on interventional studies showed that long-term consumption (at least eight weeks) of 5.0 g/day of PUFA improved glycaemic control in patients with T2D, although evidence is heterogeneous (Coelho et al., 2017). It was hypothesised that the PUFA anti-inflammatory pathway and signalling molecules in the cell processes and immunological processes (e.g. PGR40, PGR120 or GLUT4) could improve insulin sensitivity and secretion (Coelho et al., 2017). However, the latest evidence suggested that potential adverse effects were noted at supplemental long-chain omega-3 intakes exceeding 4.4 g/day. The associations of α -linolenic acid, omega-6, and total PUFA intake with T2D risk remain unclear due to very low-quality evidence. No consistent effects were observed on glucose metabolism, although α -linolenic acid may modestly increase fasting insulin (~7%). There was no evidence supporting a role for the omega-3/omega-6 ratio in T2D or glycaemic regulation (Brown et al., 2019). Therefore, well-established randomised controlled trials might be warranted to investigate the causality between fish, PUFA, and T2D risk as well as glycaemic control.

Although vegetarian diets, typically rich in fibre, antioxidants, and phytochemicals, are generally associated with a lower risk of T2D, this protective effect is not consistently observed across studies. One possible explanation is that some vegetarians may consume diets of poor quality,

characterised by high intakes of refined carbohydrates, added sugars, and saturated fats from sources such as cheese and processed foods. Such dietary patterns may attenuate or even reverse the metabolic benefits typically attributed to plant-based diets. Misclassification of dietary status due to inconsistent adherence or underreporting further complicates the interpretation of the evidence (Satija et al., 2016, Kahleova and Pelikanova, 2015, Orlich et al., 2013). Similarly, in the present study, although vegetarians reported higher intakes of fruits, vegetables, and certain plant-based products, they also had higher intakes of total carbohydrates, sugar, and fat compared with omnivores. This suggests that the overall dietary quality among vegetarians in this cohort may have been suboptimal, potentially offsetting any protective effects of meat avoidance. These findings reinforce the importance of considering the nutritional composition and quality of the overall diet, rather than vegetarian status alone, when evaluating T2D risk.

Differences between studies on individual food groups and dietary patterns

Analysing individual food group exposures offers added value beyond whole diet approaches by providing clearer mechanistic insights, enhancing the interpretability of findings, and improving public health relevance. While dietary pattern analyses capture overall eating behaviours and synergistic effects, reflecting what people actually consume in real life, they may obscure the specific contributions of key foods. For example, the study by Boonpor et al. (2023) demonstrated consistent inverse dose-response associations between several healthy dietary patterns, e.g. the Mediterranean Diet Adherence Screener (MEDAS-14) and the Recommended Food Score (RFS), and incident T2D. These findings reinforce the value of whole-diet approaches in capturing the cumulative effects of diverse dietary behaviours and guiding broad public health messaging (Boonpor et al., 2023).

However, in the present study, no significant association was observed between vegetarian diets and T2D risk, suggesting that adherence to a dietary pattern alone may not fully capture differences in metabolic risk, particularly when the underlying dietary quality varies. Indeed, analysis of individual food group intakes in this present cohort revealed that vegetarians consumed higher amounts of total carbohydrates, sugars, and fats, and similar levels of saturated fat compared with omnivores, indicating suboptimal dietary composition despite adherence to a meat-free pattern.

Whereas Boonpor et al.'s findings illustrate the protective potential of high-quality diets when scored comprehensively, these present results suggest that the health benefits of a given pattern may be diluted or absent when the overall quality of the component foods is poor. By examining individual food groups, it becomes possible to identify specific contributors to metabolic risk and clarify inconsistencies in pattern-disease associations. Taken together, this highlights the importance of evaluating both overall patterns and detailed food-level exposures to improve mechanistic interpretation, inform public health advice, and account for heterogeneity within dietary groups.

Strengths and limitations

This study has several strengths. First, this study quantified the mediating role of obesity using a counterfactual causal framework. The study also used a comprehensive adjustment scheme in a large cohort. To minimise reverse causation, the analyses have excluded prevalent and undiagnosed diabetes at baseline, as well as incident diabetes cases diagnosed over the first two years of follow-up.

However, several limitations remain in the present study. UK Biobank is not representative of the UK general population in terms of sociodemographic, physical, lifestyle and health-related characteristics. However, a previous study

has confirmed that the effect size estimates derived from UK Biobank are consistent with those from more representative general population cohorts (Batty et al., 2020).

FFQs and 24-hour dietary recalls are subjected to inherent sources of measurement error. A key limitation of these tools is their susceptibility to recall bias, particularly in the case of FFQs, which typically require participants to retrospectively estimate their usual intake over extended periods. In addition, both methods are vulnerable to intentional misreporting of food consumption, which may be influenced by individual characteristics such as age, sex, and body weight status (e.g., overweight or obesity). Such biases can lead to differential misclassification, potentially introducing unanticipated distortions in the observed associations. Further inaccuracies may arise from relying on food composition databases to estimate energy and nutrient intakes. These errors typically occur due to natural variations in food ingredients or insufficient information on processed, packed, or prepared foods consumed outside the home (NaskaLagiou and Lagiou, 2017).

To improve the accuracy of dietary assessments, 24-hour dietary recalls used in conjunction with FFQs offer a practical and effective approach for nutritional epidemiology (Carroll et al., 2012). This current study sought to minimise potential biases by analysing the primary findings using data from the FFQ, while supplementary data from 24-hour dietary recalls were used to evaluate the consistency and reliability of reported dietary intake. Due to the smaller sample size of participants who completed the 24-hour dietary recalls, there is insufficient power to study variables derived from that questionnaire. Importantly, both tools rely on participants' reports and are subject to underreporting bias, which potentially skews the associations identified. This is likely a differential misclassification bias since under-/mis-reporting could be dependent on participants' health and socioeconomic status, both of which are related to the T2D outcome in this study. However, since people with worse

health and socioeconomic status were more likely to underreport and to develop T2D, the bias is plausibly skewed towards the null, providing a more conservative estimate (NaskaLagiou and Lagiou, 2017).

This study focuses on healthier diets rather than the dosage of individual food items. Future studies should consider the total consumption of these food items to identify whether there is a dose-response relationship. The omnivores were heterogeneous but there were very few people who only had red meat but not fish or poultry (0.04%), limiting the study from further categorisation. Similarly, for participants who reported having varied diet, there was insufficient information to identify the dietary components that can be attributed to their higher risk. Future studies could consider other tools (e.g. diet quality) to further risk-stratify the meat-based diet group. Lastly, despite the best efforts, the study cannot rule out residual confounding and reverse causation as in all observational studies.

5.6 Conclusion

This study showed that fish diets were associated with a lower risk of incident T2D compared to diets including red meat. The associations were partially mediated by adiposity. This measurement error may have attenuated the associations, particularly in self-identified vegetarians, whose reported diets may not accurately reflect their actual intake. The quality of plant-based diets may attenuate their benefits.

5.7 Reference Chapter 5

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5.8 Additional File Chapter 5

Table S5-1 Cohort characteristics in women

	Vegetarians	Fish eaters	Fish & poultry eaters	Omnivores	Varied diets
Participants, n (%)	2,180 (1.9)	3,182 (2.8)	1,699 (1.5)	97,529 (85.7)	9,165 (8.1)
Sociodemographic					
Age (years), mean (SD)	52.9 (7.8)	54.0 (8.0)	56.4 (8.1)	56.4 (7.9)	56.0 (7.9)
Townsend Deprivation Index, n (%)					
Lower deprivation	604 (27.7)	974 (30.6)	492 (29.0)	33,730 (34.6)	2,817 (30.7)
Middle deprivation	719 (33.0)	1,111 (34.9)	613 (36.1)	33,877 (34.7)	3,000 (32.7)
Higher deprivation	857 (39.3)	1097 (34.5)	594 (35.0)	29,922 (30.7)	3,348 (36.5)
Ethnicity, n (%)					
Whites	1,822 (83.8)	2,997 (94.8)	1,609 (94.8)	94,171 (96.8)	8,571 (93.8)

South Asians	316 (14.5)	88 (2.8)	42 (2.5)	899 (0.9)	211 (2.3)
Black	7 (0.3)	30 (1.0)	16 (0.9)	877 (0.9)	147 (1.6)
Chinese	3 (0.1)	5 (0.2)	1 (0.1)	268 (0.3)	32 (0.4)
Mixed	26 (1.2)	43 (1.4)	29 (1.7)	1,120 (1.2)	177 (1.9)
Education, n (%)					
College or University degree	1,177 (59.3)	1,853 (62.8)	706 (49.4)	35,396 (44.4)	3,286 (44.5)
A levels/AS levels or equivalent	276 (13.9)	399 (13.5)	210 (14.7)	11,367 (14.3)	1,011 (13.7)
O levels/GCSEs or equivalent	389 (19.6)	529 (17.9)	348 (24.4)	23,288 (29.2)	2,084 (28.2)
SEs or equivalent/NVQ or HND or HNC	143 (7.2)	171 (5.8)	164 (11.5)	9,664 (12.1)	999 (13.5)
Lifestyle					

Smoking status, n (%)					
Never	1,443 (66.2)	1,877 (59.0)	1,013 (59.6)	58,664 (60.2)	5,122 (55.9)
Previous	617 (28.3)	1,103 (34.7)	566 (33.3)	30,391 (31.2)	2,871 (31.3)
Current	120 (5.5)	202 (6.4)	120 (7.1)	8,474 (8.7)	1,172 (12.8)
Sleep categories, n (%)					
Short sleep (<7 h per day)	614 (28.2)	770 (24.2)	457 (26.9)	22,710 (23.3)	6,451 (70.4)
Normal (7-9 h per day)	1,531 (70.2)	2,372 (74.5)	1,208 (71.1)	73,142 (75.0)	2,503 (27.3)
Long sleep (>9 h per day)	35 (1.6)	40 (1.3)	34 (2.0)	1,677 (1.7)	211 (2.3)
Types of physical activity, n (%)					
Walking for pleasure	1,617 (79.3)	2,570 (83.7)	1,301 (81.1)	72,222 (79.4)	6,554 (78.2)

Other exercises: swimming, cycling,	238 (11.7)	340 (11.1)	191 (11.9)	10782 (11.9)	1,015 (12.1)
Strenuous sports	18 (0.9)	19 (0.6)	8 (0.5)	325 (0.4)	20 (0.2)
Light DIY: pruning, watering the lawn	140 (6.9)	120 (3.9)	85 (5.3)	6,186 (6.8)	648 (7.7)
Heavy DIY: weeding, lawn mowing, carp	27 (1.3)	21 (0.7)	19 (1.2)	1,420 (1.6)	143 (1.7)
Sedentary time, n (%)					
Low	1,393 (63.9)	2,016 (63.4)	998 (58.7)	49,703 (51.0)	4,563 (49.8)
Middle	545 (25.0)	814 (25.6)	467 (27.5)	33,237 (34.1)	2,955 (32.2)
High	242 (11.1)	352 (11.1)	234 (13.8)	14,589 (15.0)	1,647 (18.0)
Adiposity					
WC, cm (mean, SD)	80.9 (11.7)	79.5 (10.8)	79.8 (11.4)	84.1 (11.9)	87 (12.6)

BMI, kg/m ² (mean, SD)	25.5 (4.8)	24.9 (4.4)	25.2 (4.5)	26.9 (4.9)	28.2 (5.3)
BMI category, n (%)					
Underweight (<18.5 kg/m ²)	46 (2.1)	68 (2.1)	34 (2.0)	637 (0.7)	39 (0.4)
Normal (18.5-24.9 kg/m ²)	1,097 (50.3)	1,800 (56.6)	912 (53.7)	38,031 (39.0)	2,745 (30.0)
Overweight (25-29.9 kg/m ²)	729 (33.4)	954 (30.0)	507 (29.8)	37,117 (38.1)	3,554 (38.8)
Obese (≥ 30.0 kg/m ²)	308 (14.1)	360 (11.3)	246 (14.5)	21,744 (22.3)	2,827 (30.9)

Data are presented as mean and standard variation (SD) for continuous variables and as frequency and percentage (%) for categorical variables. Sedentary time was classified by tertile into low, middle and high. A levels/AS levels, Advance/Advanced Subsidiary level; BMI, body mass index; GCSEs, General Certificate of Secondary Education; HNC, Higher National Certificate; HND, Higher National Diploma; NVQ, National Vocational Qualification; O levels, Ordinary level; SE, Secondary Education; PA, physical activity; WC, waist circumference.

Table S5-2 Cohort characteristics in men

	Vegetarians	Fish eaters	Fish & poultry eaters	Omnivores	Varied diets
Participants, n (%)	1,057 (1.2)	1,223 (1.4)	518 (0.6)	80,475 (89.4)	6,762 (7.5)
Sociodemographic					
Age (years), mean (SD)	52.7 (7.9)	54.4 (8.0)	56.4 (8.6)	56.6 (8.2)	56 (8.2)
Townsend Deprivation Index, n (%)					
Lower deprivation	263 (24.9)	321 (26.3)	142 (27.4)	28,309 (35.2)	2,090 (30.9)
Middle deprivation	340 (32.2)	440 (36.0)	168 (32.4)	27,420 (34.1)	2,224 (32.9)
Higher deprivation	454 (43.0)	462 (37.8)	208 (40.2)	24,746 (30.8)	2,448 (36.2)
Ethnicity, n (%)					
Whites	863 (82.4)	1,158 (95.1)	443 (85.7)	77,428 (96.5)	6,374 (94.9)

South Asians	171 (16.3)	38 (3.1)	46 (8.9)	1,243 (1.6)	162 (2.4)
Black	2 (0.2)	10 (0.8)	15 (2.9)	667 (0.8)	79 (1.2)
Chinese	1 (0.1)	1 (0.1)	0 (0.0)	162 (0.2)	13 (0.2)
Mixed	11 (1.1)	11 (0.9)	13 (2.5)	736 (0.9)	90 (1.3)
Education, n (%)					
College or University degree	627 (64.6)	755 (66.6)	243 (56.6)	31,227 (47.0)	2,464 (44.6)
A levels/AS levels or equivalent	118 (12.2)	136 (12.0)	47 (11.0)	8,311 (12.5)	644 (11.7)
O levels/GCSEs or equivalent	135 (13.9)	157 (13.9)	69 (16.1)	15,234 (22.9)	1,261 (22.8)
SEs or equivalent/NVQ or HND or HNC	90 (9.3)	85 (7.5)	70 (16.3)	11,669 (17.6)	1,159 (21.0)
Lifestyle					

Smoking status, n (%)					
Never	642 (60.7)	686 (56.1)	312 (60.2)	40,714 (50.6)	3,020 (44.7)
Previous	323 (30.6)	445 (36.4)	166 (32.1)	30,314 (37.7)	2,586 (38.2)
Current	92 (8.7)	92 (7.5)	40 (7.7)	9,447 (11.7)	1,156 (17.1)
Sleep categories, n (%)					
Short sleep (<7 h per day)	281 (26.6)	285 (23.3)	137 (26.5)	19,504 (24.2)	4,738 (70.1)
Normal (7-9 h per day)	765 (72.4)	920 (75.2)	365 (70.5)	59,818 (74.3)	1,908 (28.2)
Long sleep (>9 h per day)	11 (1.0)	18 (1.5)	16 (3.1)	1,153 (1.4)	116 (1.7)
Types of physical activity, n (%)					
Walking for pleasure	765 (76.7)	936 (79.1)	356 (72.8)	56,346 (73.7)	4,664 (73.3)

Other exercises: swimming, cycling,	145 (14.5)	162 (13.7)	89 (18.2)	10,705 (14.0)	855 (13.4)
Strenuous sports	11 (1.1)	19 (1.6)	7 (1.4)	1,081 (1.4)	66 (1.0)
Light DIY: pruning, watering the lawn	63 (6.3)	43 (3.6)	23 (4.7)	5,340 (7.0)	487 (7.7)
Heavy DIY: weeding, lawn mowing, carp	14 (1.4)	24 (2.0)	14 (2.9)	2,984 (3.9)	295 (4.6)
Sedentary time, n (%)					
Low	569 (53.8)	657 (53.7)	262 (50.6)	30,489 (37.9)	2,475 (36.6)
Middle	272 (25.7)	345 (28.2)	149 (28.8)	28,939 (36.0)	2,275 (33.6)
High	216 (20.4)	221 (18.1)	107 (20.7)	21,047 (26.2)	2,012 (29.8)
Adiposity					
WC, cm (mean, SD)	92.3 (10.5)	91.2 (10.0)	91.1 (10.6)	96.2 (10.6)	98.1 (11.4)

BMI, kg/m ² (mean, SD)	25.9 (3.8)	25.6 (3.4)	25.9 (3.8)	27.6 (4.0)	28.4 (4.4)
BMI category, n (%)					
Underweight (<18.5 kg/m ²)	4 (0.4)	8 (0.7)	5 (1.0)	165 (0.2)	20 (0.3)
Normal (18.5-24.9 kg/m ²)	482 (45.6)	560 (45.8)	218 (42.1)	2,0511 (25.5)	1,372 (20.3)
Overweight (25-29.9 kg/m ²)	435 (41.2)	528 (43.2)	234 (45.2)	41,127 (51.1)	3,255 (48.1)
Obese (≥30.0 kg/m ²)	136 (12.9)	127 (10.4)	61 (11.8)	18,672 (23.2)	2,115 (31.3)

Data are presented as mean and standard deviation (SD) for continuous variables and as frequency and percentage (%) for categorical variables. Sedentary time was classified by tertile into low, middle and high. A levels/AS levels, Advance/Advanced Subsidiary level; BMI, body mass index; GCSEs, General Certificate of Secondary Education; HNC, Higher National Certificate; HND, Higher National Diploma; NVQ, National Vocational Qualification; O levels, Ordinary level; SE, Secondary Education; PA, physical activity; WC, waist circumference.

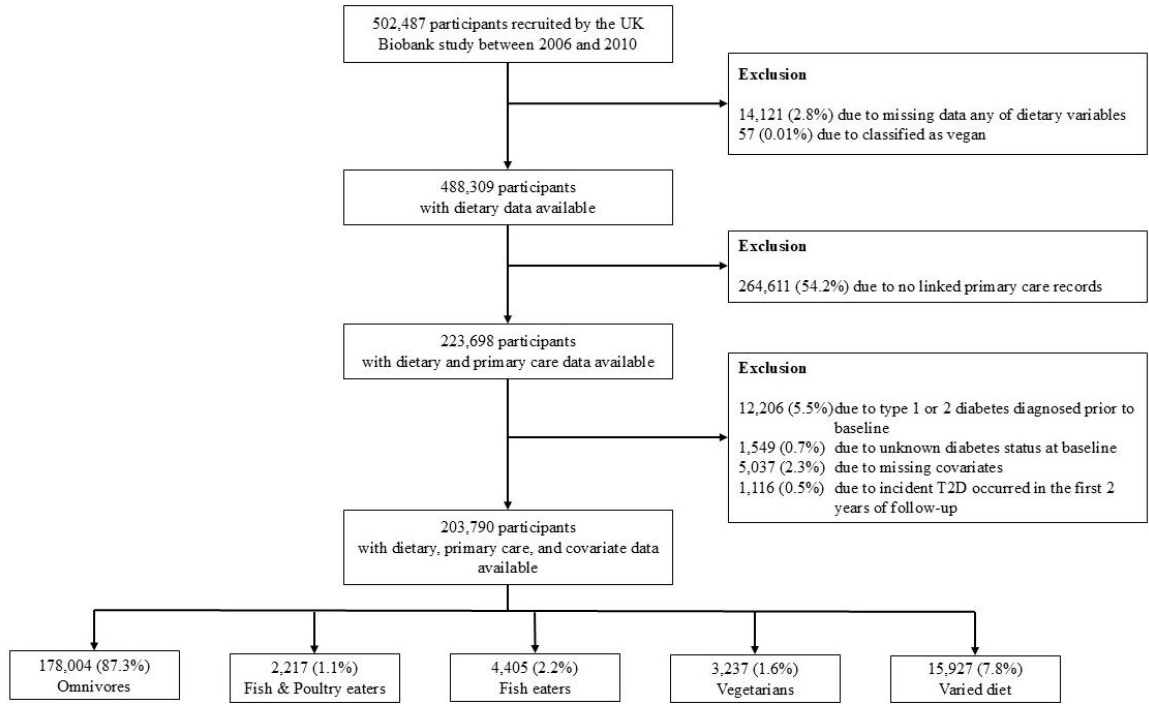


Figure S5-1: Flowchart of participants

Chapter 6 Associations and predictive performance of eleven anthropometric measures with incident type 2 diabetes: A prospective cohort study from the UK Biobank

The original article of this chapter has been published in *Obesity*. The contents, style, and order of structures have been modified to conform to the standard thesis format.

Boonpor, J, Parra-Soto, S, Talebi, A, et al. Associations and predictive performance of 11 anthropometric measures with incident type 2 diabetes: A prospective cohort study from the UK Biobank. *Obesity (Silver Spring)*. 2023; 31(10): 2648-2657. doi:10.1002/oby.23849.

Contributions: I developed research questions, prepared study materials, prepared the dataset and performed data analyses. I drafted the manuscript with inputs from my supervisors (CCM, SRG and FKH). I led the submission of the manuscript and responded to reviewer comments, with input and support from my supervisors.

6.1 Abstract

Introduction To investigate associations of eleven anthropometric measures with incident T2D and compare their predictive performance.

Methods A prospective cohort study of 161,127 white-European UK Biobank participants who were free of diabetes at baseline. Anthropometric measures included height, body mass, BMI, ABSI, WC, WHR, WHtR, HC, VAI, HI and ARI. The associations were examined using Cox proportional hazard models. The differences in C-index were used to compare predictive performance between BMI and other anthropometric measures.

Results The median follow-up was 10.0 (IQR: 9.3-10.8) years, during which 6,315 participants developed T2D. All markers -except height and HI- were positively associated with incident T2D. The strongest association was found for WHtR (HR per 1-SD increment: 2.27 (95% CI: 2.19-2.35) in women; 1.96 (95% CI: 1.90-2.01 in men). Compared with BMI, WHtR and ARI had significantly better T2D risk discrimination.

Conclusions Although most adiposity markers were associated with T2D, the magnitude of the association differed. WHtR had the strongest associations and prediction ability for T2D and thus may be the most suitable marker for clinical use.

Keywords Adiposity, C-index, Diabetes predictor, Type 2 diabetes mellitus

Study Importance

What is already known?

- Anthropometric measurements have been used to predict the risk of T2D. However, the predictive performance of those has been inconsistent.

What does this study add?

- Most anthropometric measurements were positively associated with incident T2D. However, WHtR and anthropometric risk index had a significantly better predictive performance of T2D risk than BMI.
- Being shorter and having smaller hips were associated with a higher risk of T2D.

How might these results change the direction of research or the focus of clinical practice?

- More complex markers did not outperform simple, conventional measures such as BMI and WHtR.
- WHtR had the strongest associations and prediction ability for T2D and thus may be the most suitable marker for clinical use.

6.2 Introduction

T2D is a major global public health challenge and a leading contributor to the burden of NCDs. Individuals with T2D face a significantly increased risk of CVD, chronic kidney disease, and premature mortality (Chan et al., 2021). Obesity, defined as an abnormal or excessive accumulation of body fat that may impair health, is a strong risk factor for the development of T2D (Guh et al., 2009, Abdullah et al., 2010, PichéTchernof and Després, 2020). The term adiposity refers more broadly to the quantity and distribution of fat tissue in the body. Adiposity is typically estimated using anthropometric-derived indicators such as BMI and WC, both of which are well-established predictors of T2D risk (Freemantle et al., 2008, Guh et al., 2009, BrowningHsieh and Ashwell, 2010).

However, other markers, such as WHtR, have more recently been proposed as better predictors of obesity-related comorbidities, including T2D, than BMI and other traditional adiposity markers alone (BrowningHsieh and Ashwell, 2010, JanssenKatzmarzyk and Ross, 2004). Furthermore, in recent years, novel anthropometric indices of adiposity have been developed to better capture metabolic risk, including the VAI, ABSI, HI, and ARI (Krakauer and Krakauer, 2016, Krakauer and Krakauer, 2018, Amato et al., 2010, Krakauer and Krakauer, 2012). These newer indices have been shown to be associated with cardiometabolic risk and mortality (Krakauer and Krakauer, 2018, Amato et al., 2010), although their specific role in predicting T2D remains poorly investigated (Jayedi et al., 2022).

The biological mechanisms linking increased adiposity to a higher risk of T2D are complex and multifactorial. Excess adipose tissue, particularly visceral fat, promotes insulin resistance through several interrelated pathways, including the release of pro-inflammatory cytokines, altered adipokine secretion (e.g., decreased adiponectin and increased leptin), ectopic fat deposition in organs such as the liver and pancreas, and impaired lipid metabolism (KahnHull and

Utzschneider, 2006, Wellen and Hotamisligil, 2005, Guilherme et al., 2008). These mechanisms contribute to β -cell dysfunction and impaired glucose regulation, ultimately increasing the risk of developing T2D (Prentki and Nolan, 2006, Czech, 2020).

A recent systematic review and meta-analysis have examined the association between various anthropometric markers and T2D risk (Jayedi et al., 2022). However, the number of studies included was small, and they were subject to between-study confounding in their dose-response analysis (Jayedi et al., 2022). Moreover, this review did not assess the predictive utility of these markers, nor did it examine whether associations differed by sex, both of which are critical for informing risk stratification and personalised prevention strategies.

The current study contributes novel and methodologically robust evidence to the current understanding of the relationship between anthropometric-derived markers and the risk of T2D. Using data from the UK Biobank, a large, contemporary, prospective cohort with detailed anthropometric, demographic, and clinical data, the study examined a broad range of anthropometric-derived indices. These included height and body mass, ABSI, BMI, WC, WHR, WHtR, HC, VAI, HI, and ARI.

The analysis evaluated the dose-response associations between these markers and incident T2D, aiming to provide a more comprehensive and nuanced understanding of their predictive value. In addition, the current study assessed the discriminatory performance of each marker and explored whether these associations varied by sex, addressing important gaps in the existing literature (Jayedi et al., 2022). Notably, previous studies have been limited by small sample sizes, between-study heterogeneity, and lack of sex-stratified or predictive performance analyses (Jayedi et al., 2022).

Therefore, the study aimed to investigate the dose-response associations of anthropometric-derived indicators (height and body mass, ABSI, BMI, WC, WHR, WHtR, HC, VAI, HI and ARI) with incident T2D in the UK Biobank, a large prospective cohort study. This study also explored whether these associations differed by sex and compared the markers' prediction performance.

The study hypotheses were that:

- Markers reflecting central or visceral adiposity (e.g., WC, WHR, WHtR, VAI) will be more strongly associated with incident T2D than general adiposity markers such as BMI.
- Sex-specific differences exist in the strength and shape of these associations, reflecting underlying biological and metabolic differences.
- Markers capturing body fat distribution will demonstrate superior predictive performance in identifying individuals at high risk of developing T2D.

6.3 Methods

Study design and population

The UK Biobank study recruited over 502,000 participants between 2006 and 2010 (5.5% response rate, men and women aged 37-73 years) from the general population (Collins, 2012). Participants attended 1 of 22 assessment centres across England, Wales, and Scotland (Sudlow et al., 2015, Palmer, 2007). Participants completed electronic consent, touch screen questionnaires, and physical measurements at the assessment centres, including anthropometric measurements. The current study included 161,127 white-European participants who had data available for incident T2D, anthropometric-derived indicators and covariates. Participants were excluded if they had prevalent type 1, type 2 or undiagnosed diabetes ($HbA1c \geq 48$ mmol/mol) at the baseline assessment as well

as if they had a non-white European background due to ethnic differences in adiposity. Also, participants with missing data on exposures and covariates or those who developed T2D in the first 2-years were excluded from this present study (Additional File **Figure S6-1**).

Ethical Approval

The UK Biobank study was approved by the North West Multi-Centre Research Ethics Committee (Ref 11/NW/0382 on June 17, 2011) and all participants provided written informed consent to participate. The study protocol is available online (<http://www.ukbiobank.ac.uk/>). This research has been conducted using the UK Biobank resource under application number 7155.

Outcome

Incident T2D was derived from linkage to primary care data in UK Biobank. Records were extracted for 45% of the UK Biobank cohort (228,449 participants). The end of coverage (extract date) was September 2021. Detailed linkage procedures are available at http://biobank.ndph.ox.ac.uk/showcase/showcase/docs/primary_care_data.pdf. This present study defined incident T2D as primary care diagnosed with ICD-10 code E11. The READ codes used in the primary care data were converted into ICD-10 codes using UK Biobank's look-up table.

Exposures

The exposures included eleven anthropometric-derived indicators, i.e. height, body mass, ABSI, BMI, WC, WHR, WHtR, HC, VAI, HI and ARI. The measurements were undertaken by trained staff using standardised protocols across the assessment centres at baseline. Height was measured to the nearest centimetre, using a Seca 202 stadiometer, and body weight to the nearest 0.1 kg, using a

Tanita BC-418 body composition analyser. BMI was calculated as body weight (kg) divided by height (m) squared and classified into the following categories: underweight ($<18.5 \text{ kg/m}^2$), normal weight ($18.5 - <25 \text{ kg/m}^2$), overweight ($25 - <30 \text{ kg/m}^2$), obesity ($\geq 30 \text{ kg/m}^2$) (World Health Organization, 2000). The natural indent was used to measure WC (the umbilicus was used if the natural indent could not be observed) using a non-elastic SECA 200 tape. ABSI was calculated based on WC, BMI and height, as shown in Additional File **Table S6-1** (Krakauer and Krakauer, 2012). HC was recorded at the widest part of the hips. WHR and WHtR are the ratios of waist-to-hip circumference and WC to height, respectively. HI was calculated from HC, body mass and height (Additional File **Table S6-1**) (Christakoudi et al., 2021). VAI was calculated based on BMI, WC, TG and HDL (Amato et al., 2010). ARI was calculated by the sum of height, BMI, ABSI and HI, as explained elsewhere (Krakauer and Krakauer, 2016).

Covariates

Age was calculated from the date of birth and baseline assessment; sex was self-reported. The Deprivation Index, an area-based measure of socioeconomic status, was derived from the postal code of residence using the Townsend deprivation index (TownsendPhillimore and Beattie, 1988). Fruits and vegetables, red meat, and processed meat intakes were recorded using a touch screen questionnaire asking about the reported frequency of consumption. Alcohol intake was self-reported and categorised as daily or almost daily, 3-4 times a week, once or twice a week, 1-3 times a month, special occasions only and never. Smoking status was categorised into never, former, and current. Leisure screen time was self-reported as discretionary screen time, TV viewing and leisure PC screen time in hours per day. Sleep duration was categorised as short sleep $<7 \text{ h/day}$, normal sleep $7-9 \text{ h/day}$ and long sleep $>9 \text{ h/day}$ (Cappuccio et al., 2010). Type of PA was self-reported in relation to five groups: walking for pleasure, other exercises (e.g. swimming, cycling), strenuous sports, light do-it-yourself (DIY) (e.g. pruning, watering the lawn) and heavy DIY (e.g.

weeding, lawn mowing, carpentry and digging). A family history of diabetes was self-reported at baseline. Systolic blood pressure was derived from the mean of two readings recorded in the left arm using a standardised protocol. Additional details about these measurements can be found in the UK Biobank online protocol (Biobank, 2007).

Statistical Analyses

Continuous variables are expressed as means with SDs, and categorical variables are presented as frequencies and percentages (%). The Pearson correlation coefficients were used to evaluate the correlations between variables. Cox-proportional hazard models were used to investigate the associations of anthropometric markers, standardised by sex (expressed as a 1-SD), with incident T2D with follow-up as the timeline variable. Results are reported as HRs together with 95% CIs, representing the ratio of hazards averaged across the follow-up period (Stensrud and Hernán, 2020). The association analyses were conducted within a 2-year landmark period and excluded all participants with prevalent or undiagnosed diabetes at the baseline assessment or those with missing data on exposures and covariates to reduce reverse causation (Additional File **Figure S6-1**). Due to ethnic differences in adiposity, inclusion in the study was restricted to participants of a white European background.

The association of anthropometric-derived indicators with incident T2D was adjusted for covariates using 2 models with an increasing number of covariates. Model 1 (minimally adjusted model) was adjusted for sex, age, and deprivation index. Model 2 (lifestyle model) was adjusted for all variables in model 1 and additionally smoking, fruit and vegetable intake, red meat intake, processed meat intake, alcohol intake, type of PA, total sedentary time, and sleep duration. These were adjusted due to they were likely to be confounders of the associations.

Women-to-men HRs were then estimated using Cox-proportional hazard models with sex by anthropometric-derived indicator interaction terms. This term represents the statistical interaction between sex and the predictor and can be interpreted as the ratio of HR between sexes.

In the predictive analysis comparing T2D risk discrimination between BMI and the remaining markers, we calculated Harrell's C-index (the probability of concordance between observed and predicted responses) from a Cox model that included the markers and covariates (age, sex, systolic blood pressure and family history of diabetes). These covariates, instead of the one in the association analysis, were chosen because they were commonly used in the clinical prediction model of T2D and in this analysis, we are interested in the predictive performance, which would not be affected by confounding. No 2-year landmark analysis was used because reverse causation is not a concern in predictive analysis. BMI was a baseline model used to compare with models replacing BMI with other anthropometric-derived indicators. The C-index differences between the models using BMI and other anthropometric-derived parameters were calculated. The variance of the C-indices was calculated using the formula previously described (Hanley and McNeil, 1982). These were then used to calculate 95% CIs and p-values using the normal approximation.

Nonlinear analyses were also conducted to investigate the associations of sex-specific z-scores of anthropometric-derived indicators with incident T2D. Nonlinear associations were examined using penalised cubic splines fitted in Cox proportional hazard models. The penalised spline is a variation of the basis spline, which is not as sensitive to knot numbers and placements as restricted cubic splines (Govindarajulu et al., 2009). The likelihood ratio tests were used to compare the models using splines and those assuming linearity.

Statistical analyses were performed using the statistical software STATA 17 (StataCorp LP) and R 4.0.2 with the survival, compareC, psych and corrplot packages. P-values <0.05 were regarded as statistically significant.

6.4 Results

A total of 161,127 (55.0% women) participants with available data for incident T2D, anthropometric-derived indicators, and covariates were included in this study (Additional File **Figure S6-1**). After excluding the first two years, the median follow-up period was 10.0 years (IQR: 9.3-10.8). Over the follow-up, 6,315 (3.9%) participants were diagnosed with incident T2D (2,638 women (1.6%) and 3,677 men (2.3%)).

Table 6.1 presents the characteristics of the total study population stratified by BMI category as BMI is used to derive the reference group, without sex-specific classification. Accordingly, participant characteristics are summarised based on the overall sample to maintain consistency with this categorisation. However, the primary analyses were stratified by sex to account for potential sex-specific differences in associations, which may arise from underlying biological, hormonal, or behavioural factors known to influence adiposity and related T2D (FaerchHulmán and Solomon, 2016).

The overall cohort characteristics by BMI categories show that the average age was 56.6 (8.0) years. Participants classified as obesity (22.0%) were older and more deprived than their counterparts with a lower BMI. The group with obesity had a higher proportion of previous smokers, 1-3 times a month alcohol intake and higher sedentary time. The cohort characteristics of women and men were similar. However, men had more daily alcohol drinking and higher BMI as presented in Additional File **Table S6-2**.

Table 6-1 Baseline characteristics by BMI categories

Variable	Underweight (N=775, 0.5%)	Normal weight (N=54289, 33.7%)	Overweight (N=70566, 43.8%)	Obesity (N=35501, 22.0%)	Overall (N=161,127)
Sex, n (%)					
Women	624 (80.9)	35,756 (65.9)	33,455 (47.4)	18,722 (52.7)	88,557 (55.0)
Men	147 (19.1)	18,533 (34.1)	37,111 (52.6)	16,779 (47.3)	72,570 (45.0)
Age (year), mean \pm SD	55.5 \pm 8.1	55.9 \pm 8.1	57.1 \pm 8.0	56.7 \pm 7.8	56.6 \pm 8.0
Townsend deprivation index, n (%)					
Lower deprivation	237 (30.7)	20,328 (37.4)	25,969 (36.8)	11,102 (31.3)	57,636 (35.8)
Middle deprivation	250 (32.4)	19,123 (35.2)	24,949 (35.4)	12,320 (34.7)	56,642 (35.2)
Higher deprivation	284 (36.8)	14,838 (27.3)	19,648 (27.8)	12,079 (34.0)	46,849 (29.1)
Smoking status, n (%)					
Never	465 (60.3)	32,469 (59.8)	38,140 (54.1)	18,496 (52.1)	89,570 (55.6)

Previous	154 (20.0)	16,266 (30.0)	25,904 (36.7)	13,910 (39.2)	56,234 (34.9)
Current	152 (19.7)	5,554 (10.2)	6,522 (9.2)	3,095 (8.7)	15,323 (9.5)
Alcohol intake, n (%)					
Daily or almost daily	185 (24.0)	12,309 (22.7)	15,474 (21.9)	5,897 (16.6)	33,865 (21.0)
3-4 times a week	148 (19.2)	14,111 (26.0)	18,209 (25.8)	7,522 (21.2)	39,990 (24.8)
Once or twice a week	155 (20.1)	14,339 (26.4)	19,192 (27.2)	9,941 (28.0)	4,3627 (27.1)
1-3 times a month	86 (11.2)	5,544 (10.2)	7,510 (10.6)	4,853 (13.7)	17,993 (11.2)
Special occasions only	99 (12.8)	4,790 (8.8)	6,315 (9.0)	4,738 (13.4)	15,942 (9.9)
Never	98 (12.7)	3,196 (5.9)	3,866 (5.5)	2,550 (7.2)	9,710 (6.0)
Fruits and vegetables, mean \pm SD (portion/day)	4.2 \pm 2.8	4.2 \pm 2.3	4.1 \pm 2.3	4.0 \pm 2.3	4.1 \pm 2.3

Red meat, mean \pm SD (portion/week)	1.6 \pm 1.4	1.9 \pm 1.3	2.2 \pm 1.4	2.3 \pm 1.5	2.1 \pm 1.4
Processed meat, mean \pm SD (portion/week)	1.5 \pm 1.2	1.7 \pm 1.1	1.9 \pm 1.0	2.0 \pm 1.0	1.9 \pm 1.0
Leisure screen time, mean \pm SD (hour/day)	4.0 \pm 1.9	4.5 \pm 1.9	5.1 \pm 2.1	5.6 \pm 2.3	5.0 \pm 2.2
Sleeping time, n (%)					
<7 hrs a day	550 (71.3)	42,252 (77.8)	53,445 (75.7)	25,173 (70.9)	12,1420 (75.4)
7 - 8 hrs a day	205 (26.6)	11,462 (21.1)	16,104 (22.8)	9,620 (27.1)	3,7391 (23.2)
>9 hrs a day	16 (2.1)	575 (1.1)	1,017 (1.4)	708 (2.0)	2,316 (1.4)
Type PA, n (%)					
Walking for pleasure	621 (80.5)	43,705 (80.5)	54,799 (77.7)	25,313 (71.3)	12,4438 (77.2)
Other exercises	76 (9.9)	6,273 (11.6)	8,913 (12.6)	5,035 (14.2)	20,297 (12.6)
Strenuous sports	2 (0.3)	434 (0.8)	606 (0.9)	254 (0.7)	1,296 (0.8)

Light DIY	56 (7.3)	2836 (5.2)	4394 (6.2)	3648 (10.3)	10934 (6.8)
Heavy DIY	16 (2.1)	1041 (1.9)	1854 (2.6)	1251 (3.5)	4162 (2.6)
Body mass index, mean \pm SD (kg/m ²)	17.7 \pm 0.8	22.9 \pm 1.5	27.3 \pm 1.4	33.5 \pm 3.5	27.1 \pm 4.5
Height, mean \pm SD (cm)	166.8 \pm 8.7	167.9 \pm 8.9	169.4 \pm 9.4	168.0 \pm 9.4	168.6 \pm 9.3
WC, mean \pm SD (cm)	66.1 \pm 5.6	78.4 \pm 8.0	90.6 \pm 8.4	103.6 \pm 10.4	89.2 \pm 12.8
Body mass, mean \pm SD (Kg)	49.3 \pm 5.8	64.7 \pm 8.4	78.5 \pm 9.6	94.9 \pm 13.5	77.3 \pm 15.2
ABSI, mean \pm SD	0.08 \pm 0.006	0.08 \pm 0.005	0.08 \pm 0.005	0.08 \pm 0.005	0.08 \pm 0.005
HC, mean \pm SD (cm)	86.8 \pm 4.3	96.2 \pm 4.8	103.1 \pm 4.8	113.4 \pm 8.5	103.0 \pm 8.6
WHR, mean \pm SD	0.8 \pm 0.06	0.8 \pm 0.07	0.9 \pm 0.08	0.9 \pm 0.09	0.9 \pm 0.09
WHtR, mean \pm SD	0.4 \pm 0.03	0.5 \pm 0.04	0.5 \pm 0.04	0.6 \pm 0.06	0.5 \pm 0.07
ARI, mean \pm SD	-2.8 \pm 0.5	-1.6 \pm 0.7	-0.1 \pm 0.8	2.0 \pm 0.9	-0.1 \pm 1.6

HI women, mean \pm SD	0.09 \pm 0.005	0.07 \pm 0.005	0.07 \pm 0.004	0.06 \pm 0.005	0.07 \pm 0.008
HI men, mean \pm SD	0.09 \pm 0.004	0.08 \pm 0.004	0.07 \pm 0.003	0.07 \pm 0.004	0.07 \pm 0.006
VAI women, mean \pm SD	1.1 \pm 0.9	1.4 \pm 1.0	2.1 \pm 1.5	2.7 \pm 1.8	1.9 \pm 1.5
VAI men, mean \pm SD	0.8 \pm 0.6	1.5 \pm 1.2	2.3 \pm 1.6	3.0 \pm 2.0	2.2 \pm 1.7

Data are presented as mean \pm standard deviation (SD) for continuous variables and as frequency (N) and percentage (%) for categorical variables. Abbreviations: ABSI, A Body Shape Index; ARI, anthropometric risk index; DIY, do - it - yourself; HC, hip circumference; HI, hip index; PA, physical activity; WC, waist circumference; WHR, waist to hip ratio; WHtR, waist to height ratio; VAI: visceral adiposity index.

A correlation matrix between the eleven anthropometric-derived indicators is shown in Additional File **Figure S6-2**. Overall, BMI shows a strong correlation with ARI, WHtR, HC, body mass and WC ($r > 0.80$). The weakest correlations were observed for BMI with HI, height and ABSI ($r < 0.20$) (Additional File **Figure S6-2**).

Among women, the majority were classified as having overweight or obesity and tended to be older than those with underweight or normal weight. A higher proportion of former smokers and alcohol consumers was observed among women with excess weight. Additionally, women with overweight or obesity reported higher intake of red and processed meat and spent more time in leisure screen-based activities. While walking for pleasure was a commonly reported activity across all BMI categories, its prevalence was lower among women with obesity. Participation in strenuous sports was generally low across all BMI groups (**Table 6-2**).

Among men, the majority were also classified as overweight or obese. Unlike women, the average age of men remained consistent across BMI categories, at approximately 64 years. Men with overweight or obesity had a higher prevalence of former smoking, but a lower prevalence of current smoking, compared to their normal-weight or underweight counterparts. They also reported greater alcohol consumption and higher intake of red and processed meats. As with women, men with obesity engaged more frequently in leisure screen time and were less likely to participate in walking or strenuous PAs, as shown in **Table 6-3**.

In summary, both women and men with overweight or obesity have less favourable lifestyle behaviours. These included higher consumption of alcohol, red and processed meat, and greater engagement in sedentary leisure activities such as screen time, accompanied by lower levels of PA.

Table 6-2 Baseline characteristics of women participants by BMI category

Variables	Underweight (N=624, 0.7%)	Normal weight (N=35756, 40.4%)	Overweight (N=33455, 37.8%)	Obesity (N=18722, 21.1%)
Age (year), mean \pm SD	55.3 (8.0)	55.6 (8.0)	57.2 (7.8)	56.8 (7.7)
Townsend deprivation index, n (%)				
Lower deprivation	208 (33.3)	13,517 (37.8)	12,028 (36.0)	5,675 (30.3)
Middle deprivation	205 (32.9)	12,759 (35.7)	11,962 (35.8)	6,431 (34.4)
Higher deprivation	211 (33.8)	9,480 (26.5)	9,465 (28.3)	6,616 (35.3)
Smoking status, n (%)				
Never	394 (63.1)	22,071 (61.7)	19,599 (58.6)	10,905 (58.3)
Previous	127 (20.4)	10,582 (29.6)	11,197 (33.5)	6,438 (34.4)
Current	103 (16.5)	3,103 (8.7)	2,659 (8.0)	1,379 (7.4)
Alcohol intake, n (%)				
Daily or almost daily	136 (21.8)	7,229 (20.2)	5,497 (16.4)	2,041 (10.9)
3-4 times a week	123 (19.7)	8,866 (24.8)	7,407 (22.1)	3,110 (16.6)
Once or twice a week	125 (20.0)	9,701 (27.1)	9,349 (28.0)	5,040 (26.9)
1-3 times a month	68 (10.9)	4,047 (11.3)	4,468 (13.4)	3,220 (17.2)
Special occasions only	88 (14.1)	3,634 (10.2)	4,363 (13.0)	3,576 (19.1)
Never	84 (13.5)	2,279 (6.4)	2,371 (7.1)	1,735 (9.3)

Fruits and vegetables, mean \pm SD (portion/day)	4.5 (2.7)	4.4 (2.3)	4.4 (2.2)	4.3 (2.2)
Red meat, mean \pm SD (portion/week)	1.5 (1.3)	1.9 (1.3)	2.0 (1.3)	2.1 (1.4)
Processed meat, mean \pm SD (portion/week)	1.3 (1.1)	1.5 (1.0)	1.6 (1.0)	1.7 (1.0)
Leisure screen time, mean \pm SD (hour/day)	3.9 (1.9)	4.3 (1.8)	4.7 (1.9)	5.1 (2.1)
Sleeping time, n (%)				
<7 hrs a day	445 (71.3)	27,848 (77.9)	25,323 (75.7)	13,356 (71.3)
7 - 8 hrs a day	166 (26.6)	7,530 (21.1)	7,561 (22.6)	4,950 (26.4)
>9 hrs a day	13 (2.1)	378 (1.1)	571 (1.7)	416 (2.2)
Type PA, n (%)				
Walking for pleasure	511 (81.9)	29,483 (82.5)	26,972 (80.6)	13,749 (73.4)
Other exercises	59 (9.5)	3,847 (10.8)	3,849 (11.5)	2,508 (13.4)
Strenuous sports	2 (0.3)	160 (0.5)	89 (0.3)	47 (0.3)
Light DIY	41 (6.6)	1,822 (5.1)	2,052 (6.1)	2,002 (10.7)
Heavy DIY	11 (1.8)	444 (1.2)	493 (1.5)	416 (2.2)
Body mass index, mean \pm SD (kg/m ²)	17.7 (0.8)	22.7 (1.6)	27.2 (1.4)	34 (3.8)
Height, mean \pm SD (cm)	164.4 (7.0)	163.4 (6.2)	162.3 (6.1)	161.5 (6.1)

WC, mean \pm SD (cm)	64.6 (4.6)	74.6 (6.1)	85.0 (6.7)	99.0 (9.6)
Body mass, mean \pm SD (Kg)	47.8 (4.7)	60.7 (6.0)	71.7 (6.4)	88.8 (11.9)
ABSI, mean \pm SD	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)
HC, mean \pm SD (cm)	86.3 (4.2)	95.8 (4.9)	103.5 (5.1)	115.7 (9.1)
WHR, mean \pm SD	0.7 (0.0)	0.8 (0.1)	0.8 (0.1)	0.9 (0.1)
WHtR, mean \pm SD	0.4 (0.0)	0.5 (0.0)	0.5 (0.0)	0.6 (0.1)
ARI, mean \pm SD	-2.7 (0.5)	-1.5 (0.7)	0.1 (0.7)	2.1 (0.9)
HI women, mean \pm SD	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)
VAI women, mean \pm SD	1.1 (0.9)	1.4 (1.0)	2.1 (1.5)	2.7 (1.8)

Data are presented as mean \pm standard deviation (SD) for continuous variables and as frequency (N) and percentage (%) for categorical variables. Abbreviations: ABSI, A Body Shape Index; ARI, anthropometric risk index; DIY, do - it - yourself; HC, hip circumference; HI, hip index; PA, physical activity; WC, waist circumference; WHR, waist to hip ratio; WHtR, waist to height ratio; VAI: visceral adiposity index.

Table 6-3 Baseline characteristics of men participants by BMI category

Variables	Underweight (N=147, 0.2%)	Normal weight (N=18533, 25.5%)	Overweight (N=37111, 51.1%)	Obesity (N=16779, 23.1%)
Age (year), mean \pm SD	56.4 (8.3)	56.4 (8.3)	56.9 (8.1)	56.6 (8.0)
Townsend deprivation index, n (%)				
Lower deprivation	29 (19.7)	6,811 (36.8)	13,941 (37.6)	5,427 (32.3)
Middle deprivation	45 (30.6)	6,364 (34.3)	12,987 (35.0)	5,889 (35.1)
Higher deprivation	73 (49.7)	5,358 (28.9)	10,183 (27.4)	5,463 (32.6)
Smoking status, n (%)				
Never	71 (48.3)	10,398 (56.1)	18,541 (50.0)	7,591 (45.2)
Previous	27 (18.4)	5,684 (30.7)	14,707 (39.6)	7,472 (44.5)
Current	49 (33.3)	2,451 (13.2)	3,863 (10.4)	1,716 (10.2)
Alcohol intake, n (%)				
Daily or almost daily	49 (33.3)	5,080 (27.4)	9,977 (26.9)	3,856 (23.0)
3-4 times a week	25 (17.0)	5,245 (28.3)	10,802 (29.1)	4,412 (26.3)
Once or twice a week	30 (20.4)	4,638 (25.0)	9,843 (26.5)	4,901 (29.2)
1-3 times a month	18 (12.2)	1,497 (8.1)	3,042 (8.2)	1,633 (9.7)
Special occasions only	11 (7.5)	1,156 (6.2)	1,952 (5.3)	1,162 (6.9)

Never	14 (9.5)	917 (5.0)	1,495 (4.0)	815 (4.9)
Fruits and vegetables, mean \pm SD (portion/day)	3.1 (2.8)	3.8 (2.4)	3.7 (2.3)	3.8 (2.4)
Red meat, mean \pm SD (portion/week)	2.1 (1.6)	2.1 (1.4)	2.3 (1.4)	2.4 (1.5)
Processed meat, mean \pm SD (portion/week)	2.2 (1.3)	2.1 (1.1)	2.2 (1.0)	2.3 (1.0)
Leisure screen time, mean \pm SD (hour/day)	4.3 (2.1)	4.8 (2.1)	5.4 (2.3)	6.0 (2.5)
Sleeping time, n (%)				
<7 hrs a day	105 (71.4)	14,404 (77.7)	28,122 (75.8)	11,817 (70.4)
7 - 8 hrs a day	39 (26.5)	3,932 (21.2)	8,543 (23.0)	4,670 (27.8)
>9 hrs a day	3 (2.0)	197 (1.1)	446 (1.2)	292 (1.7)
Type PA, n (%)				
Walking for pleasure	110 (74.8)	14,222 (76.7)	27,827 (75)	11,564 (68.9)
Other exercises	17 (11.6)	2,426 (13.1)	5,064 (13.7)	2,527 (15.1)
Strenuous sports	0 (0.0)	274 (1.5)	517 (1.4)	207 (1.2)
Light DIY	15 (10.2)	1,014 (5.5)	2,342 (6.3)	1,646 (9.8)
Heavy DIY	5 (3.4)	597 (3.2)	1,361 (3.7)	835 (5.0)

Body mass index, mean \pm SD (kg/m ²)	17.7 (0.7)	23.2 (1.4)	27.3 (1.4)	33.0 (3.0)
Height, mean \pm SD (cm)	176.9 (7.7)	176.5 (6.8)	175.9 (6.7)	175.3 (6.8)
WC, mean \pm SD (cm)	72.6 (4.7)	85.7 (6.0)	95.7 (6.1)	108.7 (8.8)
Body mass, mean \pm SD (Kg)	55.5 (5.7)	72.4 (6.9)	84.7 (7.6)	101.6 (12.0)
ABSI, mean \pm SD	0.1 (0.0049)	0.1 (0.0043)	0.1 (0.004)	0.1 (0.0039)
HC, mean \pm SD (cm)	88.8 (4.0)	97.0 (4.4)	102.7 (4.4)	110.9 (6.8)
WHR, mean \pm SD	0.8 (0.1)	0.9 (0.1)	0.9 (0.1)	1.0 (0.1)
WHtR, mean \pm SD	0.4 (0.0)	0.5 (0.0)	0.5 (0.0)	0.6 (0.0)
ARI, mean \pm SD	-3.2 (0.6)	-1.8 (0.7)	-0.2 (0.8)	1.9 (0.9)
HI men, mean \pm SD	0.1 (0.004)	0.1 (0.004)	0.1 (0.003)	0.1 (0.004)
VAI men, mean \pm SD	0.8 (0.5)	1.5 (1.2)	2.3 (1.6)	3.0 (2.0)

Data are presented as mean \pm standard deviation (SD) for continuous variables and as frequency (N) and percentage (%) for categorical variables. Abbreviations: ABSI, A Body Shape Index; ARI, anthropometric risk index; DIY, do - it - yourself; HC, hip circumference; HI, hip index; PA, physical activity; WC, waist circumference; WHR, waist to hip ratio; WHtR, waist to height ratio; VAI: visceral adiposity index.

The associations between the eleven anthropometric-derived indicators and incident T2D are presented in **Table 6-4**. When the association between the eleven anthropometric-derived indicators and incident T2D was stratified by sex, women had a higher T2D risk compared with men (sex interaction in **Table 6-4**).

After adjusting for all covariates (Model 2), a 1-SD increment for most indicators was associated with higher risk of T2D. In women, a 1-SD increment in WHtR was associated with a 2.3-times (HR: 2.27; 95% CI: 2.19-2.35) higher risk of T2D, followed by 2.0-times (HR: 2.03; 95% CI: 1.96-2.10) for WHR and 1.9-times (HR: 1.93; 95% CI: 1.88-1.99) for BMI. In men, the risk of T2D with a 1-SD increment in WHtR was greater by 96% (HR: 1.96; 95% CI: 1.90-2.01) followed by 85% (HR: 1.85; 95% CI: 1.80-1.90) for BMI and 77% (HR: 1.77; 95% CI: 1.73-1.82) for body weight. However, a 1-SD increment of height and HI were associated with a lower risk of T2D for both women and men (**Table 6-4**). The associations for all participants are shown in Additional File **Table S6-3**.

Table 6-4 Association between anthropometric-derived indicators and incident type 2 diabetes by sex and women-to-men HR on type 2 diabetes incidence

	Women				Men				Sex interaction	
	Total	Events	HR (95% CI)	p-value	Total	Events	HR (95% CI)	p-value	Ratio of HR* (HR _{men} / HR _{women})	p-value
Height	88,557	2,638	0.92 (0.89; 0.96)	<0.001	72,570	3,677	0.96 (0.93; 0.99)	0.019	1.05 (1.00; 1.11)	0.059
Body mass			1.85 (1.79; 1.91)	<0.001			1.77 (1.73; 1.82)	<0.001	0.96 (0.92; 0.99)	0.024
ABSI			1.51 (1.46; 1.57)	<0.001			1.23 (1.18; 1.27)	<0.001	0.81 (0.77; 0.85)	<0.001
BMI			1.93 (1.88; 1.99)	<0.001			1.85 (1.80; 1.90)	<0.001	0.96 (0.92; 0.99)	0.014
WC			1.69 (1.64; 1.74)	<0.001			1.59 (1.55; 1.63)	<0.001	0.94 (0.90; 0.98)	0.002
HC			1.69 (1.64; 1.74)	<0.001			1.59 (1.55; 1.63)	<0.001	0.94 (0.90; 0.98)	0.002
WHR			2.03 (1.96; 2.10)	<0.001			1.46 (1.44; 1.48)	<0.001	0.72 (0.69; 0.75)	<0.001
WHtR			2.27 (2.19; 2.35)	<0.001			1.96 (1.90; 2.01)	<0.001	0.86 (0.83; 0.90)	<0.001

VAI			1.46 (1.43; 1.49)	<0.001			1.40 (1.37; 1.43)	<0.001	0.96 (0.93; 0.98)	0.001
HI			0.46 (0.45; 0.48)	<0.001			0.51 (0.49; 0.52)	<0.001	1.09 (1.04; 1.15)	<0.001
ARI			1.70 (1.66; 1.75)	<0.001			1.60 (1.57; 1.64)	<0.001	0.94 (0.91; 0.97)	<0.001

Data are presented as hazard ratios (HRs) with 95% confidence intervals (CIs) per 1-standard deviation (SD) increment in each adiposity marker. Abbreviations: ABSI, A Body Shape Index; ARI, anthropometric risk index; HC, hip circumference; HI, hip index; VAI, visceral adiposity index; WC, waist circumference; WHR, waist to hip ratio; WHtR, waist to height ratio.

*Hazard ratios above 1 suggest a higher risk in women compared with men, whereas hazard ratios below 1 suggest a higher risk in men compared with women. The model was adjusted for age, deprivation, smoking, alcohol, fruits and vegetables, red meat, processed meat, type of physical activity, and leisure screen time. All analyses were conducted using 2-year landmark analyses and excluding participants with type 1, type 2, or unknown diabetes at baseline. SD for height 9.25, SD for body mass 15.19, SD for ABSI 0.01, SD for BMI 4.46, SD for WC 12.83, SD for HC 8.62, SD for WHR 0.09, SD for WHtR 0.07, SD for VAI (women) 1.68, SD for VAI (men) 1.45, SD for HI (women) 0.01, SD for HI (men) 0.01, and SD for ARI 1.55.

The dose-response association between anthropometric-derived indicators and T2D is shown in **Figure 6-1** for women and **Figure 6-2** for men. Most markers show a positive monotonic association with T2D, except height and HI, which were inversely associated with T2D risk. The dose-response association for all participants is shown in Additional File **Figure S6-3**.

The C-index are shown in **Table 6-3**. Among women, WHtR (0.80; 95% CI, 0.79-0.80) and ARI (0.79; 95% CI: 0.78-0.79) had a better predictive ability for incident T2D compared to BMI (0.78; 95% CI: 0.77-0.78). Similarly, WHtR (0.75; 95% CI: 0.74-0.75] and ARI (0.74; 95% CI: 0.73-0.75) were more predictive than BMI (0.74; 95% CI: 0.73-0.74) among men (**Table 6-3**), as well as among all participants (Additional File **Table S6-4**).

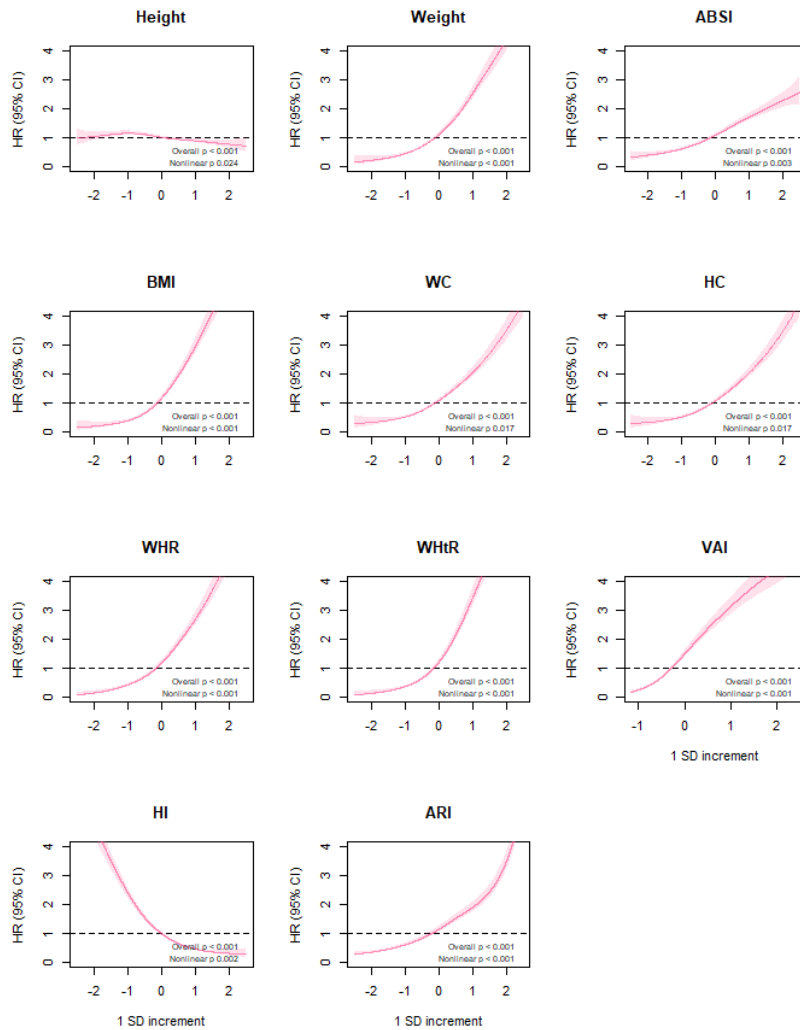


Figure 6-1 Dose–response associations between anthropometric-derived indicators and incident type 2 diabetes in women

Penalised splines were used to present the associations between anthropometric markers and incident type 2 diabetes. The anthropometric markers were sex-standardized to a 1-standard deviation (SD) increment. Analyses were adjusted for sex, age, deprivation, smoking, alcohol, fruits and vegetables, red and processed meat, type of physical activity, and leisure screen time. All analyses were conducted using 2-year landmark analyses and excluding participants with type 1, type 2, or unknown diabetes at baseline. ABSI, A Body Shape Index; ARI, anthropometric risk index; HI, hip index; HC, hip circumference; HR, hazard ratio; Weight, body weight; WHR, waist to hip ratio; WC, waist circumference; WHtR, waist to height ratio; VAI, visceral adiposity index.

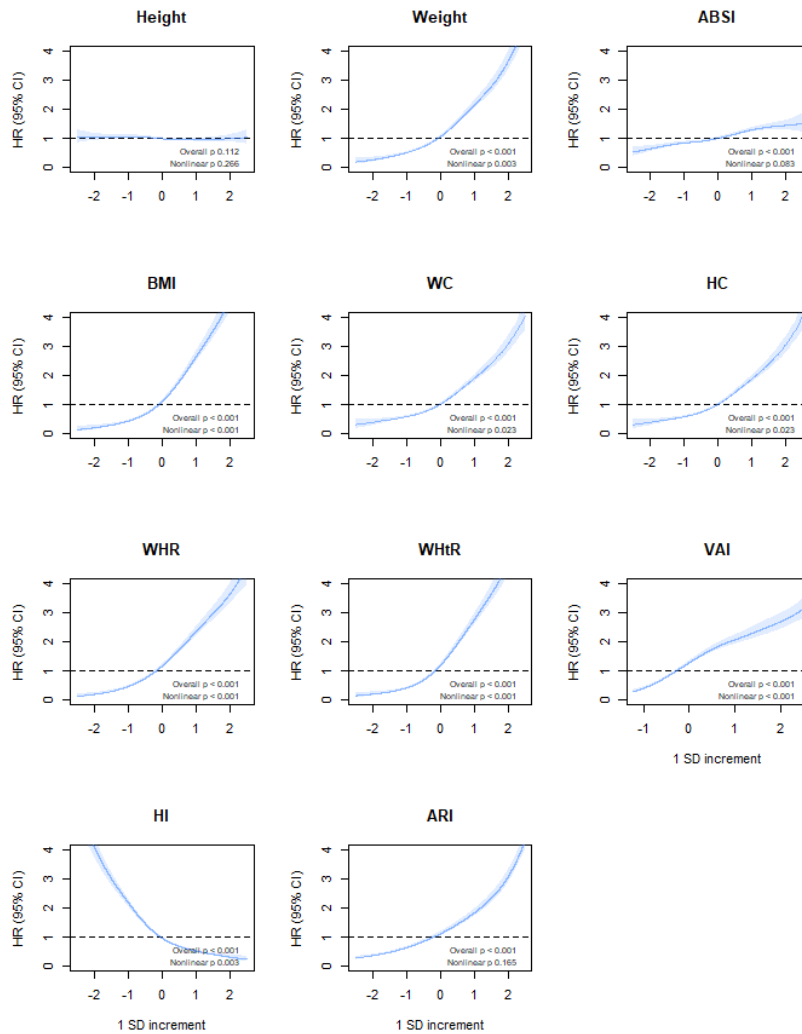


Figure 6-2 Dose–response associations between anthropometric-derived indicators and incident type 2 diabetes in men

Penalised splines were used to present the associations between anthropometric markers and incident type 2 diabetes. The anthropometric markers were sex-standardized to a 1-standard deviation (SD) increment. Analyses were adjusted for sex, age, deprivation, smoking, alcohol, fruits and vegetables, red and processed meat, type of physical activity, and leisure screen time. All analyses were conducted using 2-year landmark analyses and excluding participants with type 1, type 2, or unknown diabetes at baseline. ABSI, A Body Shape Index; ARI, anthropometric risk index; HI, hip index; HC, hip circumference; HR, hazard ratio; Weight, body weight; WHR, waist to hip ratio; WC, waist circumference; WHtR, waist to height ratio; VAI, visceral adiposity index.

Table 6-5 C-index of comparison of body mass index with anthropometric-derived indicators by sex

	Adiposity Markers (95% CI)	BMI (95% CI)	Δ C (95% CI)	p-value
Women				
Height	0.67 (0.66; 0.68)	0.78 (0.77; 0.78)	0.11 (0.10; 0.12)	<0.001
Body mass	0.76 (0.75; 0.77)		0.02 (0.02; 0.02)	<0.001
ABSI	0.71 (0.70; 0.72)		0.07 (0.06; 0.08)	<0.001
WC	0.74 (0.73; 0.74)		0.04 (0.04; 0.04)	<0.001
HC	0.74 (0.73; 0.74)		0.04 (0.04; 0.04)	<0.001
WHR	0.77 (0.76; 0.77)		0.01 (0.00; 0.02)	0.0132
WHtR	0.80 (0.79; 0.80)		-0.02 (-0.02; -0.02)	<0.001
VAI	0.75 (0.74; 0.76)		0.03 (0.02; 0.03)	<0.001
HI	0.76 (0.75; 0.77)		0.02 (0.02; 0.02)	<0.001
ARI	0.79 (0.78; 0.79)		-0.01 (-0.01; -0.01)	<0.001
Men				
Height	0.63 (0.62; 0.64)	0.74 (0.73; 0.74)	0.11 (0.10; 0.12)	<0.001
Body mass	0.71 (0.70; 0.72)		0.03 (0.02; 0.03)	<0.001

ABSI	0.64 (0.63; 0.65)		0.10 (0.09; 0.11)	<0.001
WC	0.69 (0.68; 0.70)		0.05 (0.04; 0.05)	<0.001
HC	0.69 (0.68; 0.70)		0.05 (0.04; 0.05)	<0.001
WHR	0.71 (0.70; 0.72)		0.03 (0.02; 0.03)	<0.001
WHtR	0.75 (0.74; 0.75)		-0.01 (-0.01; 0.00)	0.0001
VAI	0.69 (0.68; 0.70)		0.05 (0.04; 0.06)	<0.001
HI	0.71 (0.71; 0.72)		0.03 (0.02; 0.03)	<0.001
ARI	0.743 (0.735; 0.751)		-0.004 (-0.006; -0.001)	0.0116

ΔC [95% confidence interval; CI], differences between C-indices with the body mass index (BMI) model and their 95% CIs; p value for ΔC . The analysis was adjusted for age, systolic blood pressure, and family history of diabetes. All analyses excluded participants with type 1, type 2, or unknown diabetes at baseline. Abbreviations: ABSI, A Body Shape Index; ARI, anthropometric risk index; WHR, waist to hip ratio; HC, hip circumference; HI, hip index; VAI, visceral adiposity index; WC, waist circumference; WHtR, waist to height ratio.

6.5 Discussion

The main finding of this study was that most anthropometric-derived indicators were associated with T2D, regardless of sociodemographics, diet, and PA. Except for height and HI, higher values of all markers were associated with a higher risk of T2D monotonically. These findings are the first study reporting the prospective association of more complex measures of ABSI, ARI, HI, and VAI with incident T2D among white Europeans (Krakauer and Krakauer, 2016).

The findings corroborated the previous findings in the recent systematic review of prospective and retrospective cohort studies that BMI (relative risk; RR: 1.72), WC (RR: 1.61), WHR (RR: 1.63), WHtR (RR: 1.73), VAI (RR: 1.42), ABSI (RR: 1.09) and HC (RR: 1.11) were associated with a higher incidence of T2D (Jayedi et al., 2022). However, this systematic review included some smaller studies with strong selection bias; therefore, the findings might not be as robust as in this current large general population study. The current study provided new findings that a 1-SD increment in ARI was associated with a higher risk of T2D. Likewise, an anthropometric risk index based on combining height, body mass, waist and hip measurements, the study reported that height (RR: 0.96) and HI (HR: ~0.92-0.99) were associated with a lower risk of mortality (Krakauer and Krakauer, 2016). The present study extends the findings to show the associations between height and HI with a lower T2D risk, which was also consistent with previous studies (Shrestha et al., 2019, Snijder et al., 2003). Therefore, it would be implied that being shorter and having smaller hips were associated with a higher risk of T2D. However, current findings did not agree with a previous study about the association between ABSI and the incidence of T2D. For example, there was no association between ABSI and incident T2D for both women and men but this study was conducted in older people (Yang et al., 2018).

Moreover, the aforementioned systematic review and meta-analysis did not examine the C-index to evaluate prediction performance (Jayedi et al., 2022). These present findings used the C-index to explore the predictive ability of adiposity markers and found that WHtR and ARI were better predictors, whilst the rest of the markers were poorer predictors relative to BMI. It appears that WHtR is the strongest candidate as an adiposity marker to predict T2D in all participants. Given that the UK Biobank is not representative of the general population, the findings should be externally validated. Although the changes in the C-index in the study may appear modest, when applied to the population it could mean substantial prevention (Kassirer and Pauker, 1981, Steyerberg et al., 2010). Notably, the improvement of the C-index in this present study (ΔC_{WHR}

0.01) was larger than when total and HDL cholesterol were added to CVD prediction ($\Delta C=0.004$) (Welsh et al., 2019), both of which are staples of risk prediction.

Interestingly, ABSI was previously found to be a good predictor among Chinese and Japanese populations (He and Chen, 2013, Zhao et al., 2020). However, the results are still inconsistent among other studies because some found that the predictive ability of ABSI for T2D was not better than WC, BMI (Fujita et al., 2015) and VAI (Tsou et al., 2021). Nonetheless, the present findings are consistent: ABSI was also not better than other anthropometric-derived markers among white Europeans in the UK Biobank.

The study also demonstrates that more complex indices, such as WHtR, VAI, or ARI, offer similar predictive value to the relatively simple markers, such as BMI. This has important implications for routine clinical practice, where ease of measurement and interpretation is critical. WHtR, in particular, could be implemented more widely as a low-cost, accessible measure for T2D risk stratification (JiZhang and An, 2018). Although the current findings suggest that for T2D risk prediction and stratification, WHtR is the strongest candidate for the white-European population. A further multiethnic comparison should investigate whether this differs by ethnic group. In addition, to translate these findings into clinical practice, future studies should explore the optimal cut-off values of these anthropometric measures, particularly WHtR, for T2D screening.

The large sample size of this study enabled the analysis to explore the associations between anthropometric-derived indicators and incident T2D, as well as risk prediction. Anthropometric-derived indicators were measured by trained staff using standardised protocols, which could be believed that the values were valid. The present findings clearly show that anthropometric-derived indicators were associated with a higher risk of T2D in white people. The findings were keen to narrow the gaps of previous evidence about the

methodology and report of the development of the risk prediction models for T2D on the number of participants, continuous variables treated, and reporting missing data (Collins et al., 2011).

However, the present study is not exempt from limitations. First and foremost, the analyses were unable to include other ethnic groups in this study due to their small proportions compared to the white population; thus, the findings cannot be extrapolated to other ethnic populations. Secondly, UK Biobank is not representative of the general population of the UK in terms of sociodemographic, physical, lifestyle and health-related characteristics of the general population. Although the evidence showed healthy volunteer selection bias, exposure-disease risk estimates should be generalised to the broader population and lifestyle-related factors (Batty et al., 2020). Thirdly, the present study used the ICD-10 to define the current outcome. Therefore, any study compared with these findings should be aware of the definition and error according to the ICD. For example, previous evidence showed that the translation from the ICD-9 to ICD-10 did not regularly straighten that was providing discontinuity over a period of time. As a result, they suggested that the comparison of the measure of health and health service before and after the ICD update required the concern (Mainor et al., 2019). Lastly, the study could not rule out unobserved, unmeasured confounding as with any observational studies.

The primary hypotheses were that (1) markers of central adiposity would be more strongly associated with incident T2D than general measures such as BMI; (2) these associations would differ by sex; and (3) central adiposity markers would demonstrate superior predictive performance.

The current results supported all three hypotheses. Central adiposity markers such as WHtR and ARI showed stronger associations with T2D risk than BMI. Stratified analyses revealed sex-specific differences in the strength and shape of

these associations (detailed in Chapter 6). Additionally, WHtR outperformed other markers in predictive analyses, confirming its potential clinical utility in the early identification of high-risk individuals.

6.6 Conclusion

Most anthropometric-derived indicators were associated with a higher risk of T2D, although the strength of association and predictive performance varied. WHtR demonstrated the strongest association and highest predictive ability, outperforming both traditional (BMI) and complex indices (e.g., VAI, ABSI). This suggests that WHtR may be the most suitable marker for clinical and public health use in white-European populations. Clinical implications of these findings are substantial. WHtR is an inexpensive and easily interpretable measure that could enhance T2D risk stratification in primary care. Its routine use could support early identification and intervention, potentially reducing the growing burden of T2D. Future research should focus on developing population-specific cut-off values, validating findings in other ethnic groups, and assessing how WHtR can be integrated into existing risk prediction models to guide prevention strategies.

6.7 Reference Chapter 6

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6.8 Additional File Chapter 6

Table S6-1 Anthropometric-derived indicators formulas

Markers	Formulas
A Body Shape Index (ABSI)(Krakauer and Krakauer, 2012)	Waist circumference / (Body mass index ^{2/3} × Height ^{1/2})
Hip Index _{women} (HI)(Christakoudi et al., 2021)	Hip circumference × Body mass ^{-0.482} × Height ^{0.310}
Hip Index _{men} (HI)(Christakoudi et al., 2021)	Hip circumference × Body mass ^{-2/5} × Height ^{1/5}
Visceral Adiposity Index _{women} (VAI)(Amato et al., 2010)	(Waist circumference / 36.58 + (1.89 × Body mass index)) × (Triglyceride / 0.81) × (1.52 / High-density lipoprotein cholesterol)
Visceral Adiposity Index _{men} (VAI)(Amato et al., 2010)	(Waist circumference / 39.68 + (1.88 × Body mass index)) × (Triglyceride / 1.03) × (1.31 / High-density lipoprotein cholesterol)

Table S6-2 Characteristics by sex

Characteristics	Women	Men
	88,557 (55.0%)	72,570 (45.0%)
Age (year), mean \pm SD	56.5 \pm 7.9	56.7 \pm 8.1
Townsend deprivation index, n (%)		
Lower deprivation	31,428 (35.5)	26,208 (36.1)
Middle deprivation	31,357 (35.4)	25,285 (34.8)
Higher deprivation	25,772 (29.1)	21,077 (29.1)
Smoking, n (%)		
Never	52,969 (59.8)	36,601 (50.5)
Previous	28,344 (32.0)	27,890 (38.4)
Current	7,244 (8.2)	8,079 (11.1)
Alcohol intake, n (%)		
Daily or almost daily	14,903 (16.8)	18,962 (26.1)
3-4 times a week	19,506 (22.1)	20,484 (28.2)
Once or twice a week	24,215 (27.3)	19,412 (26.8)
1-3 times a month	11,803 (13.3)	6,190 (8.5)
Special occasions only	11,661 (13.2)	4,281 (5.9)

Never	6,469 (7.3)	3,241 (4.5)
Body mass index (kg/m²), mean ± SD	26.8 ± 4.8	27.6 ± 3.9
Height (cm), mean ± SD	162.6 ± 6.2	175.9 ± 6.8
WC (cm), mean ± SD	83.6 ± 11.7	96.1 ± 10.6
Body mass (kg), mean ± SD	70.7 ± 13.2	85.4 ± 13.5
ABSI, mean ± SD	0.07 ± 0.005	0.08 ± 0.004
HC (cm), mean ± SD	102.8 ± 9.7	103.1 ± 7.0
WHR, mean ± SD	0.8 ± 0.07	0.9 ± 0.06
WHtR, mean ± SD	0.5 ± 0.07	0.6 ± 0.06
ARI, mean ± SD	-0.2 ± 1.58	-0.1 ± 1.52
HI, mean ± SD	0.07 ± 0.008	0.07 ± 0.006
VAI, mean ± SD	1.9 ± 1.5	2.2 ± 1.7
Fruits and vegetables (portion/day), mean ± SD	4.4 ± 2.2	3.8 ± 2.3
Red meat (portion/week), mean ± SD	2.0 ± 1.3	2.3 ± 1.4
Processed meat (portion/week), mean ± SD	1.6 ± 1.0	2.2 ± 1.0
Leisure screen time (hour/day), mean ± SD	4.6 ± 1.9	5.4 ± 2.3
Sleeping time, n (%)		

<7 hrs a day	66,972 (75.6)	54,448 (75.0)
7 - 8 hrs a day	20,207 (22.8)	17,184 (23.7)
>9 hrs a day	1,378 (1.6)	938 (1.3)
Type of PA, n (%)		
Walking for pleasure	70,715 (79.9)	53,723 (74.0)
Other exercises	10,263 (11.6)	10,034 (13.8)
Strenuous sports	298 (0.3)	998 (1.4)
Light DIY	5,917 (6.7)	5,017 (6.9)
Heavy DIY	1,364 (1.5)	2,798 (3.9)

Data are presented as mean \pm standard deviation (SD) for continuous variables and as n (%) for categorical variables. ABSI, A Body Shape Index; ARI, anthropometric risk index; DIY, do-it-yourself; HC, hip circumference; HI, hip index; PA, physical activity; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; VAI, visceral adiposity index.

Table S6-3 Association between anthropometric-derived indicators and type 2 diabetes incidence in white Europeans

Marker	Total	Event	Model 1		Model 2	
			HR (95% CI)	p-value	HR (95% CI)	p-value
Height	161,127	6,315	0.92 (0.89; 0.94)	<0.001	0.94 (0.92; 0.97)	<0.001
Body mass			1.89 (1.85; 1.92)	<0.001	1.81 (1.77; 1.84)	<0.001
ABSI			1.39 (1.35; 1.42)	<0.001	1.35 (1.31; 1.38)	<0.001
BMI			1.96 (1.93; 2.00)	<0.001	1.88 (1.85; 1.92)	<0.001
WC			1.71 (1.68; 1.74)	<0.001	1.63 (1.60; 1.66)	<0.001
HC			1.71 (1.68; 1.74)	<0.001	1.63 (1.60; 1.66)	<0.001
WHR			1.50 (1.49; 1.52)	<0.001	1.51 (1.5; 1.53)	<0.001
WHtR			2.17 (2.13; 2.22)	<0.001	2.08 (2.03; 2.12)	<0.001
VAI			1.49 (1.47; 1.50)	<0.001	1.43 (1.41; 1.45)	<0.001
HI			0.46 (0.45; 0.47)	<0.001	0.49 (0.48; 0.50)	<0.001
ARI			1.70 (1.67; 1.72)	<0.001	1.64 (1.62; 1.67)	<0.001

Data are presented as hazard ratios (HRs) with their confidence intervals (95% CIs) per 1 standard deviation increment in each adiposity marker. Model 1 was adjusted for sex, age, and deprivation. Model 2 was included for Model 1 plus smoking, alcohol, fruit & vegetables, red meat, processed meat, type of physical activity and leisure screen time. All analyses were conducted using 2-year landmark analyses and excluding participants with type 1, type 2 diabetes or unknown diabetes at baseline. Standard deviation for height; 9.25, weight; 15.15, ABSI; 0.01, BMI; 4.45, WC; 12.8, HC; 8.6, WHR; 0.09, WHtR; 0.07, VAI (women);

1.67, VAI (men); 1.45, HI (women); 0.01, HI (men); 0.01 and ARI; 1.55. ABSI, A Body Shape Index; ARI, anthropometric risk index; BMI, body mass index; HC, hip circumference; HI, hip index; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; VAI, visceral adiposity index.

Table S6-4 C-index of comparison of BMI with anthropometric-derived indicators for all participants

Marker	Adiposity Markers (95% CI)	BMI (95% CI)	Δ C (95% CI)	p-value
Height	0.66 (0.66; 0.67)	0.76 (0.76; 0.77)	0.10 (0.10; 0.11)	<0.001
Body mass	0.74 (0.74; 0.75)		0.02 (0.02; 0.02)	<0.001
ABSI	0.69 (0.68; 0.69)		0.08 (0.07; 0.08)	<0.001
WC	0.72 (0.72; 0.73)		0.04 (0.04; 0.04)	<0.001
HC	0.72 (0.72; 0.73)		0.04 (0.04; 0.04)	<0.001
WHR	0.74 (0.74; 0.75)		0.02 (0.02; 0.03)	<0.001
WHtR	0.78 (0.77; 0.78)		-0.01 (-0.02; -0.01)	<0.001
VAI	0.73 (0.72; 0.74)		0.03 (0.03; 0.04)	<0.001
HI	0.74 (0.74; 0.75)		0.02 (0.02; 0.02)	<0.001
ARI	0.77 (0.77; 0.78)		-0.01 (-0.01; -0.01)	<0.001

Δ C (95% CI): Difference between C-indices with the BMI model and their 95% confidence intervals (95% CIs), **P:** p-value for Δ C. The analysis was adjusted for age, sex, systolic blood pressure and family history of diabetes. All analyses excluded participants with type 1, type 2 diabetes or unknown diabetes at baseline. **ABSI,** A Body Shape Index; **ARI,** anthropometric risk index; **BMI,** body mass index; **HC,** hip circumference; **HI,** hip index; **WC,** waist circumference; **WHR,** waist-to-hip ratio; **WHtR,** waist-to-height ratio; **VAI,** visceral adiposity index.

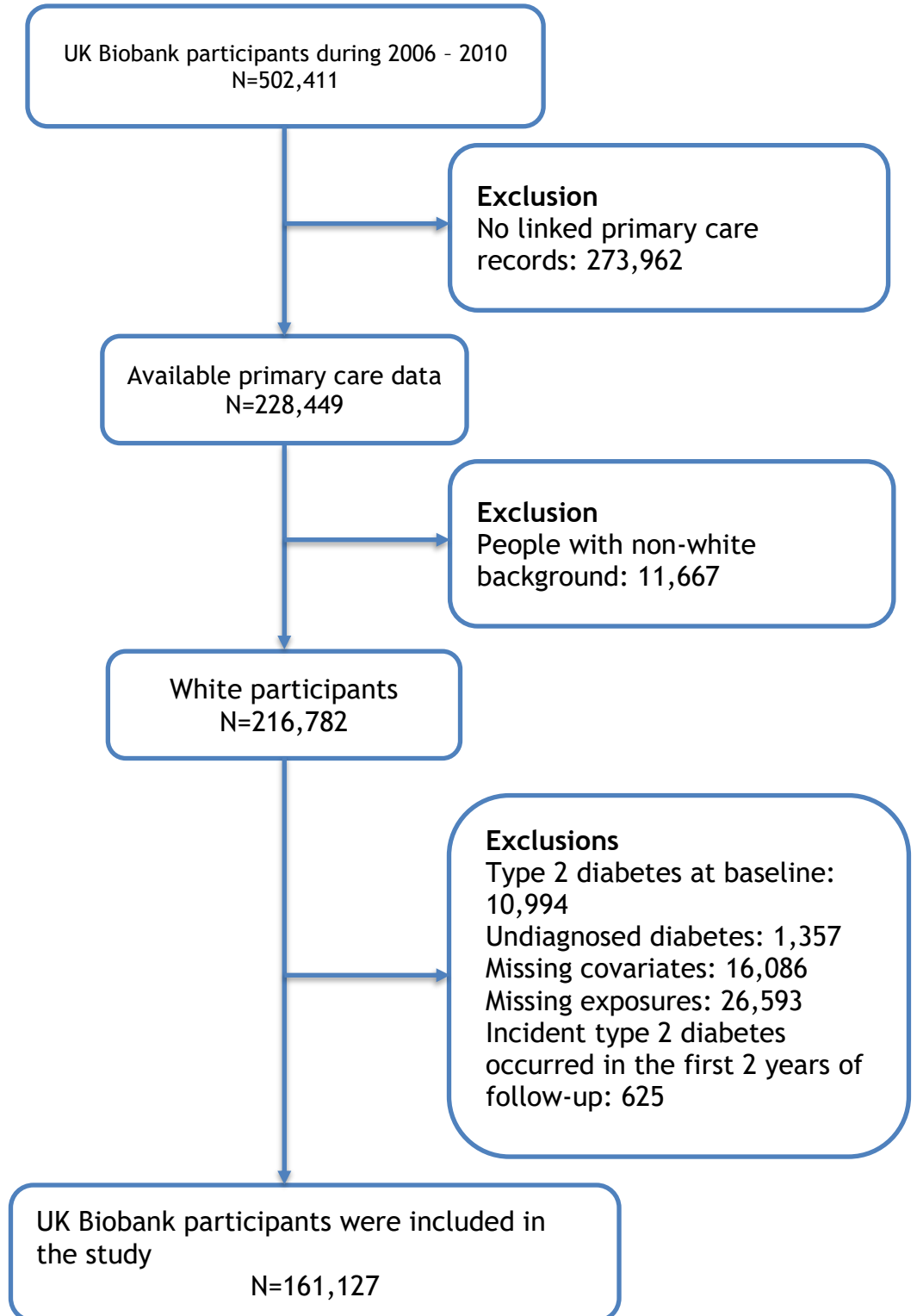


Figure S6-1 Flow chart of participants

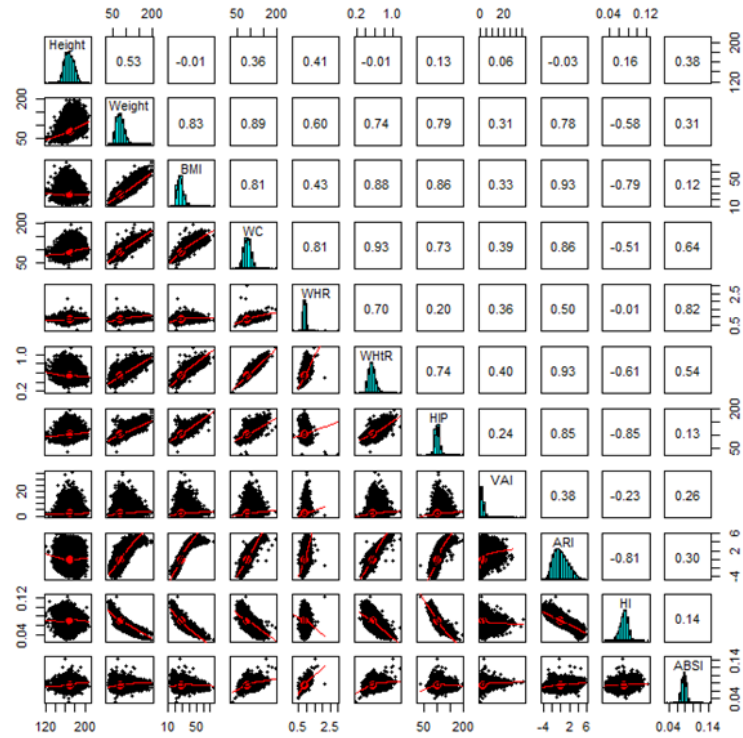


Figure S6-2 Pearson correlation coefficients between anthropometric-derived indicators

All analyses were conducted using 2-year landmark analyses, excluding participants with type 1, type 2 diabetes or unknown diabetes. ABSI, A Body Shape Index; ARI, anthropometric risk index; BMI, body mass index; HC, hip circumference; HI, hip index; WC, waist circumference; Weight, body weight; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; VAI, visceral adiposity index.

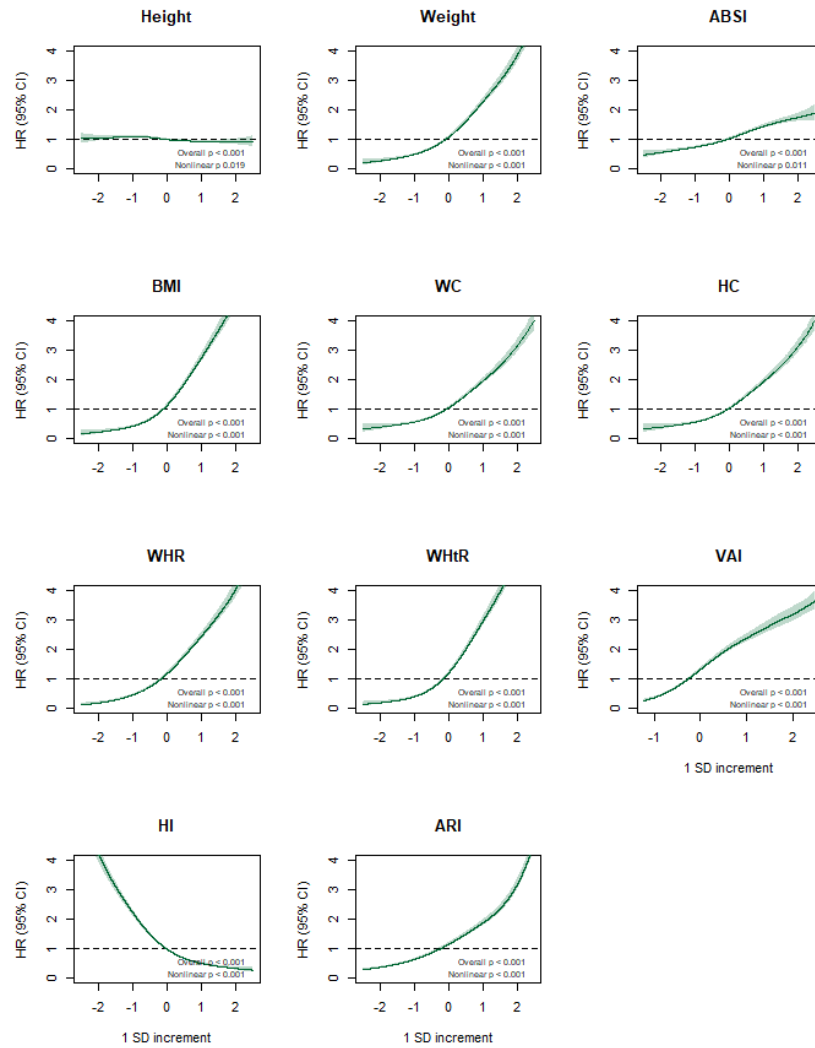


Figure S6-3 Association between anthropometric-derived indicators and incident type 2 diabetes among all participants

Penalised splines were used to present the association between anthropometric-derived markers and incident type 2 diabetes. The anthropometric markers were sex-standardised to 1-SD increment. Analyses were adjusted for sex, age, deprivation, smoking, alcohol, fruit & vegetables, red & processed meat, type of physical activity and leisure screen time. All analyses were conducted using 2-year landmark analyses and excluding participants with type 1, type 2 diabetes or unknown diabetes at baseline. ABSI, A Body Shape Index; ARI, anthropometric risk index; BMI, body mass index; HC, hip circumference; HI, hip index; WC, waist circumference; Weight, body weight; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; VAI, visceral adiposity index.

Chapter 7 General Discussion

7.1 Summary of Key Findings

This thesis examined the interrelated roles of dietary patterns, muscular strength, PA, and adiposity in shaping the risk of T2D, utilising prospective data from the UK Biobank. The findings highlight the need for an integrative approach to T2D prevention that extends beyond body weight management to include functional, behavioural, and dietary determinants.

Taking into account the link between grip strength and the onset of T2D, a distinctive feature of this thesis is the analysis of gender-specific effects. It reveals a more marked influence of lower grip strength on the risk of T2D in men than in women. Specifically, a 5 kg lower grip strength is associated with a 5% higher risk in women and an 8% higher risk in men. Although the risk increment per 5 kg reduction in grip strength might not appear substantial, the analysis of the temporal aspect, years lived with T2D based on strength levels, indicates a significantly earlier onset of T2D in individuals with lower grip strength. Women and men with low grip strength levels (14.7 kg and 27 kg, respectively) experience the onset of T2D approximately 23 and 34.5 years earlier, respectively, compared to those with higher strength levels (31 kg for women and 52 kg for men). This underscores the importance of grip strength as a vital indicator for early risk prediction of T2D, with significant differences between genders (Boonpor et al., 2021).

Chapter 4 delves more deeply than preceding studies into the impact of various PA intensities on the risk of T2D, employing accelerometers to measure PA from light to vigorous intensities. Objectively measured PA showed a clear inverse association with risk of T2D. Findings demonstrated that up to 1,500 minutes of light-intensity PA weekly is linked to a roughly 70% lower risk of T2D. Furthermore, adhering to the WHO's guideline of 150-300 minutes of moderate-intensity PA per week is associated with a 49% lower T2D risk, which increases to a 71% lower risk with over 600 minutes per week. For vigorous-intensity PA,

engaging in 25-49 minutes per week corresponds to a 38% lower risk, increasing to 64% for more than 75 minutes per week, aligning with the WHO's current recommendations for vigorous-intensity PA. Moreover, this study demonstrates that adhering to the WHO's mixed vigorous and moderate PA (MVPA) guidelines could prevent 7% of new T2D cases, while surpassing 600 minutes per week, double the recommended PA levels, could avert 41.8% of new cases (Boonpor et al., 2023a). This highlights the substantial benefits of increasing PA for T2D prevention. Additionally, it's important to note that the associations observed in this thesis are significantly larger than those derived from previous studies using self-reported PA measures (Smith et al., 2016, Ekelund et al., 2024). Recent research comparing health benefits related to mortality shows significant discrepancies when PA is quantified through self-reporting versus device-based tracking, with self-reported revealing a 40-50% underestimation in the dose-response relationships compared to device-measured PA (Ekelund et al., 2024). This work highlighted the importance of PA, with the thesis also investigating the role of diet in the risk of developing T2D.

When comparing omnivore, pesco-vegetarian, fish & poultry, and vegetarian diets, it was shown that pesco-vegetarian diets are associated with a 31% lower T2D risk, and those including fish & poultry in their diets have a 38% lower risk than diets with high meat intake. These associations were no longer significant after adjustment for BMI, highlighting adiposity partially explains the lower T2D risk in fish and fish & poultry diets. While vegetarians in this cohort reported higher intakes of fruits, vegetables, and plant-based products, they also consumed greater amounts of total carbohydrates, sugars, and fats compared with omnivores, suggesting suboptimal dietary quality. Consequently, vegetarian diets were not associated with lower T2D risk (Boonpor et al., 2022), despite previous evidence (Chen et al., 2021).

Importantly, the current thesis also examines the relative predictive value of 11 anthropometric-derived indices. The WHtR was identified as having the strongest

association with the risk of T2D among eleven evaluated anthropometric-derived measurements, doubling the risk in both women and men. Compared to BMI, WHtR demonstrates superior predictive discrimination, indicating that a greater number of T2D cases can be attributed to WHtR than to BMI. WHtR could be a more effective marker for identifying individuals at risk. This suggests that commonly used body weight-based metrics may not adequately capture T2D risk, and highlights the importance of considering fat distribution in clinical assessments. (Boonpor et al., 2023b).

Together, this thesis has, therefore, clearly advanced the understanding of the role of PA, diet and body composition in the risk of developing T2D, which highlights potential avenues for therapeutic intervention.

7.2 Possible Mechanisms Underpinning the Associations with Type 2 Diabetes

1. Dietary Patterns and Glycaemic Control

The findings of the thesis revealed that fish-based dietary patterns were associated with a lower risk T2D. This might be due to the physiological effects of dietary fats and micronutrients (De Smet, 2012). Fish diets tend to be higher in PUFAs, which are known to improve glycaemic control; cell membrane fluidity, reduce inflammatory cytokine production, enhance insulin receptor signalling and insulin resistance (Coelho et al., 2017). Interestingly, supplementation with fish oil-derived n-3 PUFA did not significantly improve insulin sensitivity compared to the placebo (Gao et al., 2017). However, a moderate beneficial effect could be found among individuals exhibiting at least one feature of metabolic dysfunction (Gao et al., 2017). Similarly, the latest evidence suggested that potential adverse effects were noted at supplemental long-chain omega-3 intakes exceeding 4.4 g/day (Brown et al., 2019). Another

mechanism, fish-based diets are typically lower in haem iron and AGEs, both of which contribute to oxidative stress and B-cell dysfunction (White and Collinson, 2013, Li et al., 2021).

In contrast, the absence of a protective association among vegetarians in this present cohort may be explained by poor dietary quality. Vegetarians had a similar amount of total energy intake as omnivores, but high intakes of total carbohydrates and added sugars can lead to postprandial glucose excursions, hepatic de novo lipogenesis, and ultimately ectopic fat deposition in the liver and pancreas (Marques-Lopes et al., 2001, Geidl-Flueck and Gerber, 2023, Janssen, 2024). These processes impair insulin sensitivity and may mask the anticipated benefits of plant-based diets.

2. Muscle Strength and Glucose Disposal

Grip strength was strongly and independently associated with T2D risk. Physiologically, skeletal muscle accounts for up to 80% of postprandial glucose uptake (DeFronzo and Tripathy, 2009, DeFronzoMandarino and Ferrannini, 2004). Low muscle strength has been increasingly recognised as both a marker and a potential contributor to impaired glucose metabolism. It may reflect underlying impairments in muscular insulin sensitivity and mitochondrial function, including reduced GLUT4 translocation and diminished oxidative capacity. Conversely, low strength may also be a consequence of metabolic dysfunction, as insulin resistance promotes anabolic resistance, muscle catabolism, and ectopic lipid accumulation, all of which impair muscle quality (Solis-Herrera et al., 2021, DeFronzo and Tripathy, 2009). In addition to impairing muscle quality, poor muscle quality is often associated with fat infiltration, or myosteatosis, which refers to the accumulation of fat both within muscle cells (intramyocellular lipid) and between muscle fibres (intermuscular fat) (Addison et al., 2014). The accumulation of intramyocellular lipids directly impairs insulin signalling pathways via activation of protein kinase C (PKC), which is frequently induced by

increased glucose concentrations, resulting in decreased glucose uptake in muscle and other cells, and subsequent inhibition of insulin receptor substrate (IRS) activity, which are essential for glucose elimination induced by insulin in muscle tissue, resulting in promoting glucose uptake and glycogen synthesis (Rod K. Dishman et al., 2022, ThironeHuang and Klip, 2006). In such bi-directional relationships, glucose uptake is compromised, leading to increased circulating glucose and promoting compensatory hyperinsulinaemia.

3. Physical Activity and Metabolic Regulation

The inverse association between objectively measured PA and T2D risk can be explained through several well-established physiological pathways. Exercise training enhances AMP-activated protein kinase (AMPK) activation, which promotes glucose uptake, fatty acid oxidation, and mitochondrial biogenesis. These adaptations improve insulin sensitivity in skeletal muscle independently of body weight (Hawley and Lessard, 2008). PA also reduces visceral adipose tissue, a metabolically active fat depot that secretes pro-inflammatory adipokines (e.g. TNF- α , IL-6), which play a role in disrupting insulin receptor signalling and pancreatic β -cell function and inhibits adiponectin, a hormone that enhances insulin action (Rod K. Dishman et al., 2022, Farrell and Turgeon, 2023, DeFronzo and Tripathy, 2009).

4. Central Adiposity and Systemic Inflammation

Among all anthropometric-derived indices examined, WHtR most strongly predicted T2D, highlighting the role of fat distribution over total fat mass. Visceral fat, which WHtR effectively captures (Nahorna and Baur, 2025), is particularly detrimental due to its endocrine activity. It secretes pro-inflammatory cytokines, contributes to lipotoxicity, and increases circulating free fatty acids, which interfere with hepatic and peripheral insulin signalling, leading to hepatic insulin resistance, which stimulates gluconeogenesis and

contributes to fasting hyperglycaemia (Heymsfield and Wadden, 2017, Solis-Herrera et al., 2021). Over time, sustained metabolic stress, which refers to the chronic and progressive disruption of normal metabolic homeostasis, often resulting from central adiposity, particularly visceral fat, impairs β -cell function, leading to a progressive decline in insulin secretion and the onset of clinical T2D (Sniderman et al., 2007).

5. Sociodemographic Modifiers of Physiology and Behaviour

Sociodemographic factors, including sex, ethnicity, and socioeconomic status, modify both exposure levels and physiological vulnerability to T2D (FletcherGulanick and Lamendola, 2002, Tabák et al., 2012). For instance, women generally have lower grip strength than men, while South Asians tend to exhibit greater visceral fat deposition at lower BMI levels, partially explaining their elevated risk of T2D (Sniderman et al., 2007).

To conclude, diet, muscle strength, PA, and fat distribution are likely to influence T2D risk through overlapping and biologically plausible mechanisms, namely, insulin resistance, inflammation, and ectopic fat accumulation, especially in skeletal muscle. These exposures may be modified by sociodemographic context. The findings underscore the importance of a physiologically informed and multidimensional approach for the early identification and prevention of T2D.

7.3 Implications of the Findings

The NCD Countdown 2030 report underscores diabetes as one of the leading causes of NCD mortality globally, setting an ambitious goal to reduce premature mortality from NCDs by one-third by 2030 (Bennett et al., 2018). This objective necessitates a focused effort on identifying and modifying risk factors for T2D to attenuate its incidence and associated health burden. Given the multifactorial

nature of T2D, encompassing both non-modifiable and modifiable risk factors, there is a significant emphasis on developing risk prediction tools to identify individuals at elevated risk and implementing lifestyle interventions to mitigate or delay disease onset.

Among potential predictors, relative grip strength emerges as a valuable indicator, especially for men exhibiting lower muscle strength, suggesting an association with increased T2D risk. The robust inverse association between grip strength and incident T2D, independent of BMI, diet, and PA, suggests that muscular strength is a valuable functional marker of metabolic health. Its simplicity and low cost make it suitable for broad clinical implementation, particularly in resource-constrained settings. However, further research is required to elucidate the relationship between muscle strength and T2D, including exploring alternative markers such as muscle mass and muscle quality. Understanding the timeline of muscle strength decline is crucial for determining the optimal period for implementing muscle strength screenings as a preventive measure against T2D. Although the findings from this thesis are prospective and do not establish causality, future studies employing methodologies such as MR could provide causal evidence linking muscle strength to T2D risk.

The identification of WHtR as the most consistent and strongest predictor of T2D highlights the limitations of BMI as a sole measure of adiposity. WHtR, as a proxy for visceral fat, better captures the pathogenic potential of central fat accumulation, which is known to drive inflammation, ectopic fat deposition, and insulin resistance. This finding supports recent calls to adopt WHtR as a routine screening tool in both clinical and public health settings. However, the effectiveness of WHtR across different age groups, ethnicities, and the establishment of clinically relevant cut-off points requires validation through clinical trials or causal modelling techniques.

From a dietary pattern perspective, fish-based diets may be encouraged as part of public health strategies aimed at lowering the risk of T2D, given their potential metabolic benefits. In this study, vegetarian dietary patterns were not associated with a lower risk of T2D, which may be attributed to suboptimal overall dietary quality among vegetarians. These findings underscore the importance of emphasising healthy food choices within vegetarian diets to achieve potential metabolic benefits.

Obesity's role as a mediator in the relationship between emerging risk factors and T2D underscores the critical importance of addressing body mass. Despite challenges in achieving significant body weight loss through behavioural interventions, robust evidence from randomised clinical trials, for instance, the DiRECT, showed that 10-15 kg of sustained body weight loss can lead to clinical remission in nearly half of people with newly diagnosed T2D (Lean et al., 2018, Lean et al., 2019). This highlights the need for further research into combining dietary interventions with exercise programs to enhance the likelihood of T2D remission.

Additionally, this thesis challenges the current PA recommendations for T2D prevention, which are based on self-reported evidence that may not accurately reflect the true dose-response relationship between PA and T2D risk. These findings suggest that benefits associated with varying PA intensities are greater than previously reported, indicating a need for further research to establish device-based PA guidelines that accurately define the minimum necessary activity levels for T2D prevention. Although this present study focuses on the British population from the UK Biobank, there is a pressing need for similar research across different ethnic groups and global populations to develop universally applicable recommendations for T2D prevention.

Moreover, this work highlights an often-overlooked aspect of PA in T2D prevention: the role of light-intensity PA. Current guidelines predominantly

advocate for MVPA, overlooking the potential benefits of light-intensity activities. These activities account for the majority of PA time for many individuals and could offer a more accessible means of reducing T2D risk, especially for those unable to engage in more strenuous exercise. This thesis proposes that even modest increases in light PA are linked with a significant reduction in T2D risk. However, to solidify this claim, further research is imperative. Observational studies and analyses using MR should be pursued to demonstrate the impact of light-intensity PA on T2D prevention comprehensively. Overall, the observed risk reduction in the most active participants, independent of adiposity, suggests direct physiological benefits including improved insulin sensitivity, reduced inflammation, and enhanced skeletal muscle metabolism. This supports the inclusion of structured activity promotion in T2D prevention strategies, irrespective of body weight loss outcomes.

Sociodemographic factors, including sex, age and ethnicity, are shown to modify both exposure distributions and T2D risk. These findings underscore the importance of targeted, equity-focused interventions that account for sociocultural context and structural determinants of health.

Finally, the integration of these findings supports a link between lifestyle and physiological exposures to T2D via central adiposity (i.e. WHtR). These suggest that addressing only one risk domain (e.g., body mass) is insufficient. Instead, multidimensional interventions targeting diet, physical function, and habitual activity are likely to yield more effective and sustainable prevention outcomes.

7.4 What Modifiable Factors Were The Most Important for Type 2 Diabetes Risk?

Of all the factors examined, central adiposity, captured by WHtR, demonstrated the strongest and most consistent association with incident T2D, surpassing BMI, PA, muscle strength, and dietary patterns in predictive utility. Although higher PA levels, greater muscular strength, and adherence to fish-based diets were independently associated with lower risk of T2D, these associations were attenuated after adjustment for adiposity, indicating partial mediation (Boonpor et al., 2021, Boonpor et al., 2022, Boonpor et al., 2023a, Boonpor et al., 2023b). Also, WHtR could play a central role linking all variables. For example, diet could lead to changes in WHtR. Lower WHtR could also indicate a leaner body and better strength-to-mass ratio, which would be indicated as a better grip strength. These findings underscore the central role of visceral adiposity in T2D aetiology and support the use of WHtR as a practical and informative marker for risk stratification.

While central adiposity demonstrated the strongest association with incident T2D in this study, its modifiability may be more challenging relative to other lifestyle factors (Franz et al., 2007). Achieving a 1-SD reduction in WHtR typically requires sustained body weight loss through structured dietary and PA interventions, which can be challenging to achieve and maintain in populations (Lean et al., 2018, Pinho et al., 2018). In contrast, gains in muscular strength, such as a 5 kg increase in grip strength, may be more attainable through targeted resistance training and regular exercise, particularly among older adults or those previously inactive (BooraMalik and Kaur, 2024, Vaishya et al., 2024, Peterson et al., 2010). Similarly, increasing PA to >600 minutes per week, while ambitious, is behaviourally modifiable through lifestyle interventions and structured support (Umpierre et al., 2011, Slentz et al., 2016). Dietary changes, such as shifting towards fish- and poultry-based patterns, are also feasible and

can yield significant metabolic benefits. Recent evidence suggested that even short-term, whole-food diet interventions, supported by practical tools such as meal plans, grocery delivery, and counselling, could lead to measurable improvements in diet quality and participant adherence, with high satisfaction and retention rates (Sneed et al., 2024). However, the effects of dietary change on T2D risk appear to be partly mediated by reductions in adiposity (Satija et al., 2016). Thus, modifications to dietary intake behaviour strategies should incorporate achieving sustainable body weight loss. Collectively, while WHtR remains the strongest predictor of T2D risk, improvements in muscle strength, PA, and dietary quality are more readily modifiable and remain essential targets for public health interventions, both directly and through their impact on adiposity.

7.5 Novelty of the Thesis

A key contribution of this thesis is its integrative and harmonised analytical approach, which is rarely accomplished in large-scale epidemiological research utilising the UK Biobank. This thesis employs consistent methodologies to assess grip strength, device-measured PA, dietary patterns, and multidimensional adiposity-related measures, facilitating direct comparisons and synthesis of their consequences for T2D risk, in contrast to previous research that often analyses lifestyle exposures in isolation. The incorporation of absolute and relative strength metrics, comprehensive accelerometer-derived movement intensities, dual dietary assessments (FFQ and 24-hour dietary recall), and advanced nonparametric adiposity mediation analyses enhances the current body of literature. These elements create a unified framework that elucidates the interaction between behavioural and physiological pathways in influencing T2D risk, providing a more comprehensive and translational understanding of T2D aetiology.

7.6 Future Research Directions

Although this thesis provides robust evidence on the associations between diet, PA, muscular strength, and adiposity with T2D risk, several key areas require further investigation to strengthen causal understanding and inform practical interventions. First, the observational nature of this work limits causal inference; therefore, future research should employ approaches such as MR, causal mediation analyses, and randomised controlled trials to disentangle direct effects from confounding, particularly regarding the role of grip strength and dietary quality. Second, dietary assessment in this thesis relied on baseline self-report and broad food categories, which may introduce measurement error and fail to capture diet quality over time. Studies incorporating repeated dietary measurements, nutrient profiling, and food substitution models (e.g., replacing red meat with plant or fish-based proteins) are needed to clarify the specific components driving risk reduction and to assess adherence trajectories.

Third, grip strength served as a useful proxy for muscle strength, yet future studies should integrate direct measures of muscle quality and function, such as DXA, MRI, and muscle biopsy-derived mitochondrial assays, to elucidate the mechanisms linking muscle health to glycaemic control and insulin sensitivity. Fourth, given the marked sex differences and the known ethnic variability in adiposity distribution and T2D risk, future research should adopt life-course and stratified approaches, examining whether critical periods such as middle or older age, pregnancy, and menopause modify these associations, and designing culturally tailored prevention strategies. Fifth, multicomponent interventions targeting diet, PA, and muscle strengthening simultaneously should be prioritised, as integrated behavioural strategies are likely to achieve synergistic benefits for T2D prevention beyond single-risk-factor interventions.

Finally, translational research and implementation science are essential to ensure findings from large cohorts like the UK Biobank can be adapted for real-

world settings. In particular, the adoption of simple screening tools such as WHtR and grip strength into primary care and community-based programmes should be tested in diverse populations to improve early detection and equitable prevention. Addressing these gaps will advance the field towards precision prevention, allowing for interventions that are evidence-based, mechanistically informed, and scalable across global contexts.

7.7 Strengths and Limitations

While robust in several aspects, the thesis also presents certain limitations that should be acknowledged for a comprehensive understanding.

The strengths of the studies conducted as part of thesis are described below:

- **Large Prospective Cohort:** Utilising a substantial prospective cohort provided an extensive participant base and numerous factors, enabling a detailed examination of the associations between emerging risk factors and T2D incidence. It also facilitated the exploration of interactions with key T2D confounders, including sociodemographic, lifestyle, adiposity, and biomarker factors.
- **Counterfactual Causal Framework:** The application of this framework, along with advanced analysis techniques, allowed for quantifying the mediation role and assessing predictive risk abilities.
- **Robustly Phenotype Participants:** The data from UK Biobank accumulated an extensive amount of data on behavioural, physiological, genetic, and environmental variables. These data were continually being collected, and the health conditions were linked to electronic health record data (Bešević et al., 2022). Moreover, all data collection and measurements were carried out by trained professionals.

- **Reduced Reverse Causation:** By implementing a 2-year landmark analysis and excluding individuals with pre-existing conditions, the study mitigated the impact of reverse causation.

The limitations that should be considered when interpreting the findings of this thesis are listed below:

- **Representativeness of UK Population:** The UK Biobank sample is not fully representative of the UK's general population, particularly in terms of sociodemographic and lifestyle characteristics (Fry et al., 2017). Therefore, external validation of the findings is necessary.
- **Residual and Unmeasured Confounding:** As with any observational study, there is a possibility of residual and unmeasured confounding factors. Therefore, while informative, the study cannot definitively establish causality.
- **Baseline Data:** Most variables were collected at baseline and may have changed over time. Future studies should consider these potential changes and evaluate the robustness of the results using follow-up data.
- **Dietary Measurement Limitations:** One of the most significant limitations lies in the dietary data collection methods in the UK Biobank. FFQs and 24-hour dietary recall are prone to several well-established biases:
 - **Recall bias and misreporting:** Participants are required to estimate their average intake over long periods, which increases susceptibility to memory lapses and systematic underreporting, especially among individuals with overweight or obesity (NaskaLagiou and Lagiou, 2017).
 - **Lack of detail on preparation and processing:** FFQs typically do not capture nuances such as cooking methods, food quality (e.g. wholegrain vs refined), or portion size variability, which are relevant to T2D risk.
 - **Measurement error and non-differential misclassification:** Errors in reporting are likely to be random with respect to future T2D status,

leading to attenuation of effect estimates (NaskaLagiou and Lagiou, 2017).

- **Temporal mismatch:** Dietary exposures may change over time, but in most participants, only a single baseline FFQ was available. This may not reflect long-term dietary patterns or the relevant exposure window for diabetes development.
- Although the 24-hour dietary recall data (WebQ) allowed for more precise estimates in a subsample, these were not collected systematically across all participants, reducing comparability and limiting power in sub-analyses.
- **Grip Strength Measurement:** Grip strength, while objectively assessed and reproducible, is a proxy for overall muscle function and may not fully reflect lower-body strength or total muscle mass. Furthermore, grip strength was measured at a single time point, precluding assessment of longitudinal changes that may be relevant to T2D development.
- **Lack of Repeated Measures:** Most key exposures, including diet, PA, and anthropometry, were measured only once. This limits the ability to assess trajectories, cumulative exposures, or behavioural changes over time, and increases susceptibility to regression dilution bias (Rutter et al., 2023). As a result, effect estimates may be conservative.

Together, these limitations suggest that observed associations are likely underestimates of the true relationships between lifestyle exposures and T2D risk. In particular, measurement error in dietary reporting and selection bias in the study population could have masked more substantial effects of diet or behavioural disparities. Caution is therefore warranted when interpreting null findings or generalising results to more diverse or disadvantaged populations.

7.8 Conclusions

This thesis significantly enhances the understanding of modifiable risk factors for T2D and introduces valuable insights into potential screening tools and preventive strategies. The findings highlight the utility of grip strength and WHtR as cost-effective methods to identify individuals at increased risk of developing T2D. These indicators, alongside the emphasis on the benefits of incorporating healthy dietary choices and engaging in regular PA particularly light-intensity PA, underscore the critical role of maintaining a healthy body weight in T2D prevention.

The research presented here advocates for a comprehensive approach to T2D risk management. It calls for integrating lifestyle modifications with regular monitoring of physical and anthropometric measures to address the multifaceted nature of T2D risk effectively. This approach not only offers a pathway to identifying at-risk individuals through simple and accessible means but also supports the broader goal of fostering healthy living practices that can mitigate the onset of T2D.

By laying a foundation for future investigation and public health initiatives, this thesis contributes to a growing body of evidence supporting the need for multifactorial intervention strategies. It opens avenues for further research to explore the effectiveness of these screening tools and lifestyle interventions across diverse populations, with the ultimate aim of refining and implementing public health policies that can prevent T2D or reduce its burden on a global scale.

7.9 Reference Chapter 7

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PhD Journey

I decided to do a PhD because I was curious whether there are any new factors for T2D. This question was raised while I gave the consultation to my patients in Thailand. I initially thought a PhD was only doing research. However, after the study periods, I know that it involves not only exploring the answer to the research question but also needs many skills for dealing with the PhD study, which is all challenging.

I began my studies with difficulty since I had to overcome the language barrier. The first meeting was a discussion with my supervisors to refine my research topic. I struggled to communicate what I was doing and what I had discovered. I felt that the language issue hindered my confidence and performance. Unfortunately, the pandemic happened only a few months into my PhD which meant I had even less opportunity for in-person communication with them. However, through my efforts in English self-training and devoting regular time to interacting with my supervisors online, I managed to develop and enhance my communication skills.

I found learning statistical application programs including Stata and R, complicated and was another obstacle to overcome. To address this, I studied the program manuals intensively in English and in Thai language to help understand the programs tools and features. The relatively short timeframes required for programme implementation and subsequent analysis were my significant challenge in studying and obtaining the desired outcomes. Fortunately, I first received support from my supervisors to initially undertake short online courses about the applications to establish the fundamentals. With continued use of the applications throughout my PhD for various types of analysis I have significantly grown my knowledge and skills such that I believe I can apply these very effectively in my future research leadership roles.

During the period where I had heightened anxiety about my English language ability, I still accepted opportunities to attend international conferences. Although I was very nervous about these events, I increased my English practising activities so that I gained more experience before attending. When the pandemic eased, I presented my work in in-person conferences. I met and exchanged my research with researchers from all over the world. I was thrilled and felt comfortable to show my contribution in English, which has really gained back my confidence.

After a few years of PhD study, I have learnt that obstacles to studying serve as my challenge to overcome through hard work and dedication to achieve successful outcomes. I also know that a PhD is about research investigation, academic writing, short course training, meetings and discussions, postgrad teaching and mentoring, manuscript submission and revisions, academic engagements, as well as effective time management and leadership. All of those experiences improve my ability, performance, and confidence, which is extremely useful for my career progression.