Metabolically healthy obesity

Associations with physical activity, sedentary behaviour, and metabolic decline

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Declaration of Authorship

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

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Abstract

Background: Obesity is a major threat to public health given its strong links with cardiometabolic morbidity and premature mortality. One-third of obese adults are metabolically healthy, but little is known about modifiable determinants of this state or its progression over time.

Aims: To determine whether physical activity and sedentary behaviour distinguish healthy from unhealthy obesity, and whether healthy obese adults have increased risk for developing metabolic ill-health and type 2 diabetes.

Methods: Data were drawn from up to 5427 men and women participating in the Whitehall II cohort study. Normal-weight, overweight, and obese adults were considered healthy if they had <2 of 5 metabolic risk factors (hypertension, low HDL-cholesterol, high triglycerides, high blood glucose, and insulin resistance). Associations of self-reported moderate-to-vigorous physical activity and leisure sitting time with prevalence and 15-year incidence of metabolic risk factor clustering were examined among healthy obese adults. Differences in accelerometer-assessed total physical activity were also examined between healthy and unhealthy obese groups. Metabolic risk factor incidence among initially healthy obese adults was described, and published risk estimates of incident type 2 diabetes were systematically searched and meta-analysed.

Results: Neither high self-reported moderate-to-vigorous physical activity nor low self-reported leisure sitting was associated with health among obese adults. Higher total physical activity among healthy versus unhealthy obese adults was evident through accelerometer assessment only (p=0.002). After 20 years, 52% of initially healthy obese adults were unhealthy obese, with insulin resistance being most commonly incident. Meta-analyses of 8 studies indicated that healthy obese adults have 4.03 (95% CI=2.66-6.09) times greater risk of incident type 2 diabetes than healthy normal-weight adults.

Conclusions: Higher physical activity rather than lower sedentary behaviour distinguishes healthy from unhealthy obesity. Healthy obesity is strongly linked with future insulin resistance and type 2 diabetes, suggesting that it is not a harmless condition.

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List of abbreviations

BMI – Body mass index

NCEP ATP III – National Cholesterol Education Program Adult Treatment Panel III

kg/m² - Kilograms per meters-squared

IDF – International Diabetes Federation

mmHg – Millimeters of mercury

mmol/l – Millimoles per litre

µg/min – Micrograms per minute

mg/min – Milligrams per minute

mg/dL – Milligrams per deciliter

CT – Computerized tomography

MRI – Magnetic resonance imaging

HbA1c – Glycated haemoglobin

MET – Metabolic equivalent

IL-6 – Interleukin-6

CRP – C-reactive protein

TNF – Tumour necrosis factor

mLO²/kg/min – Millilitres of oxygen per kilogram per minute

VO² - Volume of oxygen

HDL – High density lipoprotein

TV – Television

HOMA – Homeostatic model assessment

NHANES – National Health and Nutrition Examination Survey

mg – Milligravity

mg/week – Milligravity per week

km/h – Kilometers per hour

PR – Prevalence ratio

CI – Confidence interval

IR – Incidence ratio

AIC – Akaike information criteria

MOOSE – Meta-analysis of Observational Studies in Epidemiology

ELSA – English Longitudinal Study of Ageing

β – Standardised regression coefficient

B – Unstandardised regression coefficient

NA – Not applicable

RR – Relative risk

OR – Odds ratio

HR – Hazard ratio

N – Sample size

NEAT – Non-exercise activity thermogenesis

Section 1: Introduction

This section will first introduce obesity as a public health issue, along with its aetiology and associated chronic disease outcomes. The idea of a 'healthy' type of obesity will be introduced, along with its characterising features and known disease risks. The potential role of physical activity and sedentary behaviour in healthy obesity will be discussed based on their known associations with metabolic health. This section ends with research priorities for improving the evidence base on healthy obesity which together inspired the aims and objectives of this thesis.

1.1 Obesity: a public health priority

Human life requires the consumption of energy in the form of food, and optimal living requires that this consumption be balanced by the expenditure of energy in the form of physical activity and internal metabolic processes (1). When energy intake exceeds energy expenditure for a prolonged period of time, energy is stored in the form of excess adipose tissue, also known as fat. When this positive energy balance becomes high, this results in a condition clinically known as obesity (2). Obesity is most commonly measured at the individual and the population level through an anthropometric ratio known as the body mass index (BMI), which is calculated by dividing an individual's weight in kilograms by the square of their height in meters. Individuals are considered obese if their BMI is 30 kg/m^2 or higher (3).

Obesity is a major threat to public health. Higher BMI is strongly and consistently associated with a greater risk of premature all-cause mortality (4) as well as for the leading causes of death in modern societies including ischaemic heart disease, stroke, and some types of cancer (5).

These excess risks are evident for both sexes but are highest among men, and are robust to adjustment for other factors including age, prevalent disease, and smoking status. Obesity is also strongly linked with the incidence of numerous conditions including type 2 diabetes, atherosclerosis, cancers, and musculoskeletal conditions (6), which together act to reduce the quality of life for individuals affected while also placing a substantial economic burden on health and social care systems in developed countries. Annual treatment costs for chronic diseases directly attributable to obesity are projected to increase by $66 billion in the US and £2 billion in the UK by 2030 (7).

The primary pathway linking obesity with the development of disease and early death is dysregulated metabolism, which pertains to inefficiencies in the balancing and use of energy in the body. Carrying excess body fat is thought to result in a series of metabolic disturbances including impaired circulation of blood throughout the body as indicated by higher than normal systolic or diastolic blood pressure, impaired use of glucose by body tissues as indicated by abnormally high levels of glucose in the blood, and impaired use of lipids as indicated by unbalanced levels of cholesterol and triglycerides in the blood (1). These risk factors are closely linked and often appear together. When they do, they collectively form a condition known as metabolic risk factor clustering (1).

Prevalence of obesity has increased dramatically over the past three decades in both developed and developing countries, with upwards of 205 million men and 297 million women considered obese as of 2008 (8). The United Kingdom stands near the forefront of the obesity epidemic, with a dramatic increase in prevalence observed since 1980. As of 2012, 24% of men and 25% of women in England were considered obese, with prevalence being highest among adults of middle age (9). It has also been estimated that 11 million new cases of obesity in the UK are to be expected by 2030 (7). In light of demographic transitions taking place in developed countries including the United Kingdom, a higher proportion of the general population is entering middle-age (10). A better understanding of the aetiology and consequences of obesity in mid-life could have important implications for preventing an array of deleterious chronic diseases that

commonly emerge at this time in the life-course, and could thus have direct implications for supporting a healthy ageing process.

The range of factors considered aetiologically relevant to obesity is wide. Individual-level factors known to increase obesity risk include behaviours related to lifestyle; most predominantly an energy-dense/nutrient-poor diet and low levels of physical activity (11). These direct determinants may interact with other individual-level factors including genetic susceptibilities for the storage of body fat (12, 13), increased appetite, and decreased satiety responsiveness (14). Other susceptibilities include ethnicity (15) and socioeconomic factors of low educational attainment and low income (16) which may influence patterns of energy consumption and expenditure. Aspects of the wider contextual environment may also increase obesity risk, including residential deprivation (17) which may influence the deposition and distribution of body fat either directly through psychosocial stress pathways or indirectly through structuring patterns of diet and physical activity (11, 18-20).

Despite substantial advances in the knowledge base in recent decades, obesity remains notoriously difficult to manage. Individual-level strategies aimed at promoting a negative energy balance through decreasing energy intake and increasing energy expenditure tend to show only modest reductions in body weight (21), with effects rarely maintained in the long term (22). Population-level obesity management strategies are thought to have the greatest potential for success, such as those involving public intervention and market regulation of obesogenic food environments (23), but require greater investment and coordination among stakeholders to improve effectiveness (24). Thus, with the increasing prevalence of obesity in England as well as in numerous other developed and developing countries, and with the limited success of individual-level weight-reduction strategies, there is a clear need to look deeper into the aetiology and consequences of obesity and challenge traditional views held by researchers, clinicians, and the public alike.

1.2 A ‘healthy’ type of obesity

One recent approach to understanding obesity has involved conceptualising it as a separate entity from ‘health’, by partitioning the components of metabolic risk factor clustering from obesity status as defined by BMI. Viewing obesity in this way offers some intriguing insights. Estimates using nationally representative data from the United States and Italy indicate that obesity is a heterogeneous condition with regards to metabolic health; nearly one-third of obese adults in the general population present without a clustering of metabolic abnormalities that typically accompany excess body fat and display normal levels of blood glucose, insulin sensitivity, blood pressure, and blood lipids – forming what is known as *metabolically healthy obesity* (25, 26) (referred to as ‘healthy obesity’ from this point forward). Likewise, about one quarter of the non-obese population presents with a clustering of the same metabolic abnormalities – known as the *metabolically unhealthy non-obese*, or *normal weight-metabolically obese* phenotype (25), depending on the BMI group specified.

There is no single universal definition of healthy obesity. However, most studies in the literature define healthy obesity either based on insulin profiles alone such as being highly insulin sensitive, or based on some measure of metabolic risk factor clustering. Several consensus organizations have favoured the latter method. For example, the National Cholesterol Education Program’s Adult Treatment Panel (ATP) III criteria considers an obese individual to be metabolically healthy if they have a BMI ≥ 30 kg/m² and also display ≤ 2 of the following risk factors (27): high sex-specific waist circumference, high triglycerides, low sex-specific HDL cholesterol, high blood pressure, and high fasting glucose. The International Diabetes Federation (IDF) criterion is slightly more stringent, considering an obese individual to be healthy if they display < 2 of the same risk factors, but while also considering prescription drug use as a surrogate risk factor for hypertension and dyslipidaemia (28). Yet another criterion proposed independently by Wildman et al. (2008) (25) defines an obese individual to be healthy if they

display < 2 of the same risk factors, but also considers the homeostatic model assessment (HOMA) of insulin resistance and C-reactive protein (CRP) as a marker of systemic inflammation (25). Insulin is particularly important to include in such criteria, as it is considered a central factor in human metabolism, with a role in regulating absorption of glucose from the blood for use in skeletal muscle and in the clearance of triglycerides in the blood for appropriate storage in adipose tissue (1). Evidence so far on the role of inflammation in healthy obesity is mixed. Low-grade systemic inflammation has been shown to be lower among healthy than among unhealthy obese adults (29-31), while another study reported that healthy and unhealthy obese adults, as defined by metabolic risk factor clustering, had similar levels of inflammation in adipose tissue as measured by CRP, fibrinogen, leukocyte count, and hepatic enzymes, as well as comparable adipokine levels (32). A comparison of different candidate definitions of healthy obesity is provided below in **Box 1**.

Box 1: Candidate definitions of healthy obesity	
World Health Organization, 1999	Healthy if no glucose intolerance, impaired glucose tolerance or diabetes and/or insulin resistance, and < 2 of: • Blood pressure ≥ 140/ 90 mmHg • Triglycerides ≥ 1.7 mmol/l and/or HDL cholesterol < 0.9 mmol/l (Men); < 1.00 mmol/l (Women) • Waist-hip ratio > 0.9 (Men); > 0.85 (Women) and/or BMI > 30 kg/m² • Urinary albumin excretion rate ≥ 20 μg/min or albumin:creatinine ratio ≥ 30 mg/g
National Cholesterol Education Program Adult Treatment Panel (ATP) III, 2001	Healthy if ≤ 2 of: • Fasting plasma glucose ≥ 5.6 mmol/l • Blood pressure ≥ 130/ 85 mmHg • Triglycerides ≥ 1.7 mmol/l • HDL cholesterol < 1.03 mmol/l (Men); < 1.29 mmol/l (Women) • Waist circumference > 102 cm (Men); > 88 cm (Women)
International Diabetes Federation, 2006	Healthy if waist circumference not > 102 cm (Men); > 88 cm (Women), and <2 of: • Fasting plasma glucose ≥ 5.6 mmol/ l or previously diagnosed type 2 diabetes • Blood pressure ≥ 130 / 85 mmHg or treatment of previously diagnosed hypertension • Triglycerides ≥ 1.7 mmol/l • HDL-cholesterol < 1.03 mmol/l (Men); < 1.29 mmol/ l (Women) (or specific treatment for these lipid abnormalities)
Wildman et al., 2008	Healthy if < 2 of: • Fasting glucose ≥100 mg/dL or antidiabetic medication use • Homeostatic model assessment of insulin resistance (HOMA-IR) > 5.13 (ie, the 90th percentile) • Blood pressure ≥130/85 mmHg or antihypertensive medication use • Fasting triglycerides ≥150 mg/dL • HDL cholesterol < 40 mg/dL (Men); < 50 mg/dL (Women) or lipid-lowering medication use • C-reactive protein (CRP) > 0.1 mg/L (ie, the 90th percentile)

Each criterion aims to estimate an individual's overall metabolic risk, yet none are perfect. For instance waist circumference is often considered an important component of metabolic clustering (33) and is included in both NCEP ATPIII and IDF criteria, but not in the Wildman et al. criterion. However, the inclusion of waist circumference may be problematic when examining metabolic phenotypes of obesity as defined by BMI, given that BMI and waist circumference are highly correlated, often at 0.9 on a 0-1 scale (34). This may introduce an upward bias on the classification of ill-health given that most obese adults may be assigned a high waist circumference by default. Systemic inflammation may also be an important component of metabolic risk factor clustering (35), and is absent from both NCEP ATPIII and IDF criteria, but is included in the Wildman et al. criterion. A harmonized definition of metabolic health in obese populations would certainly improve comparability between studies; however in practice, the ability to follow any criterion is determined by the availability of data, given that most studies in the literature draw upon data from cohort studies that were collected in the past for broader purposes. It is also important to note that while the binary categorization of people as either 'healthy' or 'unhealthy' has practical value for researchers and clinicians, individual metabolic risk factors are measured on a continuous scale and thus true metabolic risk is continuous rather than dichotomous in nature.

1.3 Distinguishing features of healthy obesity

Healthy obesity is most commonly defined as obesity in the absence of metabolic risk factor clustering, and so healthy obese adults are expected to differ from unhealthy obese adults on levels of metabolic risk factors, by definition. However it is of great interest to identify other physiological and behavioural factors that distinguish healthy obese adults from their unhealthy obese counterparts, as this may reveal modifiable determinants of this preferred state.

The first candidate distinguishing factor is fat distribution. Body fat can broadly be divided into two types: subcutaneous fat located in peripheral regions such as arms and legs, and visceral fat located in intra-abdominal regions within or around organs (36-38). Visceral fat is more metabolically active than subcutaneous fat and contains a higher density of insulin resistant adipocytes resulting in a direct link with system-wide insulin resistance (39-41) which is potentially independent of total body fat volume (42). Visceral fat is also linked with higher systemic inflammation (43), and when measured objectively using ultrasonography, is strongly linked with several markers of impaired glucose metabolism including higher fasting glucose, higher oral glucose tolerance values, and higher HbA1c values (44). When measured by computerized tomography (CT) or magnetic resonance imaging (MRI), greater visceral fat volume is also associated with high blood lipids (45) and hypertension (43). The close proximity of visceral fat stores to the portal vein is also thought to result in high rates of deposition of non-esterified fatty acids to the liver (1). Fat accumulated in the liver is especially toxic, with strong links with insulin resistance documented through previous work on non-alcoholic fatty liver disease (46, 47), possibly mediated through protein kinase-induced decreases in insulin signalling (48). Fat distribution is thought to involve a high degree of heritability, with as much as 48% of the variance in fat distribution, as characterised by waist circumference and skinfold thickness, being explained by genetic susceptibilities (49).

Early studies suggest that healthy obese adults have a more favourable fat distribution than unhealthy obese adults, with at least 3 population-based studies reporting a lower waist circumference, indicating lower levels of abdominal visceral fat (25, 50, 51). Other more detailed studies have shown that while the healthy obese had similar levels of total body fat and subcutaneous fat as the unhealthy obese, they demonstrated lower visceral fat (29, 52-54), and less ectopic and liver fat (55, 56). Healthy obese adults also appear to have greater thigh subcutaneous fat compared with unhealthy obese adults (51, 57, 58), which may reflect the lower inflammatory nature of lower body fat (58) or higher levels of subcutaneous fat relative to visceral fat in general. Thus, a more favourable fat distribution, characterised mostly by lower visceral, ectopic, and muscle fat, may be key features distinguishing healthy from unhealthy obesity.

Health behaviours are other attractive candidates distinguishing healthy from unhealthy obesity. A higher diet quality may be a factor, given known protective effects of fruit, vegetable, and whole-grain consumption against abnormal glucose metabolism and risk of type 2 diabetes (59, 60), as well as apparently inverse associations of high-fat diary intake with obesity and metabolic ill-health (61). One study, however, compared the consumption of an extensive array of dietary components including proteins, carbohydrates, sugar-sweetened beverages, and vitamins between healthy and unhealthy obese men and women, and found no differences in dietary intake or quality (62). Another study comparing the dietary intake of healthy and unhealthy obese adults found that healthy obese women consumed more fruit, more whole grains, and more meat and beans as protein sources, but these differences were only evident among young adult women, and not among women of older ages or among men of any age (63). Thus, evidence supporting a higher diet quality among healthy obese adults is mixed and is limited to only two studies, which do not form a sufficiently large body of evidence from which to draw firm conclusions.

Sleep duration is another candidate factor, given known adverse associations of short sleeping duration with glucose intolerance, insulin resistance, and increased risk of type 2 diabetes, which

may act directly or indirectly through disrupting appetite regulation (64). There is some indication that sleep duration may differ between healthy and unhealthy obese groups, with unhealthy obese women reporting a shorter daily sleeping duration than their healthy obese counterparts in one study (65). However, the small evidence base as it relates to healthy obesity again prevents firm conclusions. Based on the breadth and depth of evidence available on energy expenditure and human metabolism, the strongest and perhaps most plausible candidate for distinguishing healthy from unhealthy obesity is the behaviour of physical activity.

1.3.1 Physical activity and metabolic health

Physical activity is a behaviour which directly induces energy expenditure and which therefore has a key role in balancing energy stores within the body (1). Measurements of physical activity comprise 2 main components: duration, referring to the amount of time it is performed, and intensity, referring to the extent to which energy is expended per unit of time (66). Activity intensity is expressed as a metabolic equivalent (MET) value assigned from a standard compendium of energy costs, which estimates how much energy is expended relative to lying down quietly (66). According to this compendium, a physical activity is considered to be of a light intensity if the energy expended is between 1.5 and 3 METs, of a moderate intensity if the energy expended is between 3 and 6 METs, and of a vigorous intensity if the energy expended is 6 METs or higher. Large-scale observational studies consistently link greater engagement in moderate-to-vigorous physical activity with reduced risk of developing metabolic risk factor clustering (67-69) and important clinical outcomes including type 2 diabetes (70) and cardiovascular disease (71). These protective effects appear to be dose-response with regards to intensity, with the greatest protection observed for physical activity of a vigorous intensity; but with those of a moderate intensity also conferring substantial benefits (68, 72, 73).

Associations of moderate-to-vigorous physical activity with a healthy metabolic status are thought to be explained by several key mechanisms. First, physical activity promotes the sensitivity of body tissues to the hormone insulin, which in turn allows for efficient absorption of glucose into tissues and balancing of glucose levels in the blood. This is done directly by activating key proteins and genes involved in glucose metabolism (74-76) and indirectly through inducing the contraction and expansion of skeletal muscle, which as the primary site of glucose absorption from the blood, determines system-wide capacity for insulin sensitivity and resting energy expenditure (74). Physical activity also promotes the postprandial balancing of lipids in the blood after consumption of food through mediating effects of lipoprotein-lipase activation; a protein released from skeletal muscle during contraction which decreases concentrations of triglycerides (a deleterious lipid compound), and increases concentrations of high density lipoprotein (HDL) cholesterol (a beneficial lipid compound) (77, 78). Importantly, the beneficial effects of physical activity on lipid metabolism have been shown to decrease or disappear after only several days of abstaining from physical activity (77, 79, 80), indicating that physical activity must be done on a regular basis for benefits to be sustained.

Physical activity is also thought to promote a healthy circulatory system. This is done by preventing endothelial dysfunction and reducing stiffness of the arterial walls which together provide the structural basics for the efficient circulation of blood throughout the body (81). Good circulatory health is most commonly indicated by systolic and diastolic blood pressure in a normal range, with a recent meta-analysis examining over 5000 participants from 98 randomised controlled trials finding consistent evidence for lowered blood pressure in response to resistance training; activities which involve the contraction and expansion of muscle (82). However there appears to be some heterogeneity in these effects, with another meta-analysis reporting that such improvements in blood pressure were only among normotensive or pre-hypertensive groups, and not among those who were hypertensive at baseline (83). It is presently unclear whether this reflects a true lack of effect, or just a smaller body of high quality evidence on resistance training among initially hypertensive adults. Endurance activities

involving some form of aerobic training have also been shown to consistently reduce ambulatory daytime blood pressure (84), and thus engaging in both endurance and muscle strengthening activities is commonly recommended to extract the maximum benefit from physical activity for circulation (85).

There is also evidence that physical activity helps to reduce systemic low-grade inflammation (86), a factor which is linked to risk of cardiovascular disease (87, 88). This is mediated through the contraction of skeletal muscle which triggers the release of beneficial compounds such as regulatory T-cells and anti-inflammatory cytokines known as myokines (89, 90), while inhibiting the release of pro-inflammatory cytokines such as interleukin (IL)-6 and tumour necrosis factor (TNF) from tissues (89) and toll-like receptors (91). However, these beneficial effects of physical activity on inflammation are not entirely consistent among the obese population, with several randomised controlled trials failing to show reductions in markers of systemic inflammation, including CRP or IL-6, despite improvements in fitness (92, 93). The anti-inflammatory effects of physical activity among obese adults are more evident in studies which examine differences in body composition more precisely and which demonstrate selective reductions in visceral fat. For example, in a ten-month randomised trial of older adults, aerobic exercise training resulted in reduced C-reactive protein (CRP), and these effects were partly mediated through a reduction in central adiposity (94). Similarly, in a year-long trial of moderate exercise training, CRP was lowered only in women that were obese at study entry and only in participants who lost greater than 2% body fat (95). Such interventions suggest that the anti-inflammatory effects of physical activity are partly explained by adiposity-related mechanisms involved in selective reductions of visceral fat, such as a decrease in adipose-tissue macrophages in the production of IL-6. Indeed, fat distribution is itself another key factor explaining associations of physical activity with better metabolic health, with intervention studies demonstrating reductions in visceral fat in response to engagement in physical activity even in the absence of weight-loss (96, 97). As mentioned, visceral fat is highly insulin resistant and inflammatory in nature (98), and so its reduction is directly beneficial.

Physical activity may also improve the body's capacity to utilise oxygen, known as cardiorespiratory fitness (99, 100). There is a known dose-response association between engagement in physical activity and fitness level (101), and low fitness has been associated with a higher risk of having metabolic abnormalities including inflammation, hypertension, poor lipid metabolism, and insulin resistance (40, 41, 77), as well as developing metabolic risk factor clustering (102), abnormal glucose regulation, type 2 diabetes (103), cardiovascular disease, and all-cause mortality (104, 105). Such reductions in risk may be independent of BMI (102, 106), while adjusting for fitness level has removed associations between obesity status and all-cause mortality (107), together suggesting that much of the increased risk for developing chronic disease among the obese is explained by a lack of fitness and not excess body fat *per se*. Although an attractive idea, the role of obesity cannot be discounted entirely. Although it is true that obese men with high fitness show lower risk of cardiovascular disease and all-cause mortality than non-obese men with low fitness (108), and fit obese men have nearly half the risk of developing type 2 diabetes as unfit obese men, the excess risk among the obese who are fit is still substantially elevated compared with normal-weight adults who are fit (109). Indeed, the very measure of fitness requires fitness and obesity to be conceptually linked. Cardiorespiratory fitness is best measured through a maximal oxygen uptake test which involves exercising the participant until volitional exhaustion (110), resulting in a unit of measurement of millilitres of oxygen, per kilogram of body weight, per minute (mL O^2/kg/min). Thus, by definition, fitness is a function of body weight, and an increase in fitness (the numerator) requires a decrease in body weight (the denominator). Furthermore, while physical activity remains an important modifiable factor for fitness (72), an individual's capacity for fitness also depends upon genetic susceptibilities with the degree of heritability in fitness estimated to be as high as 50% (111).

At this point, it is important to distinguish healthy obesity from the widely used term 'fat and fit', as these are not the same construct. Healthy obesity, as most commonly defined in the literature, is obesity without metabolic risk factor clustering (25, 56), while 'fat and fit' is obesity with a high level of cardiorespiratory fitness (112), as specifically measured in studies for this

classification. About 33% of obese adults in the general population are considered healthy (25, 26), while only about 10% of obese adults are considered fit (113). Healthy obesity is therefore a broader classification within which many fat and fit individuals likely fall, while few healthy obese adults likely meet the criteria for fat and fit. Several studies have examined cardiorespiratory fitness or its components in relation to the healthy obese phenotype as reviewed by Ortega et al (114); the largest and most recent study of which showed healthy obese adults to have significantly higher levels of cardiorespiratory fitness than unhealthy obese adults as measured by VO^2 maximum uptake testing (115). However, as expected, healthy obese adults showed substantially lower levels of fitness than healthy normal-weight adults, indicating that the capacity for fitness is still impaired by the presence of excess body fat, and that normal-weight therefore remains the ideal body type for optimal fitness and metabolic health.

There is also emerging evidence that one's ethnic origin may influence the degree to which metabolic health is benefited by physical activity. For instance, a recent cross-sectional study of 75 South Asian men and 83 European men demonstrated that South Asians needed to perform 266 minutes of moderate-to-vigorous physical activity per week in order to realise the same reduction in metabolic risk that Europeans realised with 150 minutes per week (116). Metabolic risk in this study was based on a clustered metabolic risk score summarising all of glycaemia, insulin resistance, lipid metabolism, and blood pressure. However, the South Asian group did demonstrate more adverse levels of metabolic risk factors including higher insulin, higher HbA1c, higher blood pressure, lower HDL cholesterol, as well as lower average durations in moderate physical activity than the European group at the study outset, and so it is unclear whether this difference in risk reduction is explained by innate ethnic differences in the metabolic response to physical activity, or to differences in population burden such as greater comorbidities experienced among ethnic minorities in Western contexts (117).

1.3.2 The role of physical activity in healthy obesity

Physical activity is clearly important for metabolic health, and would therefore seem to be a strong candidate as a distinguishing factor for healthy obesity. Evidence on its role in healthy obesity, however, has been surprisingly inconsistent. When considering durations in self-reported total physical activity, the sum of time spent in light, moderate, and vigorous intensity activities, studies to date have found no differences between healthy and unhealthy obese groups (51, 118, 119). When considering self-reported moderate-to-vigorous physical activity specifically, healthy obese men and women have reported higher durations than their unhealthy obese counterparts in some studies (25, 118), whilst not in others (51, 65). Furthermore, findings on measures of physical activity in relation of healthy obesity are so far based entirely on cross-sectional differences, and associations of physical activity with reduced risk of becoming unhealthy among initially healthy obese adults have not been investigated prospectively. Comparisons of durations in total and moderate-to-vigorous physical activity between healthy and unhealthy obese groups have also relied upon self-reported questionnaire-based measures of physical activity (25, 51, 65, 118, 119). These measures are known to have only modest correlations with objective assessments, often on the magnitude of 0.3 on a 0-to-1 scale (120, 121), possibly due to measurement errors related to inaccurate recall and social desirability (121). Although the correlation between self-reported and objectively assessed total physical activity did not appear to differ across BMI categories in a sample of the Whitehall II cohort (122), measurement error related to inaccurate recall has been shown to be lower among obese than among normal-weight adults in other studies (123). Previous studies reporting weak or null findings for differences in physical activity between healthy and unhealthy obese groups may therefore have been unable to detect true differences due to reliance on imprecise measures of activity. Differential recall bias between metabolically healthy and unhealthy obese groups may also be expected if unhealthy adults show a greater degree of measurement error, however this

has not previously been examined. Newly-developed tri-axial accelerometers have the potential to capture total physical activity in a more complete manner by recording incidental movements without relying on participant recall (124), and thus may offer valuable insight into the role of physical activity as a distinguishing feature of healthy obesity. There is also some evidence that light intensity physical activity, measured objectively, may reduce metabolic risk factor clustering independently of moderate-to-vigorous intensity activity (125), however differences in light intensity physical activity between healthy and unhealthy obese groups have not been specifically examined. This may be due to difficulties in distinguishing light intensity activity from sedentary time and moderate intensity activities (126), although light activities are captured in measures of total physical activity.

1.3.3 Sedentary behaviour and metabolic health

Previous discussions have pertained to physical activity – behaviour which involves the contraction of skeletal muscle to support movement and which expends energy at a rate greater than 1.5 METs. Sedentary behaviour, in contrast, refers specifically to seated and reclining postures performed while awake which expend energy at a rate of ≤ 1.5 METs (127, 128). This consensus definition of 'sedentary behaviour' requires both a sedentary posture and a low energy expenditure, as there may be instances where these do not occur together. Indeed, it has been shown that energy expenditure exceeds 1.5 METs if the upper body moves actively while seated such as while playing interactive video games (129, 130), while conversely, energy expenditure may be lower than 1.5 METs if standing without ambulating, especially if body weight is high (129). Sedentary behaviour represents a substantial proportion of adults' waking hours in modern societies (131), and is theorized to represent a distinct state of muscle inactivity which may influence health risk through increasing inflammation (132), preventing the release

of lipoprotein lipase from contracting skeletal muscle, and impairing insulin sensitivity and glucose absorption (78, 131, 132). Higher levels of sedentary behaviour are widely associated cross-sectionally with individual metabolic risk factors including blood pressure, plasma lipids, and blood glucose (78, 133, 134), and with a clustering of these factors (135, 136). Strong associations have also been reported between sitting and all-cause and cardiovascular-related mortality, incidence of cardiovascular disease and cancer, and with particularly high incidence of type 2 diabetes (78, 137, 138). Intriguingly, these adverse associations are evident after adjusting for engagement in moderate-to-vigorous physical activity (138), suggesting an independent influence of sitting on metabolic processes.

These reportedly independent associations have attracted much attention, driving academics (139-141), public health practitioners, and governments (142) to recommend reduced sitting time in addition to increased moderate-to-vigorous physical activity in order to promote adult health. A critical view of the evidence base, however, leads to several alternative ways of viewing associations of sitting time with metabolic health. For instance, there is evidence that the effect of sitting time on mortality risk may be modified by duration in moderate-to-vigorous physical activity, such that the excess risk associated with sitting is lower among adults with high activity than among adults with low activity (143). This particular study used television (TV) viewing as an indicator of sitting, and the effect modification observed pertained only to the magnitude of the effect, as associations of high TV viewing among highly active groups were still statistically significant. When considering other studies collectively, a recent meta-analysis found that engagement in moderate-to-vigorous physical activity does indeed modify the excess all-cause mortality risk associated with high sitting time, with excess risk observed only among those who are least active, and not among those who are most active (138). All-cause mortality is, of course, a crude outcome which does not describe the incidence or burden of disease. There is some cross-sectional evidence to suggest that moderate-to-vigorous physical activity modifies the effect of sitting on metabolic risk factors, with several studies finding high leisure sitting time to be associated with excess risk for having metabolic risk factor clustering only

among those who were physically inactive (69, 144, 145), with 2 studies finding evidence for effect modification by activity level among women but not among men (69, 146). However, most studies of this association do not test for interaction and instead adjust for moderate-to-vigorous physical activity as part of an a priori hypothesis of independence.

The strength of associations between sitting time and metabolic risk factors also appear to vary by the context in which sitting is measured. Associations appear to be weak or non-existent when using sitting duration in an occupational context as a marker of sedentary time (147-149), while associations with abnormal glucose metabolism (150, 151), insulin resistance, hypertension, and dyslipidaemia (69, 147, 152), as well as with metabolic risk factor clustering (69, 144, 146, 153-155) have been widely reported when using self-reported duration in TV viewing as a marker, with these associations being independent of engagement in moderate-to-vigorous physical activity. Possible reasons for these context-specific associations may include the tendency for screen-based activities to encourage more prolonged sitting, in contrast to occupational sitting which may involve more frequent breaks and bouts of standing, which are known to have beneficial effects on insulin sensitivity and glucose metabolism (156). Associations may also be confounded by certain eating behaviours, given the tendency for adults to consume energy-dense snack foods while viewing TV (157). Questions focusing on TV viewing also have the highest validity and reliability among leisure-time sitting questions (158), and so stronger associations with TV viewing time may also reflect a better ability to recall sitting time accurately. For example, the known duration of TV programmes that were viewed (i.e. 1 hour long) may improve the accuracy of participants' estimates for sitting duration, while work-related sitting may be more sporadic, less likely to be stored in memory, and harder to recall. The result may be a clearer patterning of data for TV viewing than for occupational sitting in relation to health outcomes and a higher likelihood of detecting associations.

When viewed prospectively, higher objectively-measured sitting time was associated with worsening insulin profiles (159) and metabolic risk factor clustering after 6 years (160), while other studies reported that increased TV viewing time (161, 162) and low physical activity (162)

independently predicted worsening metabolic health after several years of follow-up. Although cross-sectional studies suggest that the strength of associations between sitting and metabolic risk depends upon engagement in physical activity (69, 144, 145), there is no longitudinal evidence on these interactive effects as they relate to developing metabolic risk factor clustering over time.

The use of habitual moderate-to-vigorous physical activity in statistical adjustments may not adequately reflect total physical activity time, which consists of light intensity activity and incidental movements of any intensity which are not likely stored in and recalled from memory, and thus may exaggerate or misattribute observed independent effects of sitting. Mayer et al. (163) recently showed that when adjusting for total physical activity as measured objectively using accelerometry, associations between total sitting time and metabolic risk factors including inflammatory markers and blood lipids were no longer evident. This suggests that the adverse effects of sitting time which are commonly reported in other studies may reflect less engagement in light intensity activity rather than an effect of sitting itself. However, sitting time and light intensity physical activity are highly negatively correlated (r=-0.96 in one study (136)), and this complicates efforts to model these associations accurately.

Another alternative explanation for the health risks of sitting is that sitting reflects a displacement of time spent in physical activity (164). Two recent studies using objective measures of sitting time and physical activity with novel isotemporal substitution methods support this idea. In the first study, replacing 10 minutes of sitting time with an equal duration of moderate-to-vigorous physical activity was associated with improvements in HbA1C, HDL-cholesterol and triglycerides, but associations were not seen when sitting was displaced with light intensity activity (165). Similar effects were seen for improved insulin sensitivity and blood glucose in a second study which tested the displacement of a longer 30-minute duration of sitting time with an equal amount of moderate-to-vigorous activity, with associations again appearing weaker and less consistent for light intensity activity (166).

Thus, although a wealth of literature documents associations of higher leisure sitting time with metabolic risk factors independently of engagement in moderate-to-vigorous physical activity, this does not necessarily reveal the true nature of these associations as most studies do not formally test for interaction between sitting time and moderate-to-vigorous physical activity in relation to metabolic risk factors, and therefore cannot rule out the possibility of effect modification by physical activity. This is an important limitation in the evidence base, as these results would directly affect public health messaging. If high sitting time is truly associated with metabolic ill-health independently of moderate-to-vigorous physical activity, the public health message is 'Even if you exercise regularly, still limit your sitting time', while on the other hand, if moderate-to-vigorous physical activity greatly modifies or removes associations of high sitting time with ill-health, the public health message becomes 'As long as you exercise regularly, sit all you want'. These are very different messages, and from a public health practitioner's point of view, the former message is more conservative and likely preferable, as its implication would only be to increase total activity, and not to limit total activity as the latter message risks doing.

1.3.4 The role of sedentary behaviour in healthy obesity

Despite widely reported cross-sectional associations between sedentary behaviour and metabolic health, the role of sedentary behaviour in distinguishing healthy from unhealthy obesity has not been thoroughly investigated. Given theoretical mechanisms of inflammation, lipoprotein lipase inhibition, and glucose control (78), lower levels of sedentary behaviour may plausibly help explain why some obese individuals are able to maintain metabolic health. Furthermore, evidence on the nature of sedentary behaviour and metabolic health suggests that associations of low sitting time may be independent of engagement in moderate-to-vigorous physical activity (147, 151), or alternatively, low sitting time may interact with moderate-to-

vigorous physical activity such that low sitting may only be protective among certain levels of activity.

No differences in sitting time as indicated by self-reported TV viewing or other sedentary activities were observed between healthy and unhealthy obese adults in one study (65), while one other study reported lower sedentariness among healthy than among unhealthy obese adults. Sedentary behaviour in this latter study was based on a low ranking in a combination of self-reported activity duration, intensity, and frequency, and did not isolate sedentary behaviour as a distinct state of muscle inactivity as induced by sitting (51). Furthermore, no prior studies specifically hypothesised sitting time as a distinct contributor to metabolic health among the obese, and therefore did not apply an a priori model adjustment strategy appropriate to address this research question, such as adjusting for engagement in moderate-to-vigorous activity to test an independent association, or examining interaction to test modifying effects of moderate-to-vigorous activity. Likewise, it has not been examined prospectively whether low levels of leisure sitting are protective against developing future metabolic risk factor clustering among initially healthy obese adults, and whether this protective effect is independent of or interactive with moderate-to-vigorous physical activity.

1.4 Healthy obesity and metabolic decline

The recognition of an apparently healthy type of obesity has naturally been followed by an interest in its long-term clinical consequences. Building on the most widely recognised health threats linked with obesity, clinical outcomes for healthy obesity considered thus far include incident metabolic risk factor clustering, type 2 diabetes, cardiovascular morbidity, and all-cause or cardiovascular-related mortality.

1.4.1 Progressions from healthy to unhealthy obesity

The conceptual validity and clinical value of healthy obesity rest upon the assumption that it is a stable state, and not a transient phase of metabolic decline. A fundamental question therefore is whether healthy obese adults maintain this metabolically healthy profile in the long-term, or naturally transition into unhealthy obesity over time. Few studies have examined this issue, with two showing that about one-third of healthy obese adults were unhealthy obese after a period of 6 years (167) (51). Interestingly, the proportion of initially healthy obese adults who progress to unhealthy obesity seems to increase with increasing follow-up times, with 43% of initially healthy obese adults transitioning to unhealthy obesity over 7 years (168), nearly half (47.6%) progressing over 8 years (169), and half progressing over 10 years (170). Such analyses are descriptive and simply compare metabolic status at baseline with metabolic status at follow-up, irrespective of what transitions may have taken place in any intermediate follow-up periods, and thus do not examine cumulative incidence. This simple approach is preferable when addressing the question of stability, as healthy obese adults may also improve their status over subsequent follow-ups, and this would otherwise be ignored by cumulative analyses of decline.

Follow-up times used thus far in studies have not exceeded 10 years which may miss key parts of a longer-term trend. Crucially, no studies have compared the tendency for metabolic decline between initially healthy obese adults and initially healthy normal-weight adults, and thus it has not been clear whether healthy obesity carries a risk for progressing to unhealthy obesity that is far in excess of healthy normal-weight adults; such evidence would firmly support the view of healthy obesity as a phase. Furthermore, no studies have used long follow-up periods to identify the specific metabolic risk factors responsible for declines to ill-health, which is necessary for informing the management of healthy obese adults in clinical practice.

1.4.2 Healthy obesity and risk of incident type 2 diabetes

The prevalence of type 2 diabetes is immense, with upwards of 370 million diabetics globally; half of whom may be unaware of their condition (171). Type 2 diabetes confers a substantial burden for health and quality of life and has long been considered a consequence of obesity (172). While characteristics of adipose tissue play a direct role (173), much of the increased risk for type 2 diabetes among the obese is thought to stem from metabolic abnormalities associated with excess fat, such as islet beta-cell dysfunction, insulin resistance and resultant hyperglycaemia (173), as well as high chronic systemic inflammation (174, 175). Other contributing factors may include higher levels of visceral fat (176), an energy-dense/nutrient-poor diet including excessive sugar intake (177-179), and physical inactivity (180, 181) along with genetic, ethnic, and socioeconomic susceptibilities (182, 183).

Given that healthy obese adults display favourable levels of metabolic risk factors which are relevant to type 2 diabetes development including normal insulin sensitivity, normoglycemia, and low systemic inflammation (184, 185), it has been questioned whether this group also faces an increased risk. Several prospective studies have reported a substantially increased risk for

incident type 2 diabetes among healthy obese compared with healthy normal-weight adults (51, 186, 187); however estimates of this association have not yet been systematically searched and synthesized in a meta-analysis. Given that type 2 diabetes is itself a strong risk factor for a range of cardiovascular complications including atherosclerosis (188, 189), and with risk for premature mortality among diabetics being much higher among those who are obese (190), a consistently strong link between healthy obesity and type 2 diabetes incidence may signal serious problems for this group in the more distant future.

Previous work examining trajectories of insulin and glucose among adults in the British Whitehall II cohort study strongly supports a multistage model of type 2 diabetes development (191). In this model, the first noticeable sign of metabolic dysfunction is a long period of insulin resistance, with simultaneous increases in pancreatic beta-cell functioning in an effort to secrete more insulin to compensate for impaired insulin sensitivity and to promote continued absorption of glucose into skeletal tissue (191). This is then followed by a substantial decline in beta-cell functioning together with a reduction in beta-call mass as these beta-cells start to become exhausted and expire through apoptosis (192). The final result is an abrupt spike in blood glucose levels, at which point type 2 diabetes is detectable in a clinical setting. According to this model, initial changes in insulin resistance occur many years before blood glucose levels rise and a diagnosis of type 2 diabetes is made (191, 193), and trajectories of insulin resistance are highly distinct between those adults who eventually develop type 2 diabetes and those who do not, revealing key opportunities for early detection (191). Other key factors thought to determine risk of type 2 diabetes among obese adults are the robustness of pancreatic beta-cells in their ability to secrete insulin at higher volumes to compensate for a chronic overconsumption of energy, as well as levels of visceral and ectopic fat located in and around organs (194, 195). Type 2 diabetes is therefore viewed both as a disease of pancreatic beta-cell failure as well as a disease of ectopic fat deposition, and these complementary factors may determine an individual's likelihood of developing type 2 diabetes in response to accumulating body fat.

Despite these well-studied pathways linking insulin resistance with the development of type 2 diabetes in obesity, it has not been examined whether healthy obese adults carry a high excess risk for future insulin resistance. Furthermore, studies conducted thus far on healthy obesity and risk of incident type 2 diabetes have defined healthy obesity based on the absence of metabolic risk factor clustering, thus allowing for 1 or sometimes 2 metabolic risk factors to be present at baseline. It is possible that these baseline risk factors may be insulin resistance or high blood glucose which is elevated just below the clinical cut-point for type 2 diabetes but which still qualifies as prediabetic (193). It would be useful to examine whether obese adults without any metabolic abnormalities (a strictly healthy sample) also face an excess risk for developing type 2 diabetes. Excess risk among this strictly healthy sample would indicate an inherent link between excess fat and poor glucose control, and would be strong evidence against the idea that obesity can really be healthy.

1.4.3 Healthy obesity and risk of incident cardiovascular disease

Recent evidence suggests that, compared with healthy normal-weight adults, healthy obese adults show an increased risk for incident hypertension (196) and subclinical cardiovascular disease including elevated common carotid artery intima media thickness, elevated coronary artery calcification (197, 198), and poor ventricular structure and function (199). Recent large-scale work using a nationally representative sample of 71, 527 adults from the general population of Norway demonstrated that obese adults also face a significantly increased risk for both incident myocardial infarction and ischemic heart disease after a median of 3.6 years follow-up, regardless of their metabolic health profile (200). The overall trend for the healthy obese mirrored that shown in previous smaller scale studies, which showed an excess risk for cardiovascular outcomes which is intermediate between healthy normal-weight and unhealthy obese adults, and which is on the magnitude of 50-100%.

Two meta-analyses recently demonstrated that healthy obese adults face a 2-fold increased risk for cardiovascular-related events compared with healthy normal-weight adults (201, 202), with excess risk again appearing to be lower than among the unhealthy obese, but still greater than among healthy normal-weight adults. Importantly, it was observed in both meta-analyses that studies which used longer follow-up durations (greater than 15 years in Fan et al. (202) and greater than 10 years in Kramer et al. (201)) demonstrated greater risk, indicating that the tendency for healthy obese adults to develop cardiovascular disease gets stronger with time. Although Kramer et al. also considered all-cause mortality as an outcome, it is important to note that all of the studies which used longer than 10 years of follow-up and which were therefore isolated from other studies to show excess risk pertained to incident cardiovascular events, not all-cause mortality.

1.4.4 Healthy obesity and risk of all-cause and cardiovascular disease mortality

Evidence on risk of premature mortality among healthy obese adults is less consistent than for incident disease. Using a nationally representative sample of Italian middle-aged adults, Calori et al. (50) demonstrated no increased risk for all-cause or cardiovascular-related mortality among healthy obese compared with healthy normal-weight adults over 15-years follow-up, when defining metabolic health by lack of insulin resistance only. Another study using nationally representative data from England and Scotland also reported no increased risk for all-cause or cardiovascular mortality in healthy obese compared with healthy normal-weight adults, with health defined as the absence of metabolic risk factor clustering (203). This finding was evident regardless of whether obesity was defined according to BMI (indicating total body obesity) or waist circumference (indicating abdominal obesity). However, in contrast, at least two other studies suggest that obese adults who are metabolically healthy have a greater risk for all-cause

mortality compared with healthy normal-weight adults, when the phenotype is defined as being free of metabolic risk factor clustering or being highly insulin sensitive only (204, 205). Others report that the healthy obese have a substantially increased risk of death from major cardiovascular events such as acute myocardial infarction, ischemic stroke or heart failure, as compared with healthy non-obese adults over a median of 30 years follow-up (205). Furthermore, a systematic review and meta-analysis did not find significant summary evidence for excess risk for all-cause or cause-specific mortality among healthy obese adults, with only cardiovascular events being evident after at least 10 years of follow-up (201). It may be possible that longer-term follow-ups may be required to see excess risk of death, as may be expected, while shorter follow-ups are sufficient to see increased risk of incident disease.

1.5 Research priorities

1.5.1 Characteristics of healthy obesity

Several key gaps in knowledge regarding the characteristics of healthy obesity have been identified. First, although physical activity is known to be important for metabolic health among the adult population at large, it remains unclear whether higher physical activity distinguishes healthy from unhealthy types of obesity. Despite established associations of sedentary behaviour with metabolic health, the role of sedentary behaviour in distinguishing healthy obese adults from their unhealthy obese counterparts is also unknown, and it has not been investigated whether associations of high physical activity and low leisure sitting time in relation to healthy obesity are truly independent or interactive in nature. Additionally, no studies have examined differences in total physical activity between healthy and unhealthy obese groups using objective physical activity assessments, and thus the degree to which reliance on self-reported measures of physical activity have limited our understanding of its role in promoting metabolic health within obese populations is unknown.

Physiological factors such as fat distribution and fitness are strong candidates as determinants of healthy obesity, but these are known to carry genetic susceptibilities (49, 111) and are themselves influenced by engagement in physical activity (97, 98). Thus, focusing on physical activity and sedentary behaviour seem ideal, as these are the most readily modifiable and universally achievable factors, and ones which may have beneficial downstream effects on fat distribution and fitness. Evidence suggesting that a healthy type of obesity can be promoted by physical activity may provide clinicians and public health practitioners with a target for focusing their efforts, and may ultimately confer substantial reductions in disease burden for the wider population through public health interventions.

1.5.2 Clinical outcomes of healthy obesity

Likewise, several important gaps in knowledge regarding the clinical outcomes of healthy obesity have been identified. First, despite recent efforts in literature to examine the cardiovascular consequences of healthy obesity, the natural course of the healthy obese state itself has not been well described using repeat clinical data over long follow-ups to determine whether it is truly a stable state or a transient phase of metabolic decline. Second, the individual metabolic risk factors most responsible for transitions from healthy to unhealthy obesity have not been identified over long follow-ups, which is necessary to inform the management of healthy obesity in clinical practice. It has also not been established whether healthy obese adults have an increased risk of developing type 2 diabetes compared with healthy normal-weight adults. Furthermore, given that previous studies have most commonly defined healthy obesity as having < 2 metabolic risk factors, there is concern that estimates for diabetes risk may be biased by the baseline prevalence of insulin resistance or high blood glucose.

Given that initiating and maintaining weight-loss is difficult, it is of great interest whether keeping metabolic risk factors in check is sufficient to prevent the onset of disease. If so, this may lead to the allocation of limited clinical resources towards those obese individuals with the greatest risk of adverse health outcomes, and to more personalised approaches to delivering health services. If, however, healthy obesity is seen to be largely unstable and is seen to carry a consistently high risk for type 2 diabetes, including among those with no signs of metabolic dysfunction (0 metabolic risk factors), this would strongly link healthy obesity with future decline and support inseparable links between excess fat and disease. It is therefore important to clarify the long-term nature of healthy obesity in order to strengthen the academic literature, to inform clinicians who encounter these patients in practice, and to ensure appropriate public health messages.

1.7 Summary of introduction

Obesity is a great threat to public health, owing to its strong links with metabolic dysfunction and early mortality. However, nearly one-third of obese adults does not show a clustering of metabolic risk factors and are considered 'healthy'. Whether high physical activity and low sedentary behaviour distinguish healthy from unhealthy obesity is unknown, and it is not clear whether the role of these behaviours in promoting healthy obesity is independent or interactive. Additionally, no studies have examined differences in total physical activity between healthy and unhealthy obese groups using objective accelerometer assessments, and thus the evidence to date may be based upon imprecise measures of activity. Addressing these gaps in knowledge may help identify modifiable and achievable factors for improving metabolic health among obese populations.

Healthy obese adults have a greater risk for developing cardiovascular events than healthy normal-weight adults, but whether healthy obesity itself is a stable state or a transient phase of metabolic decline has not been described using repeat clinical data over sufficiently long follow-ups, nor has it been identified which metabolic risk factors drive progressions from healthy to unhealthy obesity. Furthermore, it has not been established whether healthy obese adults have an increased risk of developing type 2 diabetes compared with healthy normal-weight adults, or whether obese adults who are strictly healthy (with 0 metabolic risk factors) also face an increased risk of type 2 diabetes. Addressing these knowledge gaps may inform the effective management of healthy obese patients in clinical practice and appropriate public health messages about adult obesity.

Section 2: Thesis Aims & Objectives

This thesis will be divided into two parts. The first part will investigate physical activity and sedentary behaviour as distinguishing features of healthy obesity. The second part will investigate the risk of future metabolic decline among initially healthy obese adults with regards to incident metabolic risk factor clustering and type 2 diabetes. Although the primary interest is in obese adults, analyses will include normal-weight and overweight counterparts in order to provide reference groups, view trends across phenotypes, and provide context for interpreting results.

2.1 Part 1: Physical activity and sedentary behaviour in relation to healthy obesity

Aims

1. To determine whether high physical activity and low sedentary behaviour contribute to a healthy metabolic status among obese adults
2. To determine whether high physical activity and low sedentary behaviour reduce the risk of becoming metabolically unhealthy over time among initially healthy obese adults

Objectives

1. To examine cross-sectional associations of self-reported high moderate-to-vigorous physical activity and self-reported low leisure sitting time, separately and in combination, with prevalence of a metabolically healthy profile among normal-weight, overweight, and obese adults
2. To examine prospective associations of self-reported high moderate-to-vigorous physical activity and self-reported low leisure sitting time, separately and in combination, with incident metabolic risk factor clustering among initially healthy normal-weight, overweight, and obese adults
3. To examine cross-sectional associations of self-reported high moderate-to-vigorous physical activity and self-reported low TV viewing time, separately and in combination, with prevalence of a metabolically healthy profile among normal-weight, overweight, and obese adults
4. To examine cross-sectional differences in questionnaire- and accelerometer-assessed total physical activity between healthy and unhealthy normal-weight, overweight, and obese adults
5. To examine cross-sectional differences in the likelihood of meeting recommendations for moderate-to-vigorous physical activity, based on questionnaire and accelerometer assessments, between healthy and unhealthy normal-weight, overweight, and obese adults

2.2 Part 2: Healthy obesity and metabolic decline

Aims

1. To examine the natural course of healthy obesity in terms of its long-term metabolic stability and change
2. To identify the individual metabolic risk factors most responsible for progressions from healthy to unhealthy obesity
3. To establish whether healthy obese adults have an increased risk of developing type 2 diabetes compared with healthy normal-weight adults

Objectives

1. To describe the proportion of healthy obese adults who develop metabolic risk factor clustering over 20 years of follow-up using repeat clinical measures, and to compare the likelihood of development with that of healthy normal-weight adults
2. To describe incidence of individual metabolic risk factors over 20 years among initially healthy obese adults using repeat clinical measures, and to compare incidence with that of healthy normal-weight adults
3. To systematically search the literature for published prospective studies on the risk of incident type 2 diabetes among obese adults who are metabolically healthy
4. To synthesize estimates obtained from the literature using random-effects meta-analysis and to examine whether age, ethnicity, duration of follow-up, and study quality explain any observed between-study heterogeneity in effects
5. To produce an original effect estimate for the risk of incident type 2 diabetes among obese adults who initially have 0 metabolic risk factors (a strictly healthy sample)

Section 3: Data & Methods

This section describes the sources of data and the research methods used to meet the aims and objectives of this thesis. A description of the Whitehall II cohort study is first presented, followed by the assessment of healthy obesity, assessments of physical activity and sedentary behaviour (the behavioural features of interest), assessment of incident metabolic risk factor clustering and type 2 diabetes (the clinical outcomes of interest), and assessment of covariates considered in models. The statistical methods used to meet each objective are then described.

3.1 Study population: The Whitehall II cohort study

The Whitehall II cohort study is an occupational cohort study of London-based British civil servants (government workers). The study recruited 10,308 men and women in 1985/88 (67% male; 89% white ethnicity). The age of participants at baseline ranged from 34-56 years, with a mean age of 44.5 years; thus, Whitehall II was initially comprised of predominantly middle aged adults (206). The study was initially designed in the 1980s with the broad aim of understanding the biological mechanisms underlying work-related stress and disease risk, and the mechanisms underlying socioeconomic inequalities in health more generally. Since its inception, the Whitehall II cohort study has been a pioneering source of evidence on inequalities in health between socioeconomic groups based on middle-aged adults in Britain (206), with recent contributions focusing more on age-related health conditions as the cohort enters retirement and later stages of life.

Since 1985/88, participants have been followed-up every 2-3 years with questionnaires, and every 5 years with clinical examinations which include comprehensive assessments of metabolic health indicators. Clinical data was gathered for the first time in 1991/94, and was subsequently gathered in 1997/99, 2002/04, 2007/09 and 2012/13. This cohort study is therefore ideally, and perhaps uniquely, suited to meet the aims of this thesis, which involve investigating the long-term nature of healthy obesity, as clinical assessments are repeatedly made on the same individuals over a period of 20 years. Ethical approval for the study was obtained from the University College London research ethics committee, and participants gave written informed consent for their data to be used for bona fide research purposes at each phase of data collection.

3.2 Assessment of healthy obesity

Objectively measured anthropometrics (height and weight) and metabolic risk factors were used to define metabolic and obesity phenotype status at each respective phase in 1991/94, 1997/99, 2002/04, 2007/09 and 2012/13. Body mass index (BMI) was calculated by dividing participants' weight in kilograms (kg) by height in meters-squared (m^2). Assessments of height and weight are known to involve high inter-observer reliability (207) and BMI as an adiposity indicator has been well-validated against levels of total body fat as measured objectively by dual-energy X-ray absorptiometry (DXA) (208, 209). Normal-weight (BMI 18.50-24.99 kg/m^2), overweight (BMI 25-29.99 kg/m^2), and obesity (BMI ≥ 30 kg/m^2), were defined based on World Health Organization International Classifications (2). Underweight participants (BMI < 18.5 kg/m^2) were excluded from all analyses, as these adults represent an extreme minority in terms of sample size and can bias a theoretically healthy normal-weight group as a point of reference given known increased mortality risks among underweight adults, due largely to higher prevalence of chronic obstructive pulmonary disease and cancers (5).

A healthy metabolic profile was defined as the absence of metabolic risk factor clustering. The criteria for metabolic risk factor clustering proposed independently by Wildman et al. (2008) was used to define participants' metabolic status, as this criteria includes insulin resistance alongside other core metabolic risk factors and is more stringent than some other criteria, allowing for only 1 metabolic risk factor to be present at the point of classification (25). Normal-weight, overweight, and obese adults were considered healthy if they had < 2 of the following risk factors: HDL-cholesterol ≤ 1.03 mmol/L for men and ≤ 1.29 mmol/L for women or use of lipid lowering drugs; blood pressure ≥ 130/85 mmHg or use of anti-hypertension medication; fasting plasma glucose ≥ 5.6 mmol/L or use of diabetic medication; triglycerides ≥ 1.7 mmol/L; homeostatic model assessment (HOMA) of insulin resistance (fasting insulin * fasting glucose /

22.5) > 90th percentile value at baseline in the respective analytical sample. C-reactive protein (CRP) was excluded from criteria as this factor was not measured at the 2007/09 or 2012/13 phase of data collection, and the aim was to keep criteria consistent over follow-up periods. Data on the use of lipid lowering drugs was not collected in 1991/94, and this factor was excluded from classifications of metabolic status at this phase only, as this formed only part of one component (HDL cholesterol). The study population therefore comprised 6 groups for analyses, including the healthy obese, which are outlined in **Box 2** below.

Box 2: Definition of healthy obesity	
Obesity status	
Normal-weight	BMI 18.50 – 24.99 kg/m²
Overweight	BMI 25.00 – 29.99 kg/m²
Obese	BMI ≥ 30 kg/m²
Metabolic status	
Healthy	<2 (0 or 1) of: • HDL-cholesterol ≤ 1.03 mmol/L for men and ≤ 1.29 mmol/L for women, or use of lipid lowering drugs • Blood pressure ≥ 130/85 mmHg or use of anti-hypertension medication • Fasting plasma glucose ≥ 5.6 mmol/L or use of diabetic medication • Triglycerides ≥ 1.7 mmol/L • Homeostatic model assessed insulin-resistance (fasting insulin * fasting glucose / 22.5) > 90th percentile value in respective analytical sample
Unhealthy	≥2 (2 or more) of: • HDL-cholesterol ≤ 1.03 mmol/L for men and ≤ 1.29 mmol/L for women, or use of lipid lowering drugs • Blood pressure ≥ 130/85 mmHg or use of anti-hypertension medication • Fasting plasma glucose ≥ 5.6 mmol/L or use of diabetic medication • Triglycerides ≥ 1.7 mmol/L • Homeostatic model assessed insulin-resistance (fasting insulin * fasting glucose / 22.5) > 90th percentile value in respective analytical sample

As noted, the chosen criteria for a metabolically healthy status allowed for 1 metabolic risk factor to be present at baseline. When analysing incidence of individual metabolic risk factors among initially healthy obese adults, this definition was modified to create on a 'strictly healthy' sample defined as having none of the 5 metabolic risk factors of interest, in order to create a consistent sample for analyses. This strictly healthy sample was also used for original analyses of incident type 2 diabetes in order to reduce the possibility of insulin resistance or hyperglycaemia being present at baseline, which could bias risk estimates.

3.3 Assessment of physical activity

3.3.1 Questionnaire-assessed total and moderate-to-vigorous physical activity

From phase 5 (1997/99) onward, physical activity was assessed using a modified 20-item version of the validated Minnesota leisure-time physical activity questionnaire (210-214). Participants reported the frequency (number of occasions per week) and duration (number of hours per week) of various activities including sports, walking, cycling, home maintenance, and gardening, with two open-ended questions included to allow reporting of activities not listed. Participants were required to take into account activity patterns over the past four weeks to indicate their usual activity and asked to provide the total number of hours spent in each activity per week (original questionnaire items are included in **Appendix 1**). A MET value was assigned to each activity using a compendium of activity energy costs (66), representing the amount of energy expended for each activity relative to lying down quietly (examples of reported activities and associated MET values are included in **Appendix 2**). Total physical activity was estimated as MET-hours/week, the sum of the product of the intensity (MET) and weekly duration (hours/week) of all reported activities. This self-reported measure of total physical activity therefore considers activities of all intensities (light, moderate, or vigorous), and has previously demonstrated predictive validity for mortality and clinical risk factors including systemic inflammation in the Whitehall II cohort (215, 216).

The duration (hours/week) in activities with MET values of 3 or more, representing moderate-to-vigorous activities (66), was calculated. Additionally, participants were considered to be meeting recommendations for moderate-to-vigorous physical activity if they reported engaging in ≥ 2.5 hours of moderate or vigorous activity per week based on 2010 World Health Organization recommendations and current physical activity guidelines in England (142, 217). Although full guidelines allow for either ≥ 150 min/week of moderate intensity activity or ≥ 75 min/week of

vigorous intensity activity, or an equivalent combination of both, as well as requiring days for muscle-strengthening, balance and coordination-enhancing activities, as well as requiring limiting time spent sitting, this simplified cut-point was chosen for the purposes of making questionnaire and accelerometer assessments of physical activity comparable, given current limitations of separating moderate from vigorous intensity activities using raw tri-axial acceleration (124).

3.3.2 Accelerometer-assessed total and moderate-to-vigorous physical activity

At phase 11 (2012/13), an objective measure of physical activity was taken for the first time. Participants with no contraindications (i.e. allergies to plastic or metal; travelling abroad over the following week) were asked to wear a wrist-worn tri-axial accelerometer (**Figure 1**; GENEActiv, Activinsights Ltd., UK; www.geneactiv.org) on their non-dominant wrist, non-stop for 9 consecutive (24-hour) days.

Figure 1 The GENEActiv wrist-worn tri-axial accelerometer device

The accelerometer was sampled at 87.5 Hz and data were stored in gravity (g) units (1 g=9.81 $m.s^{-2}$). Calibration error was estimated based on static periods in the data and corrected if

necessary (218). The Euclidean norm, or vector magnitude, was used to quantify acceleration related to movement registered and expressed in milligravity (mg) units (1 mg = 0.00981 m/second^2). This norm was based on the total amount of acceleration captured from each of 3 axes according to the standard deviation of the sum of acceleration of the X axis-squared, acceleration of the Y axis-squared, and acceleration of the Z axis-squared, minus 1 g, with negative numbers rounded to zero (120, 219).

Accelerometer data were processed in R using the GGIR package (http://cran.r-project.org). Data extracted between the first and last midnight were retained for analyses leading to a maximum of 24-hour measurements for 8 days. Participants with valid data (≥ 16 hours/day) for at least 2 weekdays and 2 week-end days were included in analyses. This predefined 16-hour cut-point aimed to capture a standard waking time of 16 hours per day (allowing 8 hours for sleep). Previous studies which used waking hour accelerometers (e.g. National Health and Nutrition Examination Survey (NHANES) in the US, Health Survey for England in the UK) used a 10 hours/day cut point which corresponds to about two-thirds of the waking period. As the accelerometer is supposed to be worn for 24 hours in the present study, a day was considered valid if the device was worn for at least 16 hours, which corresponds to two-thirds of a day. In this cohort, the definition of valid daily wear-time is unlikely to influence results as adherence to the accelerometer study protocol was very high. As noted in a previous publication using the same cohort (120), only 72 participants were excluded due to significant non wear time. Non-wear time was estimated on the basis of the standard deviation (SD) and value range of each accelerometer axis (X, Y, and Z), calculated for moving windows of 60 minutes with 15-minute increments (124), a window limit which was chosen to minimise the chance of detecting sedentary bouts as non-wear time. Given that the standard deviation of the acceleration signal of a GENEActiv device when motionless has been found to be 2.6 mg in a laboratory study (219), a time window was classified as non-wear time if the standard deviation of the acceleration signal was less than 3.0 mg to allow a minor 0.4 standard deviation increase due to device noise, or if the value range was less than 50 mg, for at least 2 out of the 3 axes. For each 15 minute

period of time detected as non-wear time over the valid days, missing data were replaced by the mean acceleration calculated from measurement on other days at the same time of day (120, 218); a person-specific method which is less prone to bias than those which assume non-wear time reflects inactivity or is representative of the rest of the day (220).

For each participant, duration in moderate-to-vigorous physical activity was also calculated. No established cut-point for moderate-to-vigorous physical activity using wrist acceleration in older adults is currently available; thus a 100 mg threshold was chosen based on the fact that walking at 4 kilometers/hour is classified as moderate physical activity (66) and was equivalent to an acceleration of 100 mg in a laboratory based study on 30 adults (221). This cut-point has been used in previous publications using the Whitehall II cohort (120, 122) and in a study based on 3 Brazilian birth cohorts (222). In order to qualify as moderate-to-vigorous activity, at least 80% of the activity needed to be ≥ 100 mg, for at least a period (bout) of 10 minutes, using moving 10-minute windows. An alternative cut-point of 120 mg was used in sensitivity analyses as this was the mid-point between mean acceleration for walking at 3 km/h and 5 km/h (221). This 120 mg cut-point is more stringent, and captures activities which are more likely to be within the more intense, and not in the less intense, moderate-to-vigorous range, but reducing the possibility of contamination by light intensity activity.

As the observation period covered 8 days, the data were recoded so that the measure reflected physical activity over one week to match questionnaire-assessed physical activity. If a participant had 3 valid week-end days or 6 weekdays, the wrist acceleration of the first and last full day of measurement (for example, two Tuesdays a week apart) were averaged to represent one unique day. Thus, the mean accelerometer-assessed total physical activity (mg) over a week was calculated as: [(5 × mean daily weekday wrist acceleration) + (2 × mean daily week-end wrist acceleration)] / 7. The same rescaling was done for duration in moderate-to-vigorous physical activity per week (minutes/week). Participants undertaking ≥ 2.5 hours (150 minutes) of moderate or vigorous activity per week were considered to meet 2010 World Health Organization recommendations (217).

3.4 Assessment of sedentary behaviour

3.4.1 Self-reported total leisure sitting time

As part of the phase 5 (1997/99) questionnaire, participants were asked 'On average, how many hours a week do you spend sitting at home e.g. watching TV, sewing, at a desk?', for which participants selected one of 8 responses: none, 1, 2-5, 6-10, 11-20, 21-30, 31-40, 40+ hours. As response options represented a range of time values, the mid-point for each response option was summed to form a continuous scale with each unit representing a 1-hour change in sitting time. As no established cut-point currently exists to define high vs low levels of leisure sitting time, total leisure sitting time was divided into tertiles for analyses. Similar comprehensive measures which consider a range of leisure sitting behaviours have shown acceptable validity, the highest validity being for computer use and TV viewing (223).

3.4.2 Self-reported TV viewing time

As part of the phase 11 (2012/13) questionnaire, participants were asked, 'In the last four weeks, how much time did you spend sitting down watching TV (including DVDs and videos)?', and were given space to record the amount of hours and minutes on each weekday, and on each week-end day. Responses were then combined to form a single estimate of total time sitting while viewing TV (hours/week). Similar measures have been validated in studies of TV viewing and metabolic risk factors and have shown a high degree of reliability (158).

3.5 Assessment of incident metabolic risk factor clustering

Incident metabolic risk factor clustering from phase 3 (1991/94) to phase 5 (1997/99), phase 7 (2002/04), phase 9 (2007/09), and phase 11 (2012/13) was defined based on consistent criteria for metabolic risk factor clustering, defined as having ≥2 of the following risk factors: HDL-cholesterol ≤ 1.03 mmol/L for men and ≤ 1.29 mmol/L for women, or use of lipid lowering drugs; blood pressure ≥ 130/85 mmHg or use of anti-hypertension medication; fasting plasma glucose ≥ 5.6 mmol/L or use of diabetic medication; triglycerides ≥ 1.7 mmol/L; homeostatic model assessed insulin-resistance (fasting insulin * fasting glucose / 22.5) > 90^{th} percentile value in the respective baseline analytical sample, among participants without metabolic risk factor clustering at baseline.

Each of the 5 metabolic risk factors (hypertension, low HDL cholesterol, high triglycerides, high blood glucose, and insulin resistance) were also examined as separate outcomes in analyses of individual metabolic risk factor incidence, among those participants without any metabolic risk factors at baseline.

3.6 Assessment of incident type 2 diabetes

Incident type 2 diabetes from phase 3 (1991/94) to phase 11 (2012/13) was defined based on fasting glucose ≥ 7.0 mmol/L, or self-reported doctor diagnosis, or diabetic medication use, among participants without type 2 diabetes at baseline. This definition, as used previously in the Whitehall II cohort (191), was supported by recommendations of the World Health Organization in 2006 (224) and of the American Diabetes Association in 2010 (225). Fasting glucose was measured at each follow-up clinical phase of the Whitehall II study, allowing for consistency in diabetes definition across the full study period.

3.7 Assessment of covariates

Covariates were measured at baseline for respective analyses unless otherwise noted.

3.7.1 Basic demographic factors

Age was measured continuously in years. Sex ('male' or 'female') and ethnicity ('non-white'; 'white') were assessed at the first phase of data collection (1985/88).

3.7.2 Socioeconomic factors

Socioeconomic status was indicated by occupational position (employment grade) in the British civil service ('administrative'; 'professional/executive'; 'clerical/support'). This occupational indicator has been used in previous work on the same cohort to describe social inequalities in cardiovascular disease risk (226, 227). As many participants entered retirement before the 2012/13 assessment (n=2246, or 65% of this sample), data on pre-retirement occupational position was used from the 2002/04 assessment if required.

3.7.3 Health factors

The presence of a physically limiting illness at baseline was indicated by responses to 2 questions on the presence of an illness which limits moderate or vigorous physical activity (grouped into 'does not limit moderate or vigorous activity at all'; 'limits moderate or vigorous activity a little';

'limits moderate or vigorous activity a lot'). This variable was chosen to indicate current health status as this measure focuses on participants' perceived limitations to engaging in moderate-to-vigorous physical activity, which is of central interest in respective analyses.

3.7.4 Health behaviours

Cigarette smoking status was grouped as 'never smoker'; 'ex-smoker'; 'current smoker'. Alcohol consumption in the previous week was initially assessed in a continuous form, and then grouped into 'abstainer' (0 units/week); 'moderate' (1-14 units/week for women and 1-21 units/week for men; 'high' (> 14 units/week for women, > 21 units/week for men), given known non-linear associations between alcohol consumption and mortality risk (228).

Data on 3 dietary components (fruit and vegetable consumption, milk consumption, and bread consumption) were used to create a summary indicator of diet quality as done in a previous publication using the Whitehall II cohort study (229). Participants were assigned an individual diet component score of 0 for each of: consuming fruit and vegetables less than daily, consuming whole/full-cream milk most often, and consuming white bread most often; a score of 1 for each of: consuming fruit and vegetables daily, consuming semi-skimmed milk most often, and consuming a combination of white and brown bread or not consuming bread; and a score of 2 for each of: consuming fruit and vegetables twice or more per day, consuming skimmed/fat-free milk or other kind of milk most often, and consuming wholemeal, granary, or other brown bread most often. A total diet score was obtained by summing these individual diet components (range=0–6). Participants were considered to have an unhealthy diet if this total diet score was between 0 and 2, a moderately healthy diet if this was between 3 and 4, and a healthy diet if this was between 5 and 6. When data on milk use was not available (1991/94), frequency of fruit and vegetable consumption ('at least daily'; 'less than daily') was used alone as an indicator of diet quality.

Sleep duration was included as a covariate, and was assessed by asking participants how many hours they sleep on an average weeknight (‘≤ 5 hours’; ‘6 hours’; ‘7 hours’; ‘8 hours’; ‘≥ 9 hours’). Both high and low levels of usual sleep duration based on this indicator have been associated with increased risk for all-cause and cardiovascular mortality in the Whitehall II cohort study (230).

If participants were missing data on health behaviours at the 2012/13 assessment, data from the previous assessment (2007/09) were used to make maximum use of data. Sensitivity analyses were performed to check the potential for this approach to bias results by repeating analyses with such participants excluded.

3.8 Statistical approach

This section first describes the statistical methods used to examine physical activity and sedentary behaviour in relation to healthy obesity (Part 1) according to each previously defined study objective.

3.8.1 Part 1: Physical activity and sedentary behaviour in relation to healthy obesity

Objective 1: To examine cross-sectional associations of self-reported high moderate-to-vigorous physical activity and self-reported low leisure sitting time, separately and in combination, with prevalence of a metabolically healthy profile among normal-weight, overweight, and obese adults

Cross-sectional analyses utilised data from phase 5 (1997/99) as this was the first occasion that physical activity, leisure sitting time, anthropometrics, and metabolic risk factors were measured all together.

As the prevalence of a metabolically healthy profile was relatively high among all BMI groups (>20%), odds ratios obtained from logistic regression models are likely to inflate approximations of relative risk (231). Log binomial models are often used to approximate relative risks but these are prone to failures in model convergence, especially when dealing with continuously measured covariates (232). Poisson regression models with robust error variances are well-supported as suitable approximations of relative risks for binary outcomes (233, 234), and so, for analyses of

separate associations, Poisson regression models with robust error variances were used to compute prevalence ratios (PR) with accompanying 95% confidence intervals (CI) for mutually-adjusted associations of tertiles of moderate-to-vigorous physical activity and of leisure sitting time with the prevalence of a metabolically healthy profile among normal-weight, overweight, and obese adults.

For analyses of combined associations, tertiles of moderate-to-vigorous physical activity and of total leisure-time sitting were combined to form a 9-level exposure variable: 'Lowest activity/highest sitting' (reference group), 'lowest activity/intermediate sitting', 'lowest activity/lowest sitting', intermediate activity/highest sitting', 'intermediate activity/intermediate sitting', 'intermediate activity/lowest sitting', 'highest activity/highest sitting', highest activity/intermediate sitting, 'highest activity/lowest sitting', with group ordering based on assumed increases in energy expenditure. Associations of activity/sitting tertiles with the prevalence of a metabolically healthy profile were examined separately among normal-weight, overweight, and obese adults. Statistical interaction between moderate-to-vigorous physical activity and leisure sitting time was tested by including the product term of the corresponding tertiles in relation to metabolic health status in Poisson regression models. Given that the obese group is expected to comprise fewer participants than normal-weight and overweight groups, and that stratification by BMI group may therefore limit the detection of associations among the obese due to lower statistical power, statistical interaction was also tested between moderate-to-vigorous physical activity tertile and BMI group and between leisure sitting time tertile and BMI group, both in relation to metabolic health status in models adjusted for BMI group. A triple interaction was also examined between moderate-to-vigorous physical activity tertile, leisure sitting tertile, and BMI group, in relation to metabolic health status.

Additionally, analyses for prevalent metabolic health were repeated with moderate-to-vigorous physical activity and leisure sitting time each measured continuously (hours per week), in order to allow greater statistical power and improve model interpretations. The same interactions described above were tested based on these continuously measured variables. For each set of

analyses, the first models adjusted for age, sex, and ethnicity. The second models further adjusted for occupational position, smoking, alcohol consumption, diet quality, sleep duration, and presence of an illness which limits moderate or vigorous intensity physical activity.

Objective 2: To examine prospective associations of self-reported high moderate-to-vigorous physical activity and self-reported low leisure sitting time, separately and in combination, with incident metabolic risk factor clustering among initially healthy normal-weight, overweight, and obese adults

Phase 5 (1997/99) served as the baseline for prospective analyses. Participants who were metabolically unhealthy at baseline were excluded. Poisson regression models with robust error variances were used to compute incidence ratios (IR) with accompanying 95% confidence intervals (CI) for associations of moderate-to-vigorous physical activity and sitting time, separately and in combination, with incident metabolic risk factor clustering over 15 years of follow-up. This 15-year follow-up assessed cumulative incidence over 5-year intervals, considering incident metabolic risk factor clustering after 5 years (2002/04), 10 years (2007/09), or 15 years (2012/13).

For analyses of separate associations, mutually-adjusted associations of tertiles of moderate-to-vigorous physical activity and of leisure sitting time with incidence of metabolic risk factor clustering were examined among normal-weight, overweight, and obese adults.

For analyses of combined associations, tertiles of moderate-to-vigorous physical activity and of leisure sitting time were combined to form a 9-level exposure variable: 'Lowest activity/highest sitting' (reference group), 'lowest activity/intermediate sitting', 'lowest activity/lowest sitting', intermediate activity/highest sitting', 'intermediate activity/intermediate sitting', 'intermediate activity/lowest sitting', 'highest activity/highest sitting', highest activity/intermediate sitting,

'highest activity/lowest sitting', with group ordering based on assumed increases in energy expenditure. Associations of activity/sitting tertiles with incidence of metabolic risk factor clustering were examined among normal-weight, overweight, and obese adults. Statistical interaction between moderate-to-vigorous physical activity and leisure sitting time was tested by including the product term of the corresponding tertiles in relation to incident metabolic risk factor clustering in Poisson regression models. Statistical interaction was also tested between moderate-to-vigorous physical activity tertile and BMI group and between leisure sitting time tertile and BMI group, both in relation to incident metabolic risk factor clustering, adjusted for BMI group. A triple interaction was also examined between moderate-to-vigorous physical activity tertile, leisure sitting tertile, and BMI group, in relation to incident metabolic risk factor clustering.

Additionally, analyses for incident metabolic risk factor clustering were repeated with moderate-to-vigorous physical activity and leisure sitting time each measured continuously (hours per week), in order to allow greater statistical power and improve model interpretations. The same interactions described above were tested based on these continuously measured variables. For each set of analyses, the first models adjusted for age, sex, and ethnicity. The second models further adjusted for occupational position, smoking, alcohol consumption, diet quality, sleep duration, and presence of an illness which limits moderate or vigorous intensity physical activity.

Objective 3: To examine cross-sectional associations of self-reported high moderate-to-vigorous physical activity and self-reported low TV viewing time, separately and in combination, with prevalence of a metabolically healthy profile among normal-weight, overweight, and obese adults

Cross-sectional analyses utilised data from phase 11 (2011/12) as this was the first occasion that TV viewing time was assessed separately alongside moderate-to-vigorous physical activity, anthropometrics, and metabolic risk factors. Data on total number of minutes of TV viewing per week appeared normally distributed; however several extreme positive values were identified which were judged as outliers. Assuming 480 minutes (8 hours) of sleep per 1440-minute (24-hour) day, the realistic maximum viewing time was assumed to be 6720 minutes per 7-day week. Data values higher than this maximum value were considered missing. Values were then converted from minutes into hours for ease of interpretation.

For analyses of separate associations, Poisson regression models with robust error variances were used to compute prevalence ratios (PR) with accompanying 95% confidence intervals (CI) for mutually-adjusted associations of tertiles of moderate-to-vigorous physical activity and of TV viewing time with the prevalence of a metabolically healthy profile among normal-weight, overweight, and obese adults.

For analyses of combined associations, tertiles of moderate-to-vigorous physical activity and of TV viewing time were combined to form a 9-level exposure variable: 'Lowest activity/highest TV viewing' (reference group), 'lowest activity/intermediate TV viewing', 'lowest activity/lowest TV viewing', intermediate activity/highest TV viewing', 'intermediate activity/intermediate TV viewing', 'intermediate activity/lowest TV viewing', 'highest activity/highest TV viewing', highest activity/intermediate TV viewing, 'highest activity/lowest TV viewing', with group ordering based on assumed increases in energy expenditure. Associations of activity/TV viewing tertiles with the prevalence of a metabolically healthy profile were examined among normal-weight, overweight, and obese adults. Statistical interaction between moderate-to-vigorous physical activity and TV viewing time was tested by including the product term of the corresponding tertiles in relation to metabolic health status in Poisson regression models. Statistical interaction was also tested between moderate-to-vigorous physical activity tertile and BMI group and between TV viewing tertile and BMI group, both in relation to metabolic health status. A triple interaction was also

examined between moderate-to-vigorous physical activity tertile, TV viewing tertile, and BMI group, in relation to metabolic health status.

Additionally, analyses for prevalent metabolic health were repeated with moderate-to-vigorous physical activity and TV viewing time each measured continuously (hours per week) in order to allow greater statistical power and improve model interpretations. The same interactions described above were tested based on these continuously measured variables. For each set of analyses, the first models adjusted for age, sex, and ethnicity. The second models further adjusted for occupational position, smoking, alcohol consumption, diet quality, sleep duration, and presence of an illness which limits moderate or vigorous intensity physical activity.

General linear regression models were used in additional analyses to examine differences in continuously measured TV viewing time across metabolic and obesity groups, with healthy normal-weight as the reference group. Differences in TV viewing between healthy and unhealthy obese groups were examined through pairwise comparisons. These models were adjusted for the same covariates as considered in previous analyses in addition to moderate-to-vigorous physical activity duration.

Objective 4: To examine cross-sectional differences in questionnaire- and accelerometer-assessed total physical activity between healthy and unhealthy normal-weight, overweight, and obese adults

Questionnaire and accelerometer-assessed total physical activity variables were standardised using Z scores (mean=0.00; standard deviation=1.00) to allow comparison between measures. Regression coefficients from general linear models and accompanying 95% confidence intervals were used to examine cross-sectional differences in questionnaire- and accelerometer-assessed total physical activity across 6 phenotypes: healthy normal-weight (reference group), unhealthy

normal-weight, healthy overweight, unhealthy overweight, healthy obese, and unhealthy obese. The first model adjusted for age, sex, and ethnicity. The second model further adjusted for occupational position, smoking status, alcohol consumption, diet quality, sleep duration, and presence of an illness which limits moderate or vigorous physical activity. Models were additionally adjusted for continuous BMI to examine whether between-group differences in total physical activity were explained by residual within-group differences in BMI.

Associations of a standard deviation increase in questionnaire- and accelerometer-assessed total physical activity with the prevalence of obesity and of each individual metabolic risk factor (hypertension, high blood glucose, insulin resistance, high triglycerides, low HDL-cholesterol) were also assessed, based on Poisson regression-derived prevalence ratios. These models were adjusted for age, sex, and ethnicity.

Objective 5: To examine cross-sectional differences in the likelihood of meeting recommendations for moderate-to-vigorous physical activity, based on questionnaire and accelerometer assessments, between healthy and unhealthy normal-weight, overweight, and obese adults

Objectively assessed moderate-to-vigorous physical activity was not normally distributed, and thus was not suitable for standardisation with Z scores for comparisons with questionnaire assessments. Data on questionnaire- and accelerometer-assessed moderate-to-vigorous physical activity were therefore categorised into binary variables to compare differences in the likelihood of meeting recommendations for moderate-to-vigorous physical activity (≥ 2.5 hours/week) between metabolic groups.

The number of participants undertaking ≥ 2.5 hours/week of moderate-to-vigorous physical activity was high (54.5% based on questionnaire; 28.9% based on accelerometer); therefore, Poisson regression models with robust error variances and accompanying 95% confidence

intervals were used to estimate prevalence ratios for meeting recommendations for each group compared with healthy normal-weight adults. Akaike Information Criteria (AIC) statistics were used to compare the fit of models based on questionnaire and accelerometer assessments (comparatively lower values indicating better model fit). As in previous analyses, the first model adjusted for age, sex, and ethnicity. The second model further adjusted for occupational position, smoking status, alcohol consumption, diet quality, sleep duration, and presence of an illness which limits moderate or vigorous physical activity.

In sensitivity analyses, the likelihood of meeting physical activity recommendations based on accelerometer assessment was compared between metabolic groups using data on moderate-to-vigorous physical activity in bouts of at least 1 minute (instead of at least 10 minutes in main analyses) to examine whether bout duration of moderate-to-vigorous physical activity may influence results. Each analysis was also repeated using a more stringent cut-point of 120 mg (instead of 100 mg) to define moderate-to-vigorous physical activity, requiring at least 80% of the activity to be at 120 mg for at least 10 minutes. As mentioned, this 120 mg cut-point captures activity which is more likely to be within the more intense moderate-to-vigorous range, reducing the possibility of contamination by light intensity activity.

3.8.2 Part 2: Healthy obesity and metabolic decline

This section will describe the statistical methods used to examine healthy obesity and future metabolic decline, again according to each previously defined study objective.

Objective 1: To describe the proportion of healthy obese adults who develop metabolic risk factor clustering over 20 years of follow-up using repeat clinical measures, and to compare the likelihood of development with that of healthy normal-weight adults

Phase 3 (1991/94) served as the baseline for these analyses. Participants with data on obesity and metabolic status at this baseline and at all 4 subsequent follow-ups were analysed. Cross-tabulations were used to describe the proportion of participants according to their baseline metabolic and obesity status in each category after 5- (1997/99), 10- (2002/04), 15- (2007/09), and 20- (2012/14) years. Poisson regression models with robust error variances were used to estimate incidence ratios with 95% confidence intervals for unhealthy obesity at each follow-up, excluding unhealthy obese adults at baseline. Models were adjusted for age, sex, and ethnicity.

Given that main analyses were based on complete case samples, requiring complete metabolic risk factor data at all 4 follow-up phases, absolute numbers of healthy obese adults were expected to be relatively low. Thus, sensitivity analyses were planned with the aim of examining patterns of metabolic decline using maximum samples for each metabolic and obesity group based on participant observations. For example, a 5-year transition from healthy to unhealthy obesity was considered if this took place either:

- From phase 3 to phase 5
- From phase 5 to phase 7 (among those who were not healthy obese at phase 3)
- From phase 7 to phase 9 (among those who were not healthy obese at phase 3 or phase 5)
- From phase 9 to phase 11 (among those who were not healthy obese at phase 3, phase 5, phase 7)

This procedure allowed for the consideration of new transitions that initiate after the first measurement phase. This process was done for 10-, 15-, and 20-year follow-ups for healthy obese adults, and for each of the 5 other metabolic and obesity groups. The 20-year follow-up sample remained the same as in original analyses, as no other variations are possible to construct within the 20-year maximum time period. These categories are not expected to be mutually exclusive as it is possible for participants to contribute more than 1 observation to any

given phenotype transition within and across time periods. Incidence ratios were therefore not deemed appropriate to construct, given that observations were not expected to be independent, resulting in a likely violation of model assumptions.

Objective 2: To describe incidence of individual metabolic risk factors over 20 years among initially healthy obese adults using repeat clinical measures, and to compare incidence with that of healthy normal-weight adults

Phase 3 (1991/94) served as the baseline for these analyses. Normal-weight, overweight, and obese participants were included in analyses if they were healthy at baseline (defined as having none of the 5 previously defined metabolic risk factors of interest), and had data on all metabolic risk factors at all 4 subsequent follow-ups. Cross-tabulations were used to describe incidence of each metabolic risk factor at 5- (1997/99), 10- (2002/04), 15- (2007/09), and 20- (2012/14) year follow-ups, and Poisson regression models with robust error variances were used to estimate incidence ratios and 95% confidence intervals for having each metabolic risk factor at follow-up for initially healthy obese compared with initially healthy normal-weight adults at baseline.

Given that main analyses were based on complete case samples, requiring complete metabolic risk factor data at all 4 subsequent follow-ups, absolute numbers of healthy obese adults were expected to be relatively low. Thus, as done previously, sensitivity analyses aimed to examine metabolic risk factor incidence using maximum samples based on participant observations. For example, 5-year incidence of hypertension among initially healthy obese adults was considered if this took place either:

- From phase 3 to phase 5

- From phase 5 to phase 7 (among healthy obese adults who did not have hypertension at phase 3)
- From phase 7 to phase 9 (among healthy obese adults who did not have hypertension at phase 3 or phase 5)
- From phase 9 to phase 11 (among healthy obese adults who did not have hypertension at phase 3, phase 5, phase 7)

This procedure allowed for the consideration of new cases of metabolic risk factor incidence that initiate after the first measurement phase. This process was done for 10-, 15-, and 20-year follow-ups for incidence of each of the 5 metabolic risk factors, separately for initially healthy normal-weight, overweight, and obese groups. The 20-year follow-up sample remained the same as in original analyses as no other variations are possible to construct within the 20-year maximum time period. These categories are not expected to be mutually exclusive as it is possible for participants to contribute more than 1 observation within and across time periods. Incidence ratios were therefore not deemed appropriate to construct given that observations were not expected to be independent and that model assumptions would likely be violated.

Objective 3: To systematically search the literature for published prospective studies on the risk of incident type 2 diabetes among obese adults who are metabolically healthy

An OvidSP-led systematic search of Medline (date range 1946 to August 2013) and Embase (date range 1947 to August 2013) was performed in August 2013. Truncated search terms included ‘obese’, ‘body mass index’, ‘metabolic’, ‘diabetes’, ‘type 2’, ‘risk’, and ‘incidence’. No language restrictions were applied. The specific search formula was as follows:

obes* and metabolic* and type 2 and diabetes and risk and inciden* and body mass index

After removing duplicate results, JAB and MH independently screened search results and agreed on studies to be included. Abstracts were scanned, and references within relevant papers were hand-searched for additional works. Studies were eligible for inclusion in the meta-analysis if they met the full pre-specified criteria for exposure (metabolically healthy obesity defined by body mass index and normal metabolic risk factor clustering, insulin profile, or risk score), outcome (type 2 diabetes incidence defined by blood glucose levels or self-report), population (adults aged ≥ 18 years at baseline), and study design (original prospective estimation).

As estimates may be presented at more than one stage of statistical adjustment, the most fully adjusted estimates were used for analyses, as these were more likely to be the closest approximations of true study effects. No standard criteria currently exist for assessing the quality of observational studies for meta-analyses, and study quality was therefore assessed according to the rigor of the study's exposure, outcome, and model adjustment strategy. Regarding the exposure, 2 points were assigned if the study considered metabolic clustering and 1 point if the study considered insulin profile alone. For the outcome, 2 points were assigned if the diagnosis was based on an objective clinical measurement (I.e. fasting plasma glucose), and 1 point if the diagnosis was based only on self-report. Based on suggested importance in the literature, studies were assigned 1 point if they considered each of the following relevant covariates: family history of diabetes, ethnicity, alcohol consumption, smoking status, physical activity or cardiorespiratory fitness, dietary sugar intake, and socioeconomic status. Studies were therefore scored out of 11 points, with higher scores reflecting better study quality.

Objective 4: To synthesize estimates obtained from the literature using random-effects meta-analysis and to examine whether age, ethnicity, duration of follow-up, and study quality explain any observed between-study heterogeneity in effects

A meta-analysis was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria (235). Studies identified through the literature search were supplemented with previously unpublished individual-level data from the English Longitudinal Study of Ageing (ELSA). Details of the methodology and results from these collaborative analyses are described elsewhere (236).

Meta-analysis was used to synthesize data from published studies identified through the literature search and ELSA. Natural variation in study effects were expected due to differences in factors such as healthy obesity definition, sampling procedure, statistical adjustment strategy, and sample demographics. A random effects model was therefore used to estimate the mean of the distribution of effects, with the I^2 statistic used to describe the percentage of between-study heterogeneity (237). Odds ratios, hazard ratios, and relative risk ratios were pooled and log-transformed for analyses. Random effects meta-regression was planned *a priori* to examine the extent to which age, ethnicity, duration of follow-up, and study quality including phenotype criteria explain any observed between-study heterogeneity in effects.

Objective 5: To produce an original effect estimate for the risk of incident type 2 diabetes among obese adults who initially have 0 metabolic risk factors (a strictly healthy sample)

Phase 3 (1991/94) of the Whitehall II cohort study was used as the baseline for these analyses, when mean participant age was 50 years. Normal-weight, overweight, and obese participants were considered healthy if they had none of the 5 metabolic risk factors of interest (hypertension, low HDL cholesterol, high triglycerides, insulin resistance, high blood glucose).

Diabetics at baseline were excluded from analyses, based on the same criteria used to define diabetes incidence. Years of follow-up were used as the time scale (range 1-18 years; median=16 years). Hazard ratios from Cox proportional hazards regression and accompanying 95%

confidence intervals were used to estimate excess risk of incident type 2 diabetes among metabolic and obesity groups at baseline compared with healthy normal-weight adults. The proportional hazards assumption was assessed and confirmed using Kaplan-Meier graphs by examining cumulative survival plots grouped on each exposure variable (continuous covariates were categorised for this purpose). The first model adjusted for age, sex, and ethnicity. The second model additionally adjusted for occupational position, cigarette smoking, alcohol consumption, diet quality, moderate-vigorous physical activity, and the presence of an illness which limits moderate-to-vigorous physical activity. Data on sleep duration was not available at the phase 3 baseline, and so this covariate was not considered. Likewise, data on milk use was not available, and so frequency of fruit and vegetable consumption was used alone as an indicator of diet quality.

3.8.3 Statistical software

Variables were constructed using SPSS 21, which was also used to fit general linear models and Cox regression models. Poisson regression models with robust error variances and random effects meta-analyses were performed using Stata 13. In all cases, a two-tailed $p<0.05$ indicated statistical significance.

3.9 Summary of data and methods

Data from the Whitehall II cohort study of British government workers were used for original analyses. Healthy obesity was defined as obesity (BMI ≥ 30 kg/m^2) without metabolic risk factor clustering (<2 of HDL-cholesterol ≤ 1.03 mmol/L for men and ≤ 1.29 mmol/L for women, or use of lipid lowering drugs; blood pressure ≥ 130/85 mmHg or use of anti-hypertension medication; fasting plasma glucose ≥ 5.6 mmol/L or use of diabetic medication; triglycerides ≥ 1.7 mmol/L; homeostatic model assessment (HOMA) of insulin-resistance (fasting insulin * fasting glucose / 22.5) > 90th percentile value in each respective analytical sample at baseline).

The first set of analyses investigated physical activity and sedentary behaviour in relation to healthy obesity. Cross-sectional associations of high self-reported moderate-to-vigorous physical activity and low self-reported leisure sitting time, separately and in combination, with prevalence of being metabolically healthy among normal-weight, overweight, and obese adults was examined. Prospective associations of these behaviours with risk of incident metabolic risk factor clustering were then examined over 15 years among initially healthy participants at baseline. Additional analyses examined cross-sectional associations of high moderate-to-vigorous physical activity and low TV viewing time, separately and in combination, with prevalence of being healthy among normal-weight, overweight, and obese adults. Differences in questionnaire- and accelerometer-assessed total physical activity were examined across metabolic and obesity groups. Differences across groups in meeting current guidelines for moderate-to-vigorous physical activity based on questionnaire and accelerometer were also examined.

The second set of analyses investigated healthy obesity and future metabolic decline. The proportion of participants according to their baseline obesity and metabolic status in each group after 5-, 10-, 15-, and 20- year follow-ups along with incidence ratios for unhealthy obesity at each follow-up were estimated. Incidence of each metabolic risk factor over 20 years was

examined for initially healthy normal-weight, overweight, and obese participants at baseline. Published estimates of the risk of incident type 2 diabetes among healthy obese adults were systematically searched in literature and meta-analysed in a random effects model. Original analyses of incident type 2 diabetes among healthy obese adults with no metabolic risk factors were conducted using Whitehall II data.

Section 4: Results

Results of this thesis are divided into 2 parts. This first part begins by providing a brief rationale for studies of physical activity and sedentary behaviour in relation to healthy obesity, followed by results according to previously stated research objectives. For each research objective, a flow chart outlining the selection of the analytical sample is provided, followed by descriptive characteristics of the analytical sample, followed then by results of main statistical models.

4.1 Part 1: Physical activity and sedentary behaviour in relation to healthy obesity

Rationale

Physical activity is known to be important for metabolic health among the population at large, but whether moderate-to-vigorous physical activity distinguishes healthy from unhealthy obesity is unclear. The plausible role of sedentary behaviour in promoting healthy obesity has not been thoroughly examined, and it has not been investigated whether associations of moderate-to-vigorous physical activity and leisure sitting time in relation to healthy obesity are truly independent or interactive in nature. Additionally, no studies have examined differences in total physical activity between healthy and unhealthy obese groups using objective physical activity assessments, and thus the degree to which reliance on self-reported measures of physical activity has limited our understanding of its role in healthy obesity is unknown.

Objective 1: Cross-sectional associations of self-reported high moderate-to-vigorous physical activity and self-reported low leisure sitting time, separately and in combination, with prevalence of a metabolically healthy profile among normal-weight, overweight, and obese adults

Physical activity and sedentary behaviour were measured together for the first time at the 5th phase of data collection (1997/99), and this therefore serves as the baseline for the first analysis of these behaviours in relation to healthy obesity. A flow chart illustrating the selection of the analytical sample is provided in **Figure 2**.

Figure 2 Selection of the analytical sample for cross-sectional analyses of moderate-to-vigorous physical activity and leisure sitting time in relation to healthy obesity

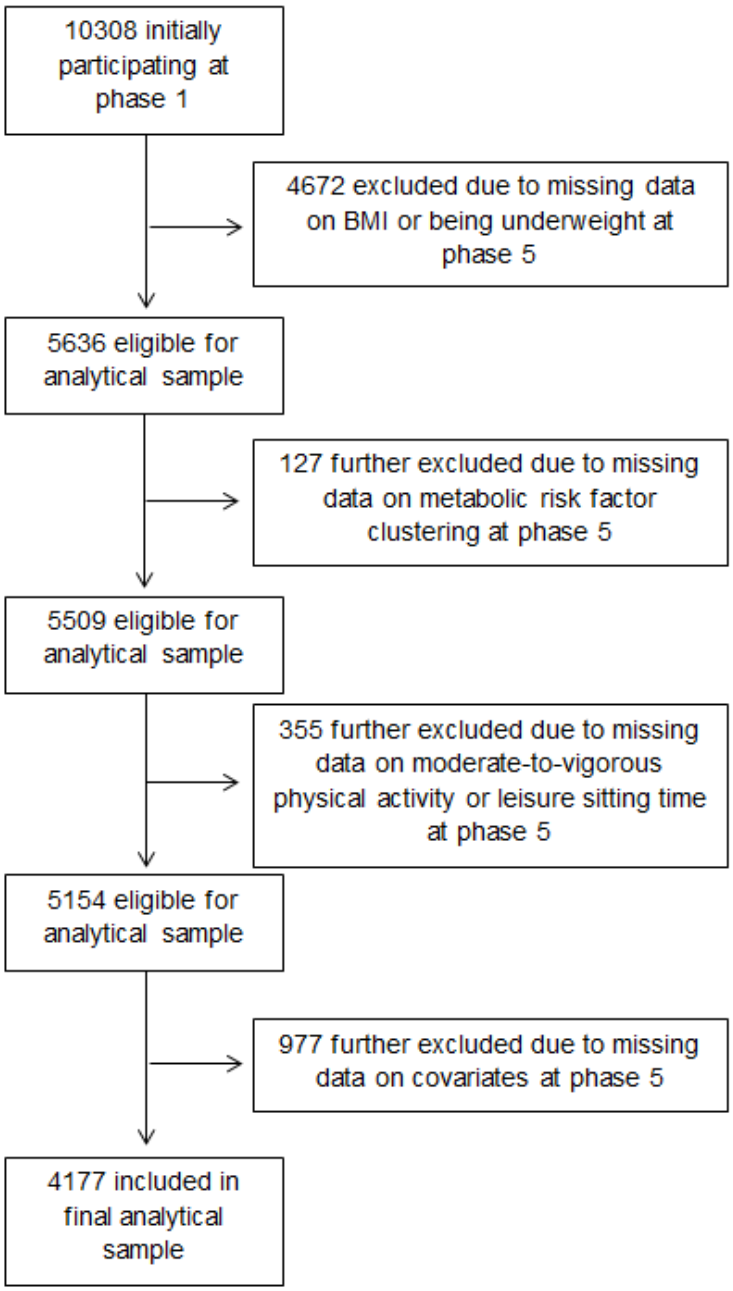


Table 1 presents baseline descriptive characteristics of participants comprising the analytic sample. Among 2991 men and 1186 women aged 45-69 years with complete data on all variables required for analyses, 1787 were normal-weight, of which 1481 (82.9%) were considered healthy normal-weight. A further 1833 were overweight, of which 1169 (63.8%) were considered healthy overweight. A further 557 were obese, of which 237 (42.5%) were considered healthy obese. Healthy obese adults were less likely than healthy normal-weight adults to be male (50.2% vs. 67.2%, $p<0.05$), while both healthy and unhealthy obese adults were more likely than healthy normal-weight adults to be of the lowest occupational position (19.8% and 15.9% versus 9.6% respectively, each $p<0.05$). Each metabolic characteristic appeared more adverse among healthy overweight and healthy obese adults compared with healthy normal-weight adults; with the exception of fasting glucose among healthy obese adults.

Healthy and unhealthy obese adults showed the highest prevalence of an illness which limits moderate or vigorous physical activity compared with healthy normal-weight adults (49.7% and 53.8% vs. 27.3% respectively, each $p<0.05$). Both healthy and unhealthy obese adults showed fewer hours per week of self-reported moderate-to-vigorous physical activity compared with healthy normal-weight adults (3 hours and 2.8 hours vs. 3.7 hours respectively, each $p<0.05$). In contrast, only unhealthy obese adults showed higher leisure sitting time compared with healthy normal-weight adults (22.8 hours vs. 20.5 hours respectively, $p<0.05$).

Compared with those included in the analytic sample (n=4177), those excluded (n=6131) were more likely to be female (36.3% vs. 28.4%, $p<0.001$), of a non-while ethnicity (13.8% vs. 6.7%, $p<0.001$) and in the lowest occupational position (18.6% vs. 11.6%, $p<0.001$) but did not differ in age (mean=55.9 years for those included vs. 56 years for those excluded, $p=0.68$). Compared with those participants included in analyses, those excluded were also more likely to be obese (17.5% vs. 13.3% respectively, $p<0.001$) but were not less likely to be metabolically healthy (69.7% vs. 69.1% respectively, $p=0.62$). Excluded participants also had lower moderate to vigorous physical activity (3.0 hours/week vs. 3.5 hours/week respectively, $p<0.001$) and higher leisure sitting time (21.0 hours/week vs. 20.1 hours/week respectively, $p=0.01$).

Table 1 Characteristics of adults aged 45-69 at baseline (71.6% male) at phase 5 (1997/99) by metabolic and obesity status (n=4177)

	Healthy normal-weight (n=1481)	Unhealthy normal-weight (n=306)	Healthy overweight (n=1169)	Unhealthy overweight (n=664)	Healthy obese (n=237)	Unhealthy obese (n=320)
Male – n (%)	995 (67.2)	254 (83%)*	866 (74.1)*	538 (81%)*	119 (50.2)*	219 (68.4)
Age (years)	55.4 (6.1)	57.9 (6.1)	55.8 (6.1)	56.9 (6.0)*	55.2 (5.8)	56 (5.7)*
Non-white ethnicity – n (%)	81 (5.5)	36 (11.8)*	60 (5.1)	60 (9)*	16 (6.8)	25 (7.8)
Lowest occupational position – n (%)	142 (9.6)	30 (9.8)	142 (12.1)*	72 (10.8)	47 (19.8)*	51 (15.9)*
Lowest quality diet – n (%)	298 (20.1)	69 (22.5)	286 (24.5)*	162 (24.4)*	45 (19)	86 (26.9)*
Consumes fruit and vegetables < daily – n (%)	322 (21.7)	67 (21.9)	313 (26.8)*	174 (26.2)*	54 (22.8)	102 (31.9)*
Consumes whole/full-fat milk most often – n (%)	255 (17.2)	46 (15)	184 (15.7)	95 (14.3)	28 (11.8)*	27 (8.4)*
Consumes white bread most often – n (%)	275 (18.6)	69 (22.5)	283 (24.2)*	174 (26.2)*	52 (21.9)	87 (27.2)*
Current smoker – n (%)	125 (8.4)	29 (9.5)	110 (9.4)	64 (9.6)	22 (9.3)	27 (8.4)
High alcohol consumption in previous week – n (%)	305 (20.6)	61 (19.9)	310 (26.5)*	185 (27.9)*	58 (24.5)	82 (25.6)*
Sleeps ≤ 5 hours/night – n (%)	92 (6.2)	19 (6.2)	76 (6.5)	57 (8.6)*	30 (12.7)*	42 (13.1)*
Has illness that greatly limits moderate or vigorous activity – n (%)	257 (17.4)	96 (31.4)*	224 (19.2)	180 (27.1)*	91 (38.4)*	126 (39.4)*
Systolic blood pressure (mmHg)	117 (14.8)	130.4 (17.2)*	121.1 (14.9)*	131.1 (16.2)*	126.7 (16.1)*	133.6 (16.3)*
Diastolic blood pressure (mmHg)	73.5 (9.6)	81.1 (10.6)*	76.7 (9.7)*	82.3 (10.0)*	78.9 (9.5)*	84.4 (11.2)*
Fasting glucose (mmol/l)	4.9 (0.5)	5.8 (2.0)*	5 (0.5)	5.7 (1.8)*	5 (0.4)	5.9 (2.2)*
HOMA insulin resistance	1.3 (0.9)	3.4 (5.3)*	1.7 (0.8)*	4.1 (6.5)*	2.2 (0.9)*	6.7 (13.0)*
Triglycerides (mmol/l)	1 (0.4)	1.8 (0.9)*	1.2 (0.6)*	2.1 (1.1)*	1.2 (0.4)*	2.1 (0.9)*
HDL cholesterol (mmol/l)	1.6 (0.4)	1.3 (0.4)*	1.5 (0.3)*	1.2 (0.3)*	1.5 (0.3)*	1.2 (0.3)*
Body mass index (kg/m²)	22.8 (1.6)	23.5 (1.2)*	26.9 (1.3)*	27.3 (1.3)*	32.9 (2.9)*	33.6 (3.5)*
Range	18.56-25.00	18.78-24.99	25.01-29.98	25.00-30.00	30.00-44.42	30.01-48.21
Moderate-to-vigorous activity [a] (hours/week)	3.7 (3.3)	3.5 (3.3)	3.7 (3.4)	3.5 (3.4)	3 (2.9)*	2.8 (2.8)*
High moderate-to-vigorous activity [b] – n (%)	515 (34.8)	98 (32)	403 (34.5)	212 (31.9)	64 (27)*	82 (25.6)*
Leisure sitting time (hours/week)	20.5 (12.7)	20.7 (12.6)	20.7 (12.1)	21.3 (13.0)	21.5 (13.8)	22.8 (14.2)*
Low leisure sitting time – n (%)	423 (28.6)	85 (27.8)	311 (26.6)	178 (26.8)	63 (26.6)	71 (22.2)*

Data are mean (standard deviation) unless otherwise noted. *Different from healthy normal-weight ($p<0.05$) based on linear regression (continuous variables) or logistic regression (binary variables). [a] Units are metabolic equivalent hours/week (duration in moderate-to-vigorous activity multiplied by its metabolic equivalent score). [b] Based on highest tertile.

Table 2 presents results of analyses examining separate cross-sectional associations between levels of moderate-to-vigorous physical activity and leisure sitting with prevalence of a metabolically healthy profile among normal-weight, overweight, and obese adults. Among normal-weight adults, being in the highest compared with the lowest moderate-to-vigorous physical activity group was associated with a 1.09 (95% CI=1.04, 1.15) times higher prevalence of being metabolically healthy, adjusting for age, sex, ethnicity, and leisure sitting time. This association remained after further adjustment for occupational position, health status, and health behaviours (PR=1.07; 1.01, 1.13). A similarly increased prevalence was observed among highly active overweight adults, but highly active obese adults showed no increased prevalence of a healthy profile compared with the least active group. Being in the lowest compared with the highest leisure sitting group was not associated with a higher likelihood of being metabolically healthy among normal-weight, overweight or obese adults at any stage of adjustment.

As shown in **Appendix 3**, multivariable-adjusted subsidiary analyses found no evidence for an interaction between moderate-to-vigorous physical activity tertile and BMI group in relation to metabolic health status (p-interaction=0.58). When adjusting for BMI group, the most active group showed a 1.10 (95% CI=1.04, 1.15) times higher prevalence of being healthy. Associations with metabolic health were not evident for leisure sitting time in these analyses.

Further subsidiary analyses examining moderate-to-vigorous physical activity as a continuous variable indicated that a 1-hour per week increase in such activity was associated with a 1.01 (95% CI=1.01, 1.02) times higher prevalence of being healthy, adjusting for continuously measured BMI and covariates (**Appendix 4**). Conversely, no association was observed with continuously measured leisure sitting time. No interactions with continuously measured BMI were found for moderate-to-vigorous physical activity (p-interaction=0.26) or leisure sitting (p-interaction=0.10).

Table 2 Separate associations of moderate-to-vigorous physical activity and leisure sitting with health among adults aged 45-69 (n=4177)

	Prevalence of being healthy					
	Among normal-weight (n=1787)		**Among overweight (n=1833)**		**Among obese (n=557)**	
	Model 1 Prevalence Ratio (95% CI)	**Model 2** Prevalence Ratio (95% CI)	**Model 1** Prevalence Ratio (95% CI)	**Model 2** Prevalence Ratio (95% CI)	**Model 1** Prevalence Ratio (95% CI)	**Model 2** Prevalence Ratio (95% CI)
Moderate-to-vigorous physical activity level*						
Lowest	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Intermediate	1.05 (1.00, 1.11)	1.04 (0.99, 1.10)	1.05 (0.96, 1.14)	1.04 (0.96, 1.14)	1.13 (0.90, 1.42)	1.11 (0.88, 1.40)
Highest	1.09 (1.04, 1.15)	1.07 (1.01, 1.13)	1.12 (1.03, 1.22)	1.10 (1.01, 1.20)	1.19 (0.94, 1.52)	1.18 (0.92, 1.51)
Leisure sitting time level*						
Highest	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Intermediate	0.97 (0.92, 1.02)	0.96 (0.91, 1.01)	1.07 (0.98, 1.15)	1.07 (0.99, 1.16)	1.07 (0.86, 1.34)	1.03 (0.82, 1.29)
Lowest	0.97 (0.92, 1.02)	0.96 (0.92, 1.01)	1.03 (0.94, 1.13)	1.01 (0.93, 1.11)	1.18 (0.92, 1.51)	1.15 (0.89, 1.49)

*Associations are mutually adjusted. **Model 1** adjusted for age sex, ethnicity. **Model 2** additionally adjusted for occupational position, smoking, alcohol consumption, diet quality, sleep duration, and presence of an illness which limits moderate or vigorous activity

Formal tests of statistical interaction between moderate-to-vigorous physical activity and leisure sitting in relation to prevalence of being metabolically healthy were non-significant for all BMI groups. As shown in **Table 3**, compared with normal-weight adults who had both low moderate-to-vigorous physical activity and high leisure sitting, only those who had an intermediate level of physical activity and a high level of leisure sitting showed a marginally increased prevalence of being healthy (PR=1.08, 95% CI=1.00, 1.18) adjusting for age, sex, and ethnicity. Among overweight adults, those who had intermediate levels of both moderate-to-vigorous physical activity and leisure sitting showed a higher prevalence of being healthy (PR=1.23, 95% CI=1.07, 1.40), as did those overweight adults who had the highest level of physical activity and lowest level of leisure-time sitting (PR=1.25, 95% CI=1.08, 1.45) in minimally adjusted models. No associations were observed among obese adults. Results remained among overweight adults after additional adjustment for other covariates (**Table 4**). In these multivariable-adjusted models, the combination of low moderate-to-vigorous physical activity and low leisure sitting was marginally associated with higher prevalence of being healthy among obese adults (PR=1.44, 95% CI=1.00, 2.07), as was the combination of high moderate-to-vigorous physical activity and low leisure sitting (PR=1.55, 95% CI=1.00, 2.43).

As shown in **Appendix 5**, multivariable-adjusted subsidiary analyses found no evidence for a triple interaction between moderate-to-vigorous physical activity tertile, leisure sitting tertile, and BMI group in relation to metabolic health status (p-interaction=0.12). Adjusting for BMI group, adults combining high moderate-to-vigorous physical activity and low leisure sitting showed a 1.14 (95% CI=1.05, 1.24) times higher prevalence of being healthy.

Table 3 Combined associations of moderate-to-vigorous physical activity and leisure sitting with health among adults aged 45-69 (n=4177)

	Prevalence of being healthy		
	Model 1 Prevalence Ratio (95% CI)		
	Among normal-weight (n=1787)		
	Leisure sitting time level		
Moderate-to-vigorous physical activity level	Highest	Intermediate	Lowest
Lowest	1.00 (reference)	1.00 (0.91, 1.09)	0.92 (0.83, 1.02)
Intermediate	1.08 (1.00, 1.18)	0.97 (0.88, 1.06)	1.05 (0.96, 1.13)
Highest	1.06 (0.97, 1.15)	1.08 (0.99, 1.17)	1.07 (0.98, 1.17)
p-interaction		0.16	
	Among overweight (n=1833)		
	Leisure sitting time level		
Moderate-to-vigorous physical activity level	Highest	Intermediate	Lowest
Lowest	1.00 (reference)	1.04 (0.90, 1.20)	1.06 (0.91, 1.23)
Intermediate	1.03 (0.89, 1.19)	1.23 (1.07, 1.40)	0.98 (0.84, 1.16)
Highest	1.14 (0.99, 1.31)	1.12 (0.97, 1.29)	1.25 (1.08, 1.45)
p-interaction		0.84	
	Among obese (n=557)		
	Leisure sitting time level		
Moderate-to-vigorous physical activity level	Highest	Intermediate	Lowest
Lowest	1.00 (reference)	0.99 (0.68, 1.45)	1.42 (0.99, 2.04)
Intermediate	1.19 (0.81, 1.75)	1.42 (0.99, 2.02)	1.09 (0.71, 1.67)
Highest	1.24 (0.84, 1.83)	1.27 (0.86, 1.86)	1.51 (0.96, 2.38)
p-interaction		0.49	

Models adjusted for age, sex, ethnicity

Table 4 Combined associations of moderate-to-vigorous physical activity and leisure sitting time with health among adults aged 45-69 (n=4177)

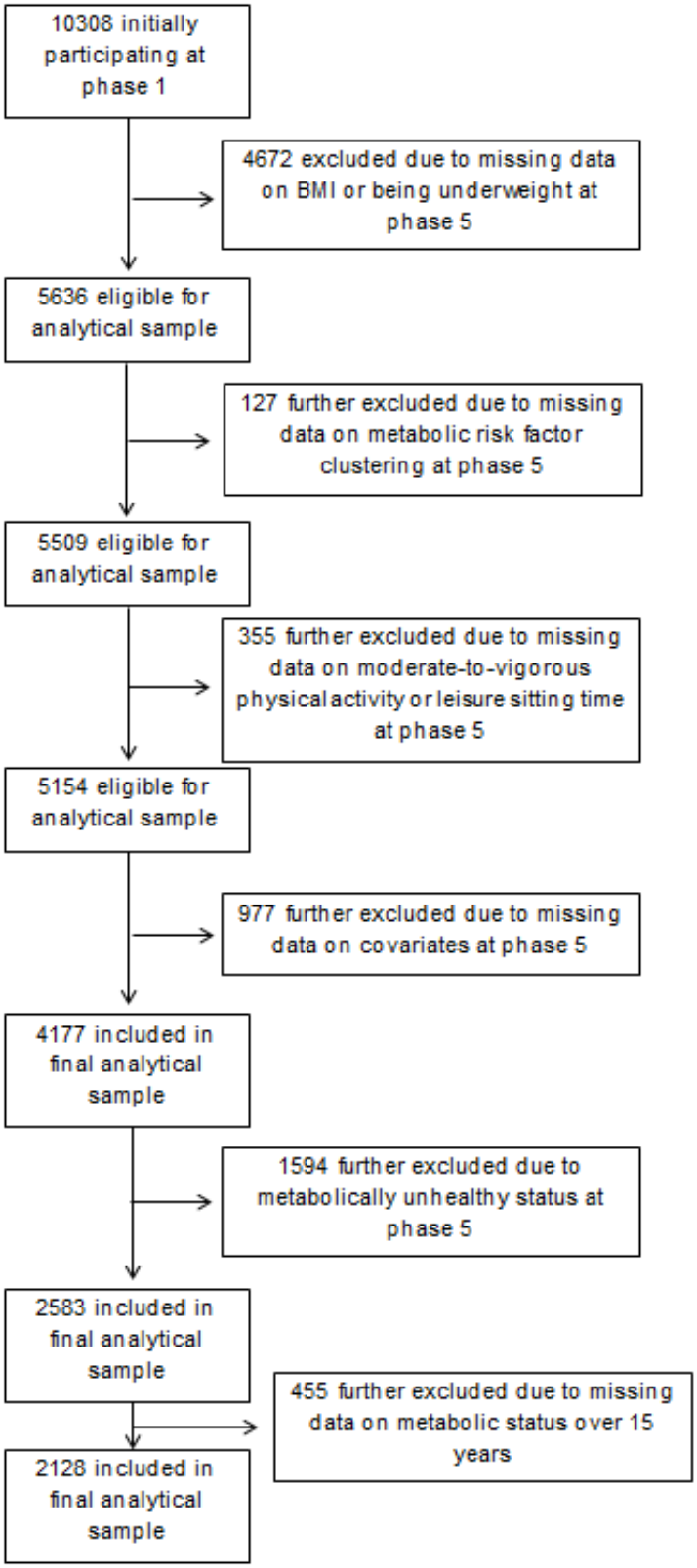
	Prevalence of being healthy		
	Model 2 Prevalence Ratio (95% CI)		
Among normal-weight (n=1787)			
	Leisure sitting time level		
Moderate-to-vigorous physical activity level	Highest	Intermediate	Lowest
Lowest	1.00 (reference)	0.98 (0.90, 1.07)	0.92 (0.82, 1.02)
Intermediate	1.07 (0.98, 1.16)	0.95 (0.86, 1.04)	1.03 (0.94, 1.11)
Highest	1.03 (0.95, 1.13)	1.05 (0.97, 1.14)	1.04 (0.95, 1.14)
p-interaction		0.17	
Among overweight (n=1833)			
	Leisure sitting time level		
Moderate-to-vigorous physical activity level	Highest	Intermediate	Lowest
Lowest	1.00 (reference)	1.06 (0.91, 1.22)	1.05 (0.90, 1.22)
Intermediate	1.03 (0.89, 1.20)	1.24 (1.08, 1.41)	0.96 (0.82, 1.13)
Highest	1.13 (0.98, 1.31)	1.10 (0.96, 1.27)	1.22 (1.05, 1.42)
p-interaction		0.93	
Among obese (n=557)			
	Leisure sitting time level		
Moderate-to-vigorous physical activity level	Highest	Intermediate	Lowest
Lowest	1.00 (reference)	0.97 (0.66, 1.41)	1.44 (1.00, 2.07)
Intermediate	1.24 (0.84, 1.81)	1.37 (0.96, 1.94)	0.99 (0.64, 1.54)
Highest	1.24 (0.84, 1.82)	1.20 (0.81, 1.78)	1.55 (1.00, 2.43)
p-interaction		0.46	

Models adjusted for age, sex, ethnicity, occupational position, smoking, alcohol consumption, diet quality, sleep duration, and presence of an illness which limits moderate or vigorous activity

Objective 2: Prospective associations of self-reported high moderate-to-vigorous physical activity and self-reported low leisure sitting time, separately and in combination, with incident metabolic risk factor clustering among initially healthy normal-weight, overweight, and obese adults

Phase 5 (1997/99) served as the baseline for these analyses as this was the first time moderate-to-vigorous physical activity, leisure sitting time, anthropometrics and metabolic risk factors were measured together. A flow chart illustrating the selection of the analytical sample is provided in **Figure 3**.

Figure 3 Selection of the analytical sample for the prospective study of moderate-to-vigorous physical activity and leisure sitting time in relation to incident metabolic risk factor clustering



The baseline for these analyses is the same as for previous cross-sectional analyses, and so descriptive characteristics were not repeated. Compared with participants included in the analytical sample (n=2128), those excluded (n=8180) were older (56.3 years vs.54.9 years respectively, p<0.001), more likely to be female (34.5% vs. 27.7% respectively, p<0.001), of a non-white ethnicity (12.3% vs. 5.7% respectively, p<0.001), and of the lowest occupational position (17.3% vs. 8.4% respectively, p<0.001). Compared with participants included in analyses, those excluded were also more likely to be obese (18.1% vs. 8.4% respectively, p<0.001), to have lower moderate-to-vigorous physical activity (3.1 hours/week vs. 3.7 hours/week respectively, p<0.001) but not higher leisure sitting time (20.6 hours/week vs. 20.6 hours/week respectively, p=0.86). Differences in the likelihood of being metabolically healthy were not relevant to test given that all participants included in the analytical sample were healthy.

Results of analyses examining separate associations between levels of moderate-to-vigorous physical activity and leisure-time sitting with incidence of metabolic risk factor clustering over 15 years among initially healthy normal-weight, overweight, and obese adults are presented in **Table 5.** Having the highest compared with the lowest moderate-to-vigorous physical activity was not associated with a lower incidence of metabolic risk factor clustering among normal-weight, overweight, or obese adults in a model adjusting for age, sex, ethnicity, and leisure sitting time; nor in a model additionally adjusting for other covariates. Initially healthy overweight adults with an intermediate level of leisure sitting showed a lower incidence of metabolic risk factor clustering compared with those with the highest level of sitting (IR=0.88, 95% CI=0.78, 0.98), which remained unchanged after additional adjustments. Leisure sitting level was not associated with risk of incident metabolic risk factor clustering among normal-weight or among obese adults at any stage of adjustment.

Subsidiary analyses also found no evidence for associations of either moderate-to-vigorous physical activity tertile or leisure sitting tertile in relation to incident metabolic risk factor

clustering when adjusting for BMI group, with no evidence for interaction with BMI group (**Appendix 6**).

Further subsidiary analyses examining continuously measured moderate-to-vigorous physical activity and leisure sitting time indicated that neither was associated with incidence of metabolic risk factor clustering, adjusting for continuously measured BMI and covariates (**Appendix 7**). No interactions with continuously measured BMI were found for moderate-to-vigorous physical activity (p-interaction=0.67) or leisure sitting (p-interaction=0.30).

Table 5 Separate associations of moderate-to-vigorous physical activity and leisure sitting with incident metabolic risk factor clustering among initially healthy normal-weight, overweight, and obese adults aged 45-69 at baseline (n=2128)

	Risk of incident metabolic risk factor clustering over 15 years		
	Among initially healthy normal-weight (n=1077)	**Among initially healthy overweight (n=872)**	**Among initially healthy obese (n=179)**
		Model 1 Incidence Ratio (95% CI)	
Moderate-to-vigorous physical activity level*			
Lowest	1.00 (reference)	1.00 (reference)	1.00 (reference)
Intermediate	0.92 (0.78, 1.09)	1.00 (0.89, 1.13)	0.90 (0.73, 1.11)
Highest	1.07 (0.90, 1.25)	0.98 (0.87, 1.11)	1.00 (0.83, 1.22)
Leisure sitting time level*			
Highest	1.00 (reference)	1.00 (reference)	1.00 (reference)
Intermediate	0.90 (0.77, 1.04)	0.88 (0.78, 0.98)	1.01 (0.82, 1.23)
Lowest	0.91 (0.78, 1.07)	1.01 (0.89, 1.13)	1.15 (0.93, 1.42)
		Model 2 Incidence Ratio (95% CI)	
Moderate-to-vigorous physical activity level*			
Lowest	1.00 (reference)	1.00 (reference)	1.00 (reference)
Intermediate	0.94 (0.79, 1.11)	1.00 (0.89, 1.13)	0.93 (0.74, 1.17)
Highest	1.10 (0.94, 1.30)	0.98 (0.87, 1.11)	1.03 (0.83, 1.27)
Leisure sitting time level*			
Highest	1.00 (reference)	1.00 (reference)	1.00 (reference)
Intermediate	0.93 (0.80, 1.08)	0.88 (0.78, 0.98)	1.00 (0.81, 1.24)
Lowest	0.94 (0.81, 1.10)	1.01 (0.90, 1.13)	1.12 (0.90, 1.40)

* Associations are mutually adjusted. Follow-up duration is cumulative, considering incidence after 5, 10, or 15 years. **Model 1** adjusted for age, sex, and ethnicity. **Model 2** additionally adjusted for occupational position, alcohol, smoking, diet quality, and presence of an illness which limits moderate or vigorous physical activity

As shown in **Table 6** and **Table 7,** formal tests of statistical interaction between moderate-to-vigorous physical activity and leisure sitting time in relation to incident metabolic risk factor clustering were non-significant for all BMI groups. Compared with initially healthy overweight adults who had both low moderate-to-vigorous physical activity and high leisure sitting time, only those who had an intermediate level of both physical activity and leisure sitting showed a marginally reduced incidence of metabolic risk factor clustering, which remained after adjustment for additional covariates (IR=0.80, 95% CI=0.65, 0.98). No combination of moderate-to-vigorous physical activity and leisure sitting time was associated with lower incidence of metabolic risk factor clustering among initially healthy normal-weight or obese adults.

Subsidiary analyses also found no evidence for associations of any combination of moderate-to-vigorous physical activity and leisure sitting in relation to incident metabolic risk factor clustering, with no evidence for triple interaction with BMI group (**Appendix 8**).

Table 6 Combined associations of moderate-to-vigorous physical activity and leisure sitting with incident metabolic risk factor clustering over 15 years among initially healthy normal-weight, overweight, and obese adults aged 45-69 at baseline (n=2128)

	Risk of incident metabolic risk factor clustering over 15 years		
	Model 1 Incidence Ratio (95% CI)		
Among initially healthy normal-weight (n=1077)			
	Leisure sitting time level		
Moderate-to-vigorous physical activity level	Highest	Intermediate	Lowest
Lowest	1.00 (reference)	1.00 (0.76, 1.32)	0.92 (0.67, 1.27)
Intermediate	1.00 (0.77, 1.28)	0.90 (0.69, 1.18)	0.80 (0.59, 1.07)
Highest	1.11 (0.88, 1.41)	0.91 (0.71, 1.18)	1.12 (0.87, 1.44)
p-interaction		0.73	
Among initially healthy overweight (n=872)			
	Leisure sitting time level		
Moderate-to-vigorous physical activity level	Highest	Intermediate	Lowest
Lowest	1.00 (reference)	0.85 (0.69, 1.05)	0.98 (0.80, 1.21)
Intermediate	1.06 (0.89, 1.26)	0.80 (0.65, 0.99)	0.99 (0.80, 1.21)
Highest	0.88 (0.73, 1.07)	0.91 (0.76, 1.09)	0.97 (0.80, 1.19)
p-interaction		0.34	
Among initially healthy obese (n=179)			
	Leisure sitting time level		
Moderate-to-vigorous physical activity level	Highest	Intermediate	Highest
Lowest	1.00 (reference)	1.06 (0.76, 1.47)	1.26 (0.92, 1.73)
Intermediate	1.01 (0.71, 1.44)	0.90 (0.64, 1.27)	1.05 (0.72, 1.52)
Highest	1.03 (0.77, 1.39)	1.08 (0.80, 1.46)	1.16 (0.86, 1.56)
p-interaction		0.61	

Follow-up duration is cumulative, considering incidence after 5, 10, or 15 years. Models adjusted for age, sex, ethnicity

Table 7 Combined associations of moderate-to-vigorous physical activity and leisure sitting with incident metabolic risk factor clustering over 15 years among initially healthy normal-weight, overweight, and obese adults aged 45-69 at baseline (n=2128)

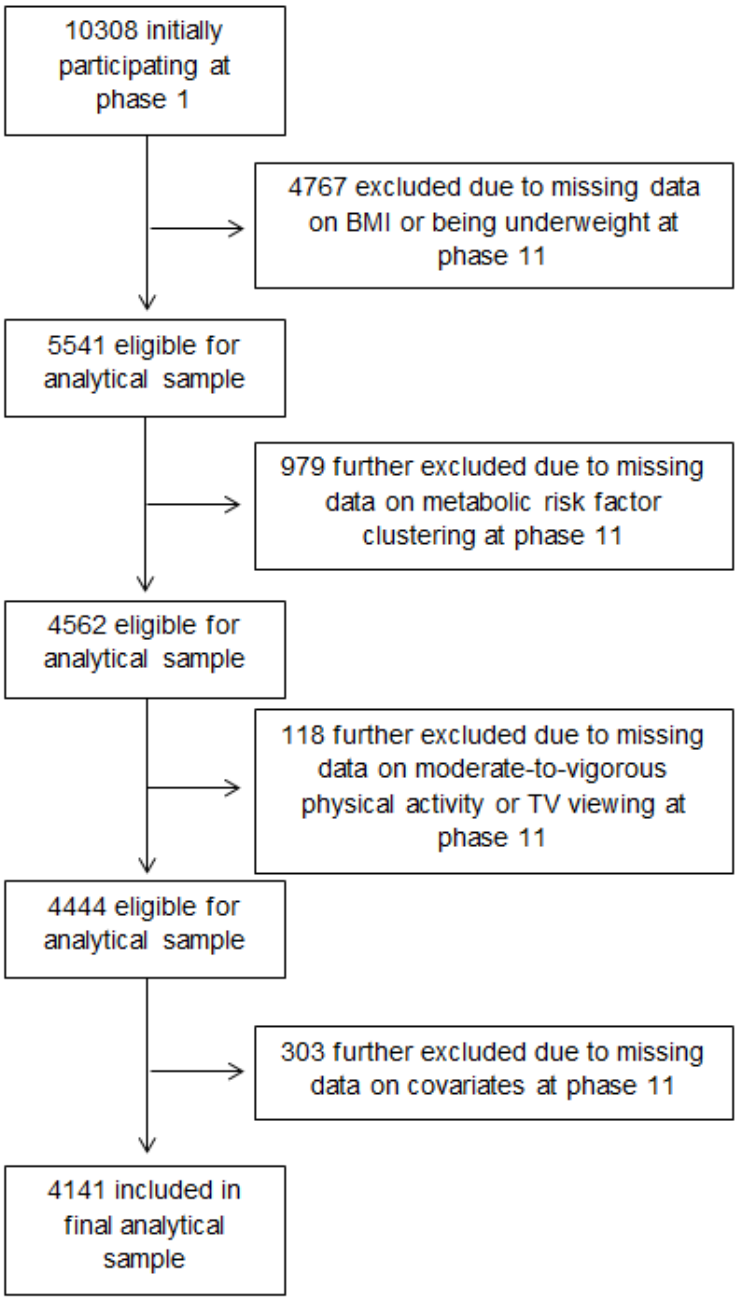
	Risk of incident metabolic risk factor clustering over 15 years		
	Model 2		
	Incidence Ratio (95% CI)		
Among initially healthy normal-weight (n=1077)			
	Leisure sitting time level		
Moderate-to-vigorous physical activity level	Highest	Middle	Lowest
Lowest	1.00 (reference)	1.02 (0.78, 1.34)	0.97 (0.71, 1.31)
Intermediate	1.02 (0.80, 1.30)	0.94 (0.72, 1.24)	0.84 (0.63, 1.13)
Highest	1.14 (0.90, 1.45)	0.99 (0.77, 1.28)	1.19 (0.92, 1.54)
p-interaction		0.73	
Among initially healthy overweight (n=872)			
	Leisure sitting time level		
Moderate-to-vigorous physical activity level	Highest	Middle	Lowest
Lowest	1.00 (reference)	0.84 (0.68, 1.04)	0.99 (0.80, 1.21)
Intermediate	1.05 (0.88, 1.25)	0.80 (0.65, 0.98)	0.99 (0.80, 1.21)
Highest	0.88 (0.73, 1.07)	0.91 (0.75, 1.09)	0.98 (0.79, 1.20)
p-interaction		0.32	
Among initially healthy obese (n=179)			
	Leisure sitting time level		
Moderate-to-vigorous physical activity level	Highest	Highest	Highest
Lowest	1.00 (reference)	1.06 (0.75, 1.48)	1.29 (0.94, 1.77)
Intermediate	1.08 (0.74, 1.58)	0.95 (0.66, 1.35)	1.03 (0.69, 1.54)
Highest	1.07 (0.80, 1.44)	1.12 (0.83, 1.52)	1.17 (0.86, 1.59)
p-interaction		0.41	

Follow-up duration is cumulative, considering incidence after 5, 10, or 15 years. Models adjusted for age, sex, ethnicity, occupational position, alcohol, smoking, diet quality, sleep duration, and presence of an illness which limits moderate or vigorous physical activity

Objective 3: Cross-sectional associations of self-reported high moderate-to-vigorous physical activity and self-reported low TV viewing time, separately and in combination, with prevalence of a metabolically healthy profile among normal-weight, overweight, and obese adults

Analyses utilised data from the 11th phase of data collection (2012/13), as this was the first occasion when TV viewing time was measured in addition to moderate-to-vigorous physical activity, anthropometrics, and metabolic risk factors. A flow chart illustrating the selection of the analytical sample is provided in **Figure 4**.

Figure 4 Selection of the analytical sample for the cross-sectional study of moderate-to-vigorous physical activity and TV viewing time in relation to healthy obesity



The sample of participants included in analyses was largely the same as in previous cross-sectional analyses of leisure sitting time, and so descriptive characteristics were not repeated. Compared with participants included in the analytical sample (n=4141), those excluded (n=6131) were older (71.3 years vs.69.0 years respectively, p<0.001), more likely to be female (39.0% vs. 24.1% respectively, p<0.001), of a non-white ethnicity (13.6% vs. 7.0% respectively, p<0.001), and of the lowest occupational position (15.4% vs. 7.4% respectively, p<0.001). Compared with those included in analyses, those excluded were also more likely to be obese (25.7% vs. 17.8% respectively, p<0.001), more likely to be metabolically healthy (53.9% vs. 49.0% respectively, p=0.04), had lower moderate-to-vigorous physical activity (2.8 hours/week vs. 3.6 hours/week respectively, p<0.001) and higher TV viewing time (22.7 hours/week vs. 20.1 hours/week respectively, p<0.001).

Table 8 presents results of separate associations of moderate-to-vigorous physical activity and TV viewing with prevalence of being metabolically healthy among normal-weight, overweight, and obese adults. In a multivariate-adjusted model considering demographic, illness, and health behaviour covariates as well as TV viewing time, high moderate-to-vigorous physical activity was associated with a 1.34 (95% CI=1.17, 1.53) times higher likelihood of being healthy among overweight adults, but was not associated with a healthy status among normal-weight or obese adults. Low TV viewing time was associated with a healthy status among normal-weight adults (PR=1.16, 95% CI=1.05, 1.28), but not among overweight or obese adults.

As shown in **Appendix 9**, multivariable-adjusted subsidiary analyses found no evidence for interaction between moderate-to-vigorous physical activity tertile and BMI group (p-interaction=0.08) or between TV viewing tertile and BMI group (p-interaction=0.25) in relation to metabolic health status. Adjusting for BMI group, adults with the highest vs. the lowest moderate-to-vigorous physical activity level showed a 1.16 (95% CI=1.07, 1.25) times higher prevalence of being healthy, while adults with the lowest vs. the highest TV viewing level showed a 1.12 (95% CI=1.04, 1.20) times higher prevalence of being healthy.

Further subsidiary analyses examining continuously measured moderate-to-vigorous physical activity indicated that a 1-hour per week increase in such activity was associated with a 1.02 (95% CI=1.01, 1.03) times higher prevalence of being healthy, adjusting for continuously measured BMI and covariates (**Appendix 10**). Conversely, no association was found with continuously measured TV viewing time. No interactions with continuously measured BMI were found for moderate-to-vigorous physical activity (p-interaction=0.12) or TV viewing (p-interaction=0.77) in relation to metabolic health status.

Table 8 Separate associations of moderate-to-vigorous physical activity and TV viewing with health among adults aged 60-82 (76% male) (n=4141)

	Prevalence of being healthy					
	Among normal-weight (n=1601)		**Among overweight (n=1803)**		**Among obese (n=737)**	
	Model 1 Prevalence Ratio (95% CI)	**Model 2** Prevalence Ratio (95% CI)	**Model 1** Prevalence Ratio (95% CI)	**Model 2** Prevalence Ratio (95% CI)	**Model 1** Prevalence Ratio (95% CI)	**Model 2** Prevalence Ratio (95% CI)
Moderate-to-vigorous physical activity level*						
Lowest	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Intermediate	1.07 (0.97, 1.17)	1.06 (0.96, 1.16)	1.17 (1.03, 1.34)	1.18 (1.03, 1.35)	0.84 (0.62, 1.14)	0.79 (0.59, 1.06)
Highest	1.07 (0.97, 1.17)	1.05 (0.95, 1.15)	1.33 (1.17, 1.52)	1.34 (1.17, 1.53)	1.32 (0.99, 1.77)	1.22 (0.90, 1.64)
TV viewing level*						
Highest	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Intermediate	1.11 (1.00, 1.22)	1.09 (0.98, 1.21)	1.02 (0.89, 1.16)	1.01 (0.89, 1.16)	1.12 (0.84, 1.49)	1.09 (0.82, 1.44)
Lowest	1.18 (1.08, 1.30)	1.16 (1.05, 1.28)	1.09 (0.97, 1.23)	1.08 (0.95, 1.22)	1.05 (0.77, 1.42)	0.98 (0.72, 1.34)

*Associations are mutually adjusted. **Model 1** adjusted for age sex, ethnicity. **Model 2** additionally adjusted for occupational position, smoking, alcohol consumption, diet quality, sleep duration, and presence of an illness which limits moderate or vigorous activity

Table 9 presents results of combined associations of moderate-to-vigorous physical activity and TV viewing with the likelihood of being healthy among normal-weight, overweight, and obese adults. Formal tests of interaction between tertiles of moderate-to-vigorous physical activity and TV viewing in relation to metabolic health status were not significant within any BMI group. In a model considering age, sex, and ethnicity, the combination of high moderate-to-vigorous physical activity and low TV viewing was associated with the highest likelihood of being healthy among normal-weight (PR=1.33, 95% CI=1.12, 1.57), overweight (PR=1.42, 95% CI=1.15, 1.75), and obese adults (PR=1.82, 95% CI=1.19, 2.78). In a multivariable-adjusted model (**Table 10**), the combination of high moderate-to-vigorous physical activity and low TV viewing with the likelihood of being healthy remained among normal-weight and overweight adults, but became non-significant among obese adults (PR=1.55, 95% CI=0.99, 2.42).

As shown in **Appendix 11**, multivariable-adjusted subsidiary analyses found no evidence for a triple interaction between moderate-to-vigorous physical activity tertile, TV viewing tertile, and BMI group in relation to metabolic health status (p-interaction=0.28). Adjusting for BMI group, adults combining high moderate-to-vigorous physical activity with low TV viewing showed a 1.31 (95% CI=1.15, 1.49) times higher prevalence of being healthy.

Table 9 Combined associations of moderate-to-vigorous physical activity and TV viewing with health among adults aged 60-82 (n=4141)

	Prevalence of being healthy		
	Model 1 Prevalence Ratio (95% CI)		
Among normal-weight (n=1601)			
	TV viewing level		
Moderate-to-vigorous physical activity level	Highest	Intermediate	Lowest
Lowest	1.00 (reference)	1.16 (0.95, 1.42)	1.28 (1.07, 1.53)
Intermediate	1.23 (1.01, 1.49)	1.20 (1.00, 1.44)	1.29 (1.08, 1.53)
Highest	1.06 (0.85, 1.31)	1.28 (1.06, 1.53)	1.33 (1.12, 1.57)
p-interaction		0.78	
Among overweight (n=1803)			
	TV viewing level		
Moderate-to-vigorous physical activity level	Highest	Intermediate	Lowest
Lowest	1.00 (reference)	1.01 (0.79, 1.30)	1.06 (0.82, 1.35)
Intermediate	1.15 (0.92, 1.43)	1.16 (0.91, 1.46)	1.29 (1.05, 1.60)
Highest	1.32 (1.07, 1.63)	1.36 (1.09, 1.71)	1.42 (1.15, 1.75)
p-interaction		0.94	
Among obese (n=737)			
	TV viewing level		
Moderate-to-vigorous physical activity level	Highest	Intermediate	Lowest
Lowest	1.00 (reference)	1.24 (0.85, 1.82)	0.76 (0.45, 1.30)
Intermediate	0.89 (0.58, 1.37)	0.84 (0.48, 1.47)	0.79 (0.47, 1.35)
Highest	1.05 (0.63, 1.73)	1.26 (0.78, 2.06)	1.82 (1.19, 2.78)
p-interaction		0.06	

Models adjusted for age, sex, ethnicity

Table 10 Combined associations of moderate-to-vigorous physical activity and TV viewing with health among adults aged 60-82 (n=4141)

	Prevalence of being healthy		
	Model 2 Prevalence Ratio (95% CI)		
Among normal-weight (n=1601)			
	TV viewing level		
Moderate-to-vigorous physical activity level	Highest	Intermediate	Lowest
Lowest	1.00 (reference)	1.14 (0.93, 1.39)	1.25 (1.04, 1.50)
Intermediate	1.21 (1.00, 1.47)	1.17 (0.97, 1.42)	1.24 (1.04, 1.48)
Highest	1.03 (0.83, 1.28)	1.22 (1.02, 1.47)	1.28 (1.07, 1.52)
p-interaction		0.90	
Among overweight (n=1803)			
	TV viewing level		
Moderate-to-vigorous physical activity level	Highest	Intermediate	Lowest
Lowest	1.00 (reference)	1.02 (0.79, 1.31)	1.07 (0.83, 1.37)
Intermediate	1.16 (0.93, 1.44)	1.16 (0.92, 1.48)	1.31 (1.05, 1.62)
Highest	1.35 (1.09, 1.67)	1.37 (1.09, 1.73)	1.41 (1.13, 1.75)
p-interaction		0.85	
Among obese (n=737)			
	TV viewing level		
Moderate-to-vigorous physical activity level	Highest	Intermediate	Lowest
Lowest	1.00 (reference)	1.21 (0.83, 1.78)	0.74 (0.43, 1.26)
Intermediate	0.85 (0.56, 1.30)	0.77 (0.44, 1.34)	0.69 (0.40, 1.19)
Highest	0.99 (0.59, 1.64)	1.13 (0.69, 1.84)	1.55 (0.99, 2.42)
p-interaction		0.09	

Models adjusted for age, sex, ethnicity, occupational position, alcohol, smoking, diet quality, sleep duration, and presence of an illness which limits moderate or vigorous physical activity

Additional results of cross-sectional differences in TV viewing time across metabolic and obesity groups are presented in **Table 11**. The mean number of hours per week of viewing TV increased steadily across groups (p-trend <0.001). Compared with healthy normal-weight adults, healthy obese adults viewed on average 5.30 (95% CI=3.50, 7.11) hours more of TV per week when adjusting for age, sex, and ethnicity. This figure reduced to 4.28 (95% CI=2.51, 6.06) hours more of TV viewing per week when additionally considering occupational position, health behaviours, activity-limiting health status, and duration of self-reported moderate-to-vigorous physical activity (hours/week). When viewing differences in TV viewing time between healthy and unhealthy obese groups specifically, healthy obese adults did not show lower levels of TV viewing than unhealthy obese adults at either stage of model adjustment (B=-0.15, 95% CI=-2.03, 1.73 in the multivariable-adjusted model).

Table 11 Differences in TV viewing duration (hours/week) across metabolic and obesity groups of adults aged 60-82 (n=4141)

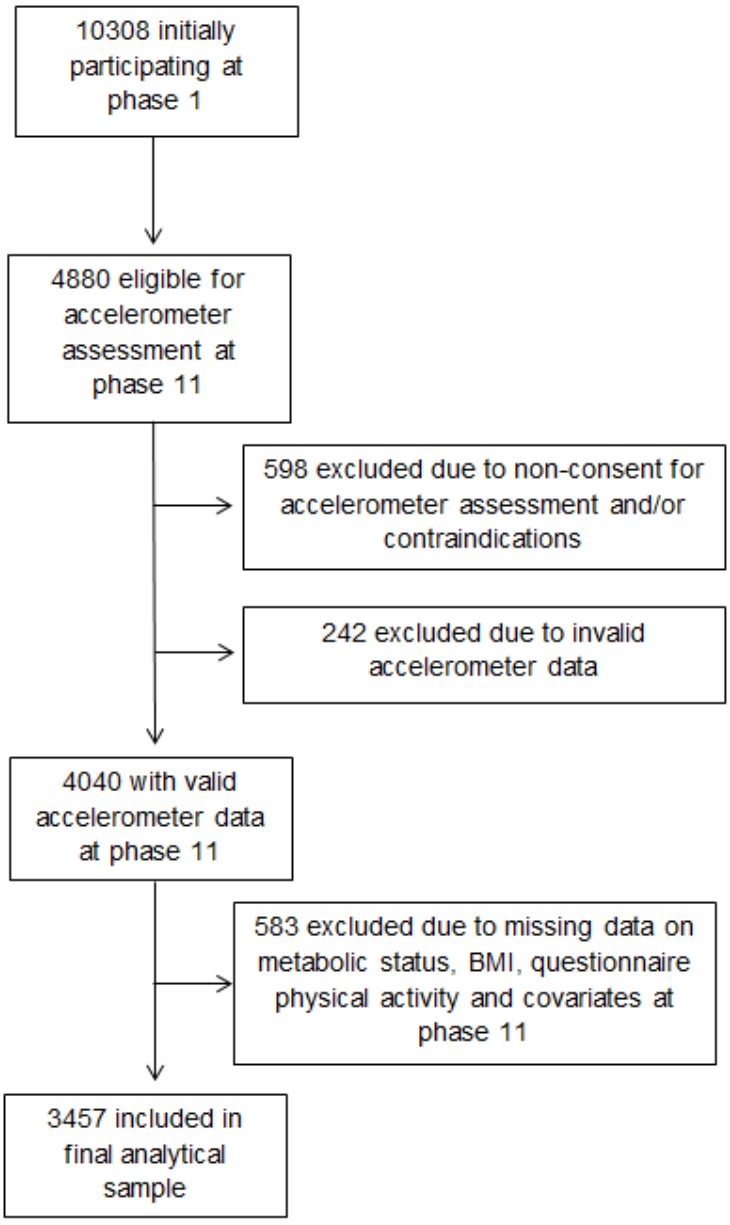
	Model 1 B (95% CI)	**Model 2** B (95% CI)
Metabolic and obesity status		
Healthy normal-weight (n=1048)	0.00 (reference)	0.00 (reference)
Unhealthy normal-weight (n=553)	2.19 (0.98, 3.39)	1.70 (0.52, 2.87)
Healthy overweight (n=795)	3.58 (2.52, 4.65)	2.85 (1.80, 3.89)
Unhealthy overweight (n=1008)	3.92 (2.91, 4.93)	3.12 (2.12, 4.12)
Healthy obese (n=186)	5.30 (3.50, 7.11)	4.28 (2.51, 6.06)
Unhealthy obese (n=551)	5.82 (4.63, 7.01)	4.43 (3.24, 5.63)
(Reference group reversed)		
Unhealthy obese (n=551)	0.00 (reference)	0.00 (reference)
Healthy obese (n=186)	-0.51 (-2.44, 1.42)	-0.15 (-2.03, 1.73)
Unhealthy overweight (n=1008)	-1.90 (-3.11, -0.69)	-1.32 (-2.50, -0.13)
Healthy overweight (n=795)	-2.24 (-3.49, -0.98)	-1.59 (-2.83, -0.34)
Unhealthy normal-weight (n=553)	-3.63 (-5.00, -2.26)	-2.74 (-4.09, -1.38)
Healthy normal-weight (n=1048)	-5.82 (-7.01, -4.63)	-4.43 (-5.63, -3.24)

Model 1 adjusted for age, sex, and ethnicity. **Model 2** additionally adjusted for occupational position, alcohol, smoking, diet quality, sleep duration, presence of an illness which limits moderate or vigorous physical activity, and self-reported moderate-to-vigorous physical activity

Objective 4: Cross-sectional differences in questionnaire- and accelerometer-assessed total physical activity between healthy and unhealthy normal-weight, overweight, and obese adults

Among the 4880 participants to whom the accelerometer was proposed, 210 had contraindications, 4282 consented and 4040 participants had valid accelerometer data (≥16 hours/day) for at least 2 weekdays and 2 week-end days. Of those, 3457 participants also had data on questionnaire-assessed physical activity, body-mass index, metabolic risk factors, and covariates. Among the 3457 participants included in analyses, 3359 (97.2%) had valid accelerometer data for the 8-day observation period, 63 (1.8%) for 6-7 days, and 34 (1%) for 5-4 days. In all, missing data were replaced on average for 0.3% of the observation period, with 103 (3%) participants having missing data replaced for 1-5% of the period and 22 (0.6%) for 5-27% of the period. A flow chart illustrating the selection of the analytical sample is provided in **Figure 5**.

Figure 5 Selection of the analytical sample for the cross-sectional study of questionnaire- and accelerometer-assessed total physical activity in relation to healthy obesity



Descriptive characteristics of the analytical sample at phase 11 (2012/13), the first time an objective measure of physical activity was taken, are shown in **Table 12**. Among 3457 participants with complete data on questionnaire- and accelerometer-assessed physical activity, anthropometrics, metabolic risk factors, and covariates, 1330 were normal-weight, of which 864 (65%) were considered healthy normal-weight. A further 1511 were overweight, of which 650 (43%) were considered healthy overweight. A further 616 were obese, of which 161 (26%) were considered healthy obese. Each metabolic factor was more adverse among healthy overweight and healthy obese adults compared with healthy normal-weight adults, with the exception of fasting glucose among healthy obese adults. Healthy and unhealthy obese adults showed lower levels of self-reported total physical activity compared with healthy normal-weight adults (43.8 and 42.6 MET-hours/week vs. 50.8 MET-hours/week respectively, each $p<0.05$). Lower levels of accelerometer-assessed total physical activity were also seen among healthy and unhealthy obese adults compared with healthy normal-weight adults (22.3 mg/week and 20.6 mg/week vs. 25.8 mg/week respectively, each $p<0.05$).

Compared with participants included in the analytical sample (n=3457), those excluded (n=1423) were older (mean age=69.6 years vs. 69.2 years, $p=0.008$), more likely to be female (36.6% vs. 23.3%, $p<0.001$), of a non-white ethnicity (10.8% vs. 6.8%, $p<0.001$), and of the lowest occupational position (11.8% vs. 7.8%, $p<0.001$). Excluded participants also showed lower total physical activity as measured by questionnaire (43.5 MET-hours/week vs. 46.9 MET-hours/week, $p<0.001$) but higher total physical activity as assessed by accelerometer (25.2 mg/week vs. 23.5 mg/week, $p=0.01$). Excluded participants were more likely to be obese (21.6% vs. 17.8%, $p=0.003$) but also more likely to be metabolically healthy (52.2% vs. 48.5%, $p=0.03$).

Table 12 Characteristics of adults aged 60-82 at baseline (77% male) at phase 11 (2012/13) by metabolic and obesity status (n=3457)

	Healthy normal-weight (n=864)	Unhealthy normal-weight (n=466)	Healthy overweight (n=650)	Unhealthy overweight (n=861)	Healthy obese (n=161)	Unhealthy obese (n=455)
Male – n (%)	626 (72.5)	378 (81.3)*	513 (78.9)*	724 (84.0)*	83 (51.6)*	325 (71.4)
Age (years)	68.6 (5.7)	70.6 (5.6)*	68.5 (5.4)	70 (5.6)*	68.2 (5.0)	68.6 (5.5)
Non-white ethnicity – n (%)	36 (4.2)	49 (10.5)*	23 (3.5)	75 (8.7)*	9 (5.6)	42 (9.2)*
Lowest occupational position – n (%)	44 (5.1)	38 (8.2)*	52 (8.0)*	56 (6.5)	22 (13.7)*	57 (12.5)*
Unhealthy diet – n (%)	81 (9.4)	63 (13.5)*	96 (14.8)*	130 (15.1)*	20 (12.4)	70 (15.4)*
Consumes fruit and vegetables < daily – n (%)	132 (15.3)	88 (18.9)	134 (20.6)*	196 (22.8)*	38 (23.6)*	110 (24.2)*
Consumes whole/full-fat milk most often – n (%)	95 (11.0)	33 (7.1)*	54 (8.3)	60 (7.0)*	7 (4.3)*	41 (9.0)
Consumes white bread most often – n (%)	108 (12.5)	82 (17.6)*	118 (18.2)*	158 (18.4)*	26 (16.1)	80 (17.6)*
Current smoker – n (%)	18 (2.1)	12 (2.6)	21 (3.2)	32 (3.7)*	5 (3.1)	15 (3.3)
High alcohol consumption in previous week – n (%)	101 (11.7)	61 (13.1)	81 (12.5)	135 (15.7)*	24 (14.9)	86 (18.9)*
Sleeps ≤ 5 hours/night – n (%)	40 (4.6)	26 (5.6)	45 (6.9)	80 (9.3)*	11 (6.8)	48 (10.6)*
Has illness that greatly limits moderate or vigorous activity – n (%)	236 (27.3)	150 (32.2)	195 (30.0)	328 (38.1)*	80 (49.7)*	245 (53.8)*
Systolic blood pressure (mmHg)	121.2 (14.6)	130.9 (16.2)*	124.2 (13.7)*	129.5 (16.6)*	125.7 (14.3)*	130.4 (15.4)*
Diastolic blood pressure (mmHg)	67.9 (9.1)	70.7 (10.3)*	70.7 (9.2)*	71.1 (10.1)*	73.2 (9.1)*	72.5 (9.7)*
Fasting glucose (mmol/l)	5.0 (0.4)	5.7 (1.5)*	5.1 (0.4)	5.8 (1.6)*	5.1 (0.4)	6.1 (2.0)*
HOMA insulin resistance	1.2 (0.7)	2.7 (3.2)*	1.9 (1.0)*	3.9 (6.5)*	2.5 (1.3)*	6.4 (10.2)*
Triglycerides (mmol/l)	0.9 (0.4)	1.1 (0.6)*	1.1 (0.4)*	1.4 (0.8)*	1.1 (0.3)*	1.6 (0.9)*
HDL cholesterol (mmol/l)	1.9 (0.5)	1.7 (0.5)*	1.6 (0.4)*	1.5 (0.4)*	1.7 (0.4)*	1.4 (0.4)*
Body mass index (kg/m²)	22.6 (1.6)	23.3 (1.4)*	27.1 (1.4)*	27.3 (1.4)*	32.6 (2.6)*	33.6 (3.3)*
Range	18.52-24.99	18.57-24.99	25.00-29.98	25.01-29.98	30.00-42.53	30.01-49.43

Data are mean (SD) unless otherwise noted. *Different from healthy normal-weight ($p<0.05$) based on linear regression (continuous variables) or logistic regression (binary variables).

Table 13 (Continued) Characteristics of adults aged 60-82 at baseline (77% male) at phase 11 (2012/13) by metabolic and obesity status (n=3457)

	Healthy normal-weight (n=864)	Unhealthy normal-weight (n=466)	Healthy overweight (n=650)	Unhealthy overweight (n=861)	Healthy obese (n=161)	Unhealthy obese (n=455)
Questionnaire-assessed total physical activity (MET-hours/week)	50.8 (28.5)	47.7 (26.6)*	48.2 (26.7)	44.4 (25.8)*	43.8 (23.3)*	42.6 (25.9)*
Questionnaire-assessed moderate-to-vigorous physical activity (hours/week) [a]	3.25 (1.25-5.88)	3.13 (1.06-5.50)	3.28 (1.13-6.00)	2.63 (0.63-4.88)	2.00 (0.63-5.16)	2.00 (0.44-4.13)
≥ 2.5 hrs/week of questionnaire-assessed moderate-to-vigorous activity – n (%) [b]	509 (58.9)	270 (57.9)	385 (59.2)	447 (51.9)*	73 (45.3)*	201 (44.2)*
Accelerometer-assessed total physical activity (mean acceleration/week, mg [b])	25.8 (7.4)	23.3 (6.5)*	24 (6.1)*	22.5 (5.9)*	22.3 (6.0)*	20.6 (5.3)*
Accelerometer-assessed moderate-to-vigorous physical activity (hours/week) [a]	1.87 (0.66-3.98)	1.27 (0.36-2.71)	1.25 (0.31-2.96)	0.98 (0.20-2.39)	0.56 (0.00-2.15)	0.50 (0.00-1.64)
≥ 2.5 hrs/week of accelerometer-assessed moderate-to-vigorous activity – n (%) [c]	368 (42.6)	128 (27.5)*	196 (30.2)*	201 (23.3)*	32 (19.9)*	74 (16.3)*

Data are mean (SD) unless otherwise noted. *Different from healthy normal-weight ($p<0.05$) based on linear regression (continuous variables) or logistic regression (binary variables). [a] Data are median (interquartile range) due to non-normal distribution; differences not tested. [b] Based on World Health Organization, 2010. [c] Units are milligravity (measure of mean weekly acceleration).

The correlation between self-reported and objectively assessed total physical activity was lower among obese adults than among normal-weight and overweight adults (Spearman's correlation=0.233 vs. 0.311 and 0.320 respectively, all p<0.001). The correlation between self-reported and objectively assessed total physical activity appeared to be non-differential between healthy normal-weight and healthy obese adults (Spearman's correlation=0.300 and 0.296, respectively, each p<0.001). This correlation was weaker within unhealthy obese adults, at 0.205, p<0.001.

When using the questionnaire measure, total physical activity was lower among unhealthy overweight, healthy obese, and unhealthy obese adults compared with healthy normal-weight adults in models adjusted for age, sex, and ethnicity (**Table 13**). In models further adjusted for occupational position, health behaviours, and health status (**Figure 6; Table 13**), unhealthy overweight, healthy obese, and unhealthy obese adults showed -0.20 (-0.30, -0.10), -0.19 (-0.36, -0.02) and -0.22 (-0.34, -0.11) lower standard deviation units of total physical activity compared with healthy normal-weight adults respectively. Pairwise comparisons showed no differences in questionnaire-assessed total physical activity between metabolically healthy and unhealthy adults within any BMI category in fully adjusted models (**Figure 6**).

When using the accelerometer measure, all groups showed lower total physical activity than the healthy normal-weight group in minimally adjusted models and after further adjustments for other covariates (**Figure 6; Table 13**), with total physical activity being -0.46 (-0.62, -0.31) standard deviation units lower in healthy obese adults and -0.72 (-0.83, -0.62) standard deviation units lower in unhealthy obese adults. Pairwise comparisons showed differences in accelerometer-assessed total physical activity between healthy and unhealthy groups within all BMI categories at both stages of adjustment, with healthy obese adults showing higher total physical activity than their unhealthy obese counterparts (p=0.002). Further adjustment for BMI did not remove significance of differences within any group (p<0.001 between normal-weight groups; p=0.01 between overweight groups; p=0.01 between obese groups). The overall fit of

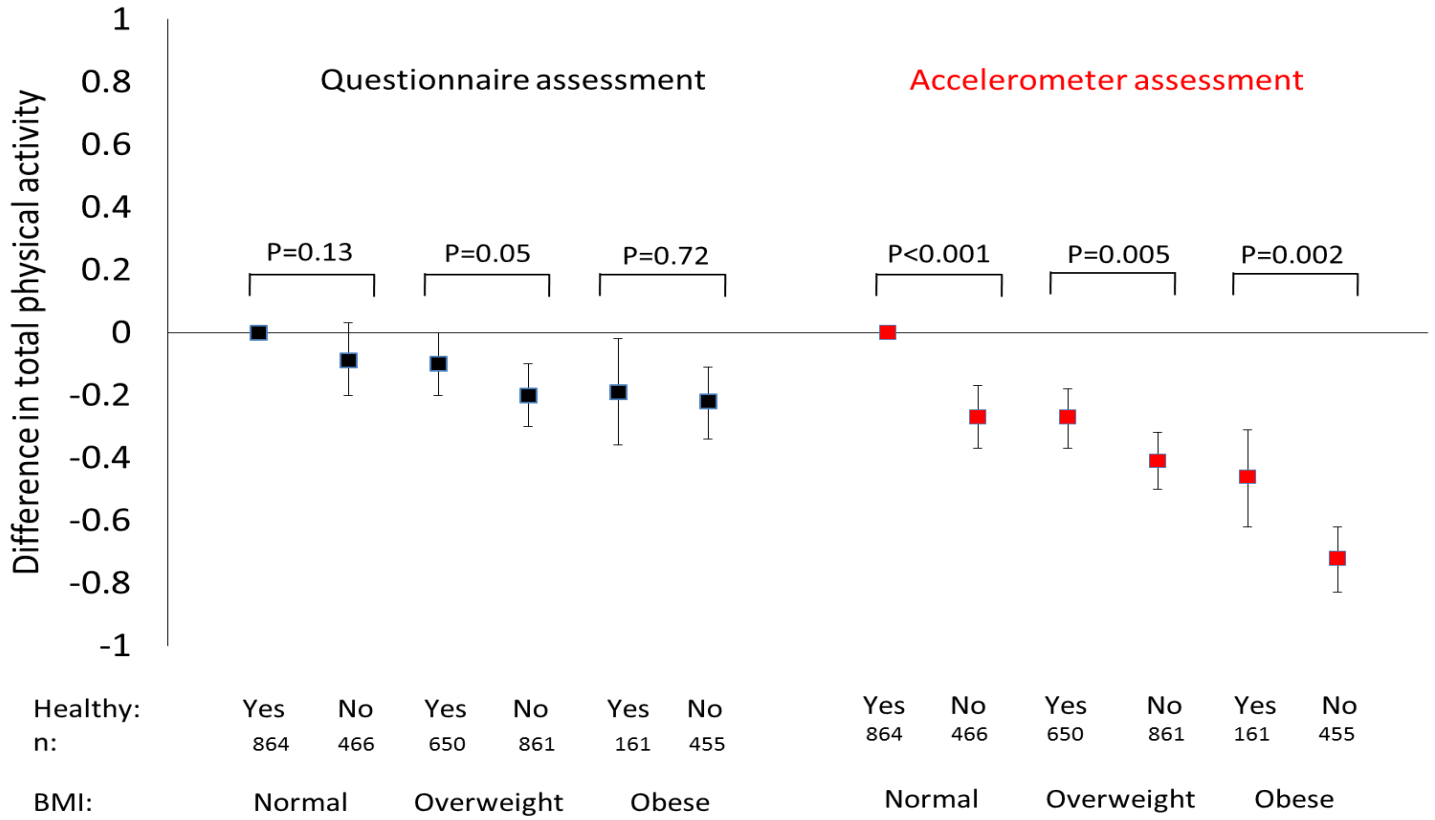
the model was better with accelerometer- compared with questionnaire-based assessments (AIC for fully-adjusted models=9149.87 vs. 9707.06 respectively).

Table 14 Differences in questionnaire- and accelerometer-assessed total physical activity across metabolic and obesity groups (n=3457)

	Questionnaire-assessed total physical activity		Accelerometer-assessed total physical activity	
	Model 1	**Model 2**	**Model 1**	**Model 2**
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Metabolic and obesity status				
Healthy normal weight (n=864)	0.00 (reference)	0.00 (reference)	0.00 (reference)	0.00 (reference)
Unhealthy normal weight (n=466)	-0.08 (-0.20, 0.03)	-0.09 (-0.20, 0.03)	-0.27 (-0.38, -0.17)	-0.27 (-0.37, -0.17)
Healthy overweight (n=650)	-0.10 (-0.20, 0.00)	-0.10 (-0.20, 0.00)	-0.28 (-0.37, -0.19)	-0.27 (-0.37, -0.18)
Unhealthy overweight (n=861)	-0.22 (-0.31, -0.12)	-0.20 (-0.30, -0.10)	-0.43 (-0.52, -0.34)	-0.41 (-0.50, -0.32)
Healthy obese (n=161)	-0.25 (-0.42, -0.09)	-0.19 (-0.36, -0.02)	-0.54 (-0.70, -0.38)	-0.46 (-0.62, -0.31)
Unhealthy obese (n=455)	-0.29 (-0.40, -0.18)	-0.22 (-0.34, -0.11)	-0.79 (-0.90, -0.69)	-0.72 (-0.83, -0.62)
(Reference group reversed)				
Unhealthy obese (n=455)	0.00 (reference)	0.00 (reference)	0.00 (reference)	0.00 (reference)
Healthy obese (n=161)	0.04 (-0.14, 0.22)	0.03 (-0.15, 0.21)	0.25 (0.09, 0.42)	0.26 (0.10, 0.43)
Unhealthy overweight (n=861)	0.07 (-0.04, 0.19)	0.02 (-0.09, 0.14)	0.36 (0.25, 0.47)	0.32 (0.21, 0.42)
Healthy overweight (n=650)	0.19 (0.07, 0.31)	0.12 (0.00, 0.24)	0.51 (0.40, 0.62)	0.45 (0.34, 0.56)
Unhealthy normal weight (n=466)	0.21 (0.08, 0.34)	0.13 (0.00, 0.26)	0.52 (0.40, 0.64)	0.45 (0.33, 0.57)
Healthy normal weight (n=864)	0.29 (0.18, 0.40)	0.22 (0.11, 0.34)	0.79 (0.69, 0.90)	0.72 (0.62, 0.83)
AIC	9764.09	9707.06	9284.09	9149.87

Standardised measures of questionnaire and accelerometer data (Z scores) were used (mean=0.00; standard deviation=1.00). **Model 1** adjusted for age, sex, and ethnicity. **Model 2** additionally adjusted for occupational position, diet quality, smoking status, alcohol consumption, sleep duration, and presence of an illness which limits moderate or vigorous activity

Figure 6 Differences in questionnaire- and accelerometer-assessed total physical activity across metabolic and obesity groups (n=3457)



Data are standardised Z-scores to allow comparability between measures. Model fit was better with accelerometer- compared with questionnaire-based assessments (AIC for fully-adjusted models=9149.87 vs. 9707.06 respectively). Models adjusted for age, sex, ethnicity, occupational position, diet quality, smoking status, alcohol consumption, sleep duration, and presence of an illness which limits moderate or vigorous activity

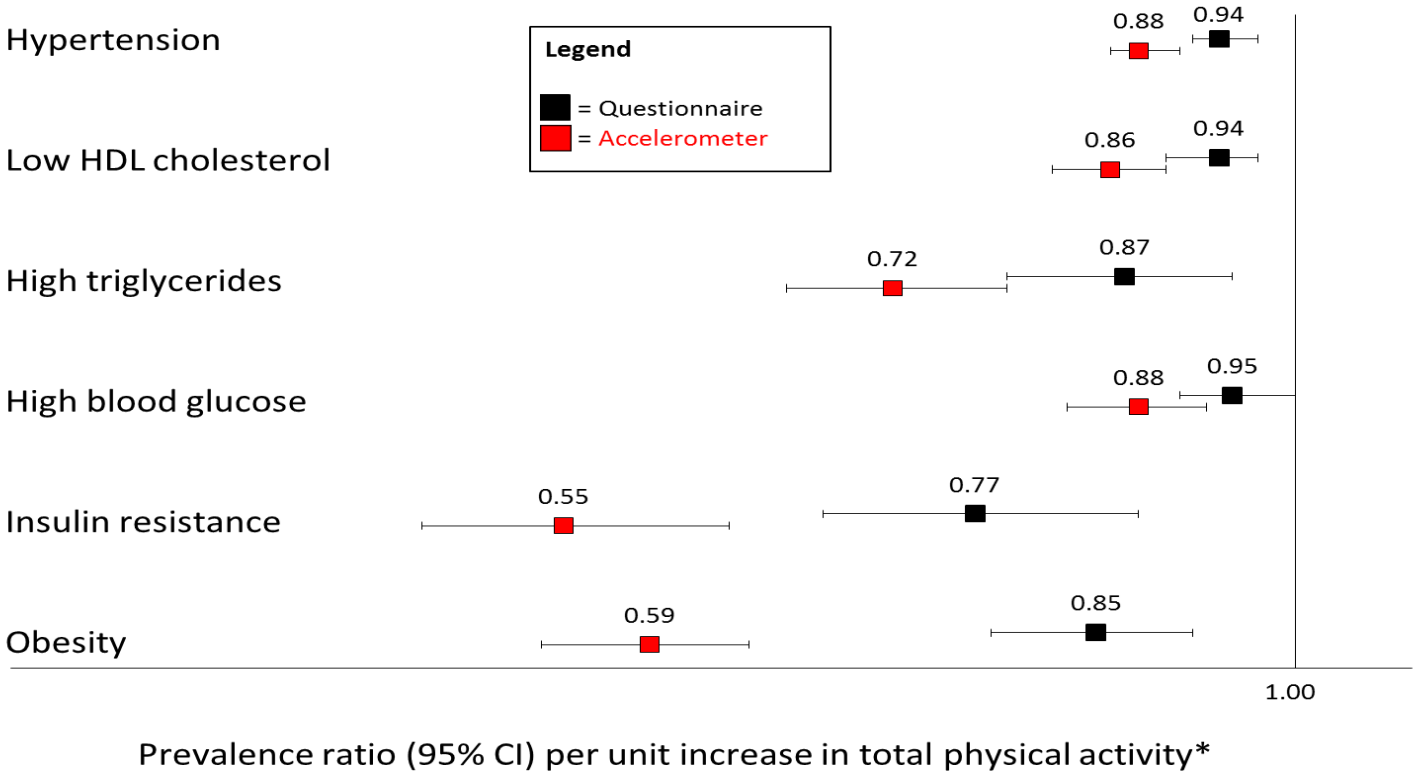
A reduced prevalence of obesity and of each individual metabolic risk factor was observed for a standard deviation increase in total physical activity, and these associations were consistently stronger with accelerometer- compared with questionnaire-based assessments (**Figure 7; Table 14**). Insulin resistance showed the greatest reduction in prevalence with higher accelerometer-assessed total physical activity (PR=0.55, 95% CI=0.49, 0.63 for 1 standard deviation increase in total physical activity).

Table 15 Associations of questionnaire- and accelerometer-assessed total physical activity with prevalence of individual metabolic risk factors (n=3457)

	Questionnaire-assessed total physical activity	**Accelerometer-assessed total physical activity**
	Prevalence ratio (95% CI)	Prevalence ratio (95% CI)
Metabolic risk factors		
No hypertension (n=1296)	1.00 (reference)	1.00 (reference)
Hypertension (n=2161)	0.94 (0.92, 0.97)	0.88 (0.86, 0.91)
Normal HDL (n=1864)	1.00 (reference)	1.00 (reference)
Low HDL (n=1593)	0.94 (0.90, 0.97)	0.86 (0.82, 0.90)
Normal triglycerides (n=2885)	1.00 (reference)	1.00 (reference)
High triglycerides (n=572)	0.87 (0.79, 0.95)	0.72 (0.66, 0.79)
Normal blood glucose (n=2386)	1.00 (reference)	1.00 (reference)
High blood glucose (n=1071)	0.95 (0.91, 1.00)	0.88 (0.83, 0.93)
No insulin resistance (n=3113)	1.00 (reference)	1.00 (reference)
Insulin resistance (n=344)	0.77 (0.68, 0.88)	0.55 (0.49, 0.63)
No obesity (n=2841)	1.00 (reference)	1.00 (reference)
Obesity (n=616)	0.85 (0.78, 0.92)	0.59 (0.54, 0.64)

Standardized measures of questionnaire and accelerometer data (Z scores) were used (mean=0.00; standard deviation=1.00). Models are adjusted for age, sex, and ethnicity.

Figure 7 Association of questionnaire- and accelerometer-assessed total physical activity and individual metabolic risk factors (n=3457)



Data are standardised Z-scores to allow comparability between measures. Case numbers (n) are as follows: Hypertension=2161; Low HDL=1593; High triglycerides=572; High blood glucose=1071; Insulin resistance=344; Obesity=616. Reference groups are the absence of each individual metabolic risk factor under consideration. Models are adjusted for age, sex, and ethnicity.

Objective 5: Cross-sectional differences in the likelihood of meeting recommendations for moderate-to-vigorous physical activity, based on questionnaire and accelerometer assessments, between healthy and unhealthy normal-weight, overweight, and obese adults

Analyses for this section are based on the same participants included in the analytical sample for the previous section examining differences in total physical activity (n=3457), and thus descriptive characteristics and comparisons between excluded and included participants are the same. However, those excluded from analyses (n=1423) were additionally found to be less likely to meet recommendations for moderate-to-vigorous physical activity as assessed by questionnaire (47.5% vs. 54.5%, p<0.001) and by accelerometer (21.3% vs. 28.9%, p<0.001) compared with those included (n=3457).

When using the questionnaire measure, the prevalence of meeting recommendations for moderate-to-vigorous physical activity was lower among unhealthy overweight, healthy obese, and unhealthy obese adults compared with healthy normal-weight adults, adjusting for age, sex, and ethnicity (**Table 15**). After adjustment for additional covariates, unhealthy overweight (PR=0.91, 95% CI=0.84, 0.99) and unhealthy obese adults (PR=0.85, 95% CI=0.76, 0.96) showed reduced prevalence, while healthy obese adults were not less likely to meet recommendations than healthy normal-weight adults. Models with unhealthy obese adults as the reference group indicated that healthy obese adults were not more likely to report ≥ 2.5 hours of moderate-to-vigorous physical activity per week than unhealthy obese adults.

When using the accelerometer measure with a 100mg cut-point and a 10-minute bout criteria to define moderate-to-vigorous physical activity, the prevalence of undertaking ≥ 2.5 hours/week of moderate-to-vigorous activity was lower in all groups compared with healthy normal-weight adults at both stages of adjustment (**Table 15**). Compared with healthy normal-weight adults, this prevalence was 0.59 (95% CI=0.43, 0.79) times lower in healthy obese adults and 0.46 (95% CI=0.37, 0.58) times lower in unhealthy obese adults after adjustment for all covariates. Models with the unhealthy obese as the reference group indicated that healthy obese adults were not

more likely to perform ≥ 2.5 hours/week of accelerometer-assessed moderate-to-vigorous physical activity than unhealthy obese adults. The overall fit of the model was better when using accelerometer compared with questionnaire assessments (AIC=4183.95 vs. 5963.40 in multivariable-adjusted models respectively).

Table 16 Likelihood of meeting 2010 World Health Organization recommendations for moderate-to-vigorous physical activity compared with healthy normal-weight adults, based on questionnaire and accelerometer assessments (n=3457)

	Meets physical activity recommendations based on questionnaire		**Meets physical activity recommendations based on accelerometer (100 mg, 10 min bouts)**	
	Model 1 Prevalence Ratio (95% CI)	**Model 2** Prevalence Ratio (95% CI)	**Model 1** Prevalence Ratio (95% CI)	**Model 2** Prevalence Ratio (95% CI)
Metabolic and obesity status				
Healthy normal weight (n=864)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Unhealthy normal weight (n=466)	1.00 (0.91, 1.10)	1.01 (0.92, 1.11)	0.74 (0.63, 0.87)	0.75 (0.64, 0.89)
Healthy overweight (n=650)	0.98 (0.90, 1.07)	1.01 (0.93, 1.10)	0.69 (0.60, 0.79)	0.71 (0.62, 0.81)
Unhealthy overweight (n=861)	0.88 (0.81, 0.95)	0.91 (0.84, 0.99)	0.59 (0.51, 0.68)	0.63 (0.55, 0.72)
Healthy obese (n=161)	0.82 (0.69, 0.98)	0.89 (0.75, 1.06)	0.50 (0.37, 0.68)	0.59 (0.43, 0.79)
Unhealthy obese (n=455)	0.77 (0.68, 0.86)	0.85 (0.76, 0.96)	0.39 (0.32, 0.49)	0.46 (0.37, 0.58)
(Reference group reversed)				
Unhealthy obese (n=455)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Healthy obese (n=161)	1.07 (0.88, 1.30)	1.05 (0.87, 1.27)	1.28 (0.90, 1.83)	1.26 (0.89, 1.80)
Unhealthy overweight (n=861)	1.14 (1.01, 1.29)	1.07 (0.95, 1.21)	1.51 (1.20, 1.90)	1.35 (1.07, 1.70)
Healthy overweight (n=650)	1.28 (1.14, 1.44)	1.19 (1.05, 1.34)	1.75 (1.39, 2.21)	1.53 (1.22, 1.93)
Unhealthy normal weight (n=466)	1.30 (1.15, 1.48)	1.19 (1.05, 1.35)	1.88 (1.47, 2.41)	1.63 (1.27, 2.08)
Healthy normal weight (n=864)	1.30 (1.16, 1.46)	1.18 (1.05, 1.32)	2.54 (2.05, 3.15)	2.16 (1.74, 2.68)
AIC	5992.47	5963.40	4226.51	4183.95

Physical activity recommendations based on 2010 World Health Organization guideline of ≥ 2.5 hrs/week of moderate-to-vigorous physical activity in bouts of at least 10 minutes. **Model 1** adjusted for age, sex, and ethnicity. **Model 2** further adjusted for occupational position, diet quality, smoking status, alcohol consumption, sleep duration, and presence of an illness which limits moderate or vigorous activity

Sensitivity analyses using a more stringent 120 mg cut-point for accelerometer-assessed moderate-to-vigorous physical activity in 10-minute bouts produced results of a similar pattern and magnitude as main analyses (**Table 16**). Healthy obese adults were not more likely to perform ≥ 2.5 hours/week of moderate-to-vigorous activity than unhealthy obese adults (PR=1.22, 95% CI=0.77, 1.92). However, when considering bouts of at least 1 minute in addition to the more stringent 120 mg cut-point, healthy obese adults were more likely than unhealthy obese adults to meet recommendations for moderate-to-vigorous activity (PR=1.31, 95% CI=1.05, 1.64 after multivariable-adjustment; **Table 17**). This difference was not evident when using 1-minute bouts with the 100 mg cut-point.

Table 17 Likelihood of meeting 2010 World Health Organization recommendations for moderate-to-vigorous physical activity across metabolic and obesity groups based on a 120 mg cut-point accelerometer assessment (n=3457)

	Meets physical activity recommendations based on accelerometer (120 mg, 10 min bouts)	
	Model 1 Prevalence Ratio (95% CI)	**Model 2** Prevalence Ratio (95% CI)
Metabolic and obesity status		
Healthy normal weight (n=864)	1.00 (reference)	1.00 (reference)
Unhealthy normal weight (n=466)	0.71 (0.57, 0.88)	0.73 (0.59, 0.91)
Healthy overweight (n=650)	0.68 (0.57, 0.81)	0.70 (0.59, 0.84)
Unhealthy overweight (n=861)	0.54 (0.45, 0.65)	0.58 (0.48, 0.70)
Healthy obese (n=161)	0.47 (0.31, 0.71)	0.57 (0.38, 0.85)
Unhealthy obese (n=455)	0.38 (0.29, 0.50)	0.47 (0.36, 0.62)
(Reference group reversed)		
Unhealthy obese (n=455)	1.00 (reference)	1.00 (reference)
Healthy obese (n=161)	1.24 (0.78, 1.98)	1.22 (0.77, 1.92)
Unhealthy overweight (n=861)	1.41 (1.05, 1.91)	1.24 (0.92, 1.67)
Healthy overweight (n=650)	1.78 (1.33, 2.39)	1.50 (1.12, 2.02)
Unhealthy normal weight (n=466)	1.85 (1.35, 2.55)	1.56 (1.13, 2.14)
Healthy normal weight (n=864)	2.62 (1.99, 3.44)	2.13 (1.61, 2.82)
AIC	3256.79	3216.37

Physical activity recommendations based on 2010 World Health Organization guideline of ≥ 2.5 hrs/week of moderate-to-vigorous physical activity in bouts of at least 10 minutes. **Model 1** adjusted for age, sex, and ethnicity. **Model 2** further adjusted for occupational position, diet quality, smoking status, alcohol consumption, sleep duration, and presence of an illness which limits moderate or vigorous activity

Table 18 Likelihood of meeting 2010 World Health Organization recommendations for moderate-to-vigorous physical activity compared with healthy normal-weight adults based on 1-minute bout accelerometer assessments (n=3457)

	Meets physical activity recommendations based on accelerometer (100 mg, 1 min bouts)		**Meets physical activity recommendations based on accelerometer (120 mg, 1 min bouts)**	
	Model 1 Prevalence Ratio (95% CI)	**Model 2** Prevalence Ratio (95% CI)	**Model 1** Prevalence Ratio (95% CI)	**Model 2** Prevalence Ratio (95% CI)
Metabolic and obesity status				
Healthy normal-weight (n=864)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Unhealthy normal-weight (n=466)	0.98 (0.92, 1.04)	0.98 (0.92, 1.05)	0.89 (0.81, 0.98)	0.90 (0.82, 0.99)
Healthy overweight (n=650)	0.92 (0.87, 0.97)	0.93 (0.88, 0.98)	0.81 (0.75, 0.89)	0.83 (0.77, 0.90)
Unhealthy overweight (n=861)	0.86 (0.81, 0.91)	0.88 (0.83, 0.93)	0.75 (0.68, 0.81)	0.77 (0.71, 0.84)
Healthy obese (n=161)	0.70 (0.61, 0.80)	0.74 (0.64, 0.85)	0.63 (0.52, 0.77)	0.70 (0.58, 0.85)
Unhealthy obese (n=455)	0.66 (0.61, 0.72)	0.71 (0.65, 0.78)	0.47 (0.41, 0.55)	0.53 (0.46, 0.61)
(Reference group reversed)				
Unhealthy obese (n=455)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Healthy obese (n=161)	1.05 (0.90, 1.23)	1.04 (0.89, 1.22)	1.33 (1.06, 1.67)	1.31 (1.05, 1.64)
Unhealthy overweight (n=861)	1.29 (1.18, 1.42)	1.24 (1.13, 1.36)	1.57 (1.35, 1.82)	1.45 (1.25, 1.68)
Healthy overweight (n=650)	1.39 (1.26, 1.52)	1.31 (1.19, 1.44)	1.71 (1.48, 1.99)	1.56 (1.35, 1.81)
Unhealthy normal-weight (n=466)	1.47 (1.33, 1.62)	1.38 (1.26, 1.53)	1.88 (1.61, 2.20)	1.69 (1.45, 1.98)
Healthy normal-weight (n=864)	1.51 (1.38, 1.64)	1.41 (1.29, 1.54)	2.11 (1.83, 2.42)	1.88 (1.63, 2.16)
AIC	6412.84	6405.07	5561.03	5531.27

Physical activity recommendations based on 2010 World Health Organization guideline of ≥ 2.5 hrs/week of moderate-to-vigorous physical activity in bouts of at least 1 minute. **Model 1** adjusted for age, sex, and ethnicity. **Model 2** further adjusted for occupational position, diet quality, smoking status, alcohol consumption, sleep duration, and presence of an illness which limits moderate or vigorous activity

In main analyses, health behaviour covariate data were used at the most recent study phase before 2012/13 for a small proportion of participants (n=84, or 2% of the sample). In order to examine potential for bias in results due to covariate data used from earlier phases, multivariate analyses were repeated on a sample of participants whose health behaviour data were used only from the 2012/13 assessment (n=3373), the results of which are shown in **Tables 18, 19, and 20** below. Trends in physical activity measures were unchanged, with differences in total physical activity between healthy and unhealthy obese groups evident only when using accelerometer assessments, and with healthy obese adults more likely than unhealthy obese adults to meet moderate-to-vigorous physical activity guidelines only when considering 1-minute bout durations and the more stringent 120 mg accelerometer cut-point.

Table 19 Differences in questionnaire- and accelerometer-assessed total physical activity across metabolic and obesity groups based on participants with complete covariate data in 2012/13 (n=3373)

	Questionnaire-assessed total physical activity Z score		**Accelerometer-assessed total physical activity** Z score	
	Model 1 β (95% CI)	**Model 2** β (95% CI)	**Model 1** β (95% CI)	**Model 2** β (95% CI)
Metabolic and obesity status				
Unhealthy obese (n=442)	0.00 (reference)	0.00 (reference)	0.00 (reference)	0.00 (reference)
Healthy obese (n=156)	0.05 (-0.13, 0.23)	0.04 (-0.14, 0.22)	0.22 (0.05, 0.39)	0.23 (0.06, 0.40)
Unhealthy overweight (n=838)	0.07 (-0.05, 0.18)	0.02 (-0.10, 0.13)	0.35 (0.24, 0.45)	0.30 (0.19, 0.41)
Healthy overweight (n=633)	0.19 (0.07, 0.31)	0.12 (-0.00, 0.24)	0.50 (0.39, 0.62)	0.44 (0.33, 0.55)
Unhealthy normal-weight (n=457)	0.22 (0.09, 0.35)	0.14 (0.01, 0.28)	0.52 (0.39, 0.64)	0.45 (0.33, 0.57)
Healthy normal-weight (n=847)	0.30 (0.18, 0.41)	0.22 (0.11, 0.34)	0.78 (0.68, 0.89)	0.71 (0.61, 0.82)

Standardised measures (Z scores) of questionnaire and accelerometer data were used. **Model 1** adjusted for age, sex, and ethnicity. **Model 2** adjusted for age, sex, ethnicity, occupational position, diet quality, smoking status, alcohol consumption, sleep duration, and presence of an illness which limits moderate or vigorous activity

Table 20 Likelihood of meeting 2010 World Health Organization recommendations for moderate-to-vigorous physical activity compared with unhealthy obese adults based on questionnaire and accelerometer assessments in the Whitehall II cohort study, using participants with complete covariate data in 2012/13 (n=3373)

	Meets physical activity recommendations based on questionnaire		**Meets physical activity recommendations based on accelerometer (100mg, 10 min bouts)**	
	Model 1 Prevalence Ratio (95% CI)	**Model 2** Prevalence Ratio (95% CI)	**Model 1** Prevalence Ratio (95% CI)	**Model 2** Prevalence Ratio (95% CI)
Metabolic and obesity status				
Unhealthy obese (n=442)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Healthy obese (n=156)	1.08 (0.89, 1.31)	1.06 (0.87, 1.28)	1.19 (0.83, 1.72)	1.18 (0.82, 1.68)
Unhealthy overweight (n=838)	1.14 (1.01, 1.29)	1.06 (0.94, 1.20)	1.46 (1.15, 1.84)	1.30 (1.03, 1.63)
Healthy overweight (n=633)	1.28 (1.13, 1.44)	1.18 (1.05, 1.33)	1.69 (1.34, 2.13)	1.48 (1.17, 1.87)
Unhealthy normal-weight (n=457)	1.31 (1.15, 1.49)	1.19 (1.04, 1.35)	1.84 (1.44, 2.35)	1.58 (1.23, 2.02)
Healthy normal-weight (n=847)	1.30 (1.16, 1.47)	1.17 (1.04, 1.32)	2.48 (2.00, 3.07)	2.10 (1.69, 2.60)

Physical activity recommendations based on 2010 World Health Organization guideline of ≥ 2.5 hrs/week of moderate-to-vigorous physical activity in bouts of at least 10 mins. **Model 1** adjusted for age, sex, and ethnicity. **Model 2** further adjusted for occupational position, diet quality, smoking status, alcohol consumption, sleep duration, and presence of an illness which limits moderate or vigorous activity

Table 21 Likelihood of meeting 2010 World Health Organization recommendations for moderate-to-vigorous physical activity based on 1-minute bouts compared with unhealthy obese adults (n=3373)

	Meets physical activity recommendations based on accelerometer using 1 min bouts	
	Model 1 Prevalence Ratio (95% CI)	**Model 2** Prevalence Ratio (95% CI)
100 mg accelerometer cut-point		
Metabolic and obesity status		
Unhealthy obese (n=442)	1.00 *(reference)*	1.00 *(reference)*
Healthy obese (n=156)	1.05 (0.89, 1.23)	1.04 (0.89, 1.22)
Unhealthy overweight (n=838)	1.29 (1.18, 1.42)	1.24 (1.13, 1.36)
Healthy overweight (n=633)	1.39 (1.27, 1.53)	1.32 (1.20, 1.45)
Unhealthy normal-weight (n=457)	1.49 (1.35, 1.65)	1.40 (1.27, 1.54)
Healthy normal-weight (n=847)	1.51 (1.39, 1.66)	1.42 (1.30, 1.55)
120 mg accelerometer cut-point		
Metabolic and obesity status		
Unhealthy obese (n=442)	1.00 *(reference)*	1.00 *(reference)*
Healthy obese (n=156)	1.29 (1.02, 1.63)	1.27 (1.01, 1.60)
Unhealthy overweight (n=838)	1.56 (1.34, 1.81)	1.43 (1.23, 1.66)
Healthy overweight (n=633)	1.69 (1.45, 1.96)	1.54 (1.33, 1.79)
Unhealthy normal-weight (n=457)	1.87 (1.60, 2.19)	1.68 (1.44, 1.97)
Healthy normal-weight (n=847)	2.09 (1.81, 2.41)	1.86 (1.61, 2.14)

Physical activity recommendations based on 2010 World Health Organization guideline of ≥ 2.5 hrs/week of moderate-to-vigorous physical activity in bouts of at least 1 min. **Model 1** adjusted for age, sex, and ethnicity. **Model 2** further adjusted for occupational position, diet quality, smoking status, alcohol consumption, sleep duration, and presence of an illness which limits moderate or vigorous activity

4.2 Summary of key findings on physical activity and sedentary behaviour in relation to healthy obesity

The first part of this thesis examined physical activity and sedentary behaviour in relation to healthy obesity, beginning by utilising self-reported measures of moderate-to-vigorous activity and leisure sitting that were available at early phases of the Whitehall II cohort study. After adjustment for covariates including basic demographics, health behaviours, and the presence of an activity-limiting illness, results showed that neither high moderate-to-vigorous physical activity nor low leisure sitting time was separately associated with a higher likelihood of being metabolically healthy among obese adults, while the combination of high moderate-to-vigorous physical activity and low leisure sitting time was marginally associated with an increased likelihood of being healthy among the obese (PR=1.55, 95% CI=1.00, 2.43). When examining prospective associations, high moderate-to-vigorous physical activity and low leisure sitting time, separately and in combination, were not associated with reduced incidence of metabolic risk factor clustering among obese adults over 15 years. Analyses comparing questionnaire and accelerometer assessments of total physical activity in relation to healthy obesity showed higher total physical activity among healthy versus unhealthy obese groups to be evident only when measured using the accelerometer (p=0.72 for difference based on questionnaire; p=0.002 for difference based on accelerometer). Healthy obese adults were not more likely than unhealthy obese adults to meet recommendations for moderate-to-vigorous physical activity when this activity was limited to traditional bouts of at least 10 minutes and an accelerometer cut-point of 100 mg; however, healthy obese adults were more likely than unhealthy obese adults to meet recommendations when considering bouts of at least 1 minute and when using a more stringent 120 mg accelerometer cut-point to define moderate-to-vigorous activity (PR=1.31, 95% CI=1.05, 1.64).

4.3 Part 2: Healthy obesity and metabolic decline

This second part of the results section begins by providing a brief rationale for studies of healthy obesity and future metabolic decline, followed by results according to each study objective. For each objective, a flow chart outlining the selection of the analytical sample is provided, followed by descriptive characteristics of the analytical sample, followed then by results of main statistical models.

Rationale

Whether healthy obesity represents a stable state or a transient phase of metabolic decline has not been well described using repeat clinical data over long follow-ups. Furthermore, the individual metabolic risk factors most responsible for progressions from healthy to unhealthy obesity have not been identified over long follow-ups, and thus the key targets for managing healthy obesity in clinical practice have not been clear. Studies suggest that healthy obese adults have an increased risk of developing type 2 diabetes compared with healthy normal-weight adults, but the literature to date has not been systematically searched and meta-analysed in order to establish the consistency and magnitude of this excess risk. Furthermore, it has not been previously examined whether healthy obese adults with 0 metabolic risk factors (those who are strictly healthy) also show excess risk for type 2 diabetes.

Objective 1: To describe the proportion of healthy obese adults who develop metabolic risk factor clustering over 20 years of follow-up using repeat clinical measures, and to compare the likelihood of development with that of healthy normal-weight adults

Anthropometric and metabolic risk factor data were first measured at phase 3 (1991/94) of the Whitehall II cohort study, and this therefore served as the baseline for this analysis. A flow chart illustrating the selection of the analytical sample is provided in **Figure 8**.

Figure 8 Selection of the analytical sample for the study of the natural course of healthy obesity over 20 years

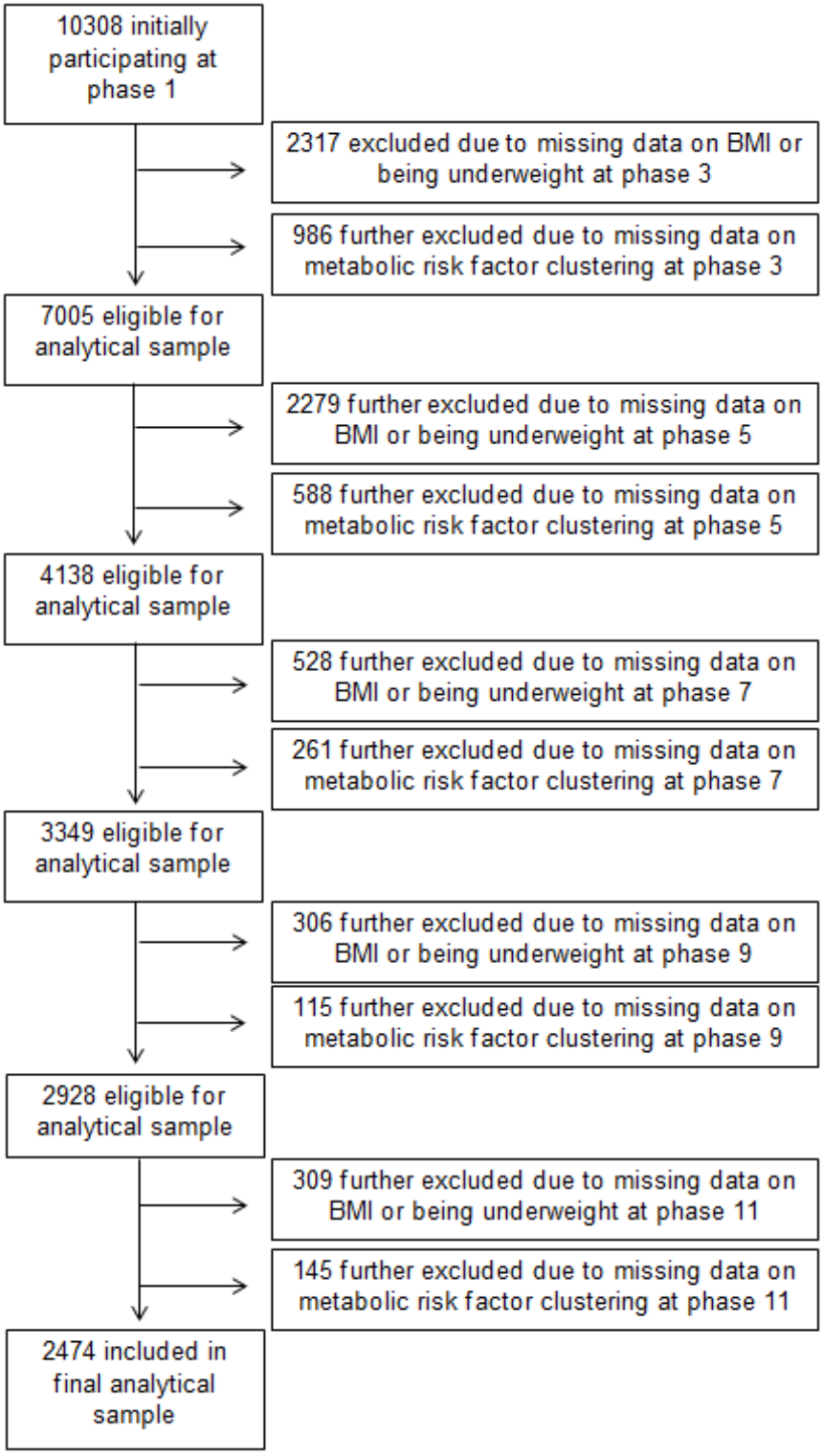


Table 21 shows descriptive characteristics of healthy and unhealthy normal-weight, overweight, and obese adults at baseline (1993/4). Of 2474 participants with necessary anthropometric and metabolic risk factor data at baseline and all 4 follow-ups, 81.2% (n=1073) of normal-weight adults, 57.5% (n=559) of overweight adults, and 36.5% of obese adults were considered healthy (having <2 metabolic risk factors). The overall sample was 75% male, aged 39-62. At baseline, 42.4% of healthy obese adults were male, this proportion being lower than among healthy normal-weight adults (42.4% vs. 72.9% respectively, $p<0.05$). 15.2% of healthy obese adults were of a non-white ethnicity, this proportion being higher than among healthy normal-weight adults (5.7%, $p<0.05$). Healthy obese adults showed higher systolic and diastolic blood pressure and higher insulin resistance at baseline than healthy normal-weight adults (all $p<0.05$), while fasting glucose and blood lipids did not differ between groups.

Compared with those included in the analytic sample (n=2474), those excluded (n=7834) were more likely to be female (36.0% vs. 24.1% respectively, $p<0.001$), of a non-white ethnicity (12.1% vs.7.3 % respectively, $p<0.001$), to be older (mean=50.3 years vs. 48.5 years respectively, $p<0.001$), more likely to be obese at baseline (11.1% vs.7.3 % respectively, $p<0.001$), and less likely to be metabolically healthy at baseline (63.2% vs. 68.6% respectively, $p<0.001$).

Table 22 Characteristics of the sample of adults at phase 3 (1993/4) (aged 39-62, 75% male) by metabolic and obesity status (n=2474)

	Healthy normal-weight (n=1073)	Unhealthy normal-weight (n=248)	Healthy overweight (n=559)	Unhealthy overweight (n=413)	Healthy obese (n=66)	Unhealthy obese (n=115)
Baseline characteristics						
Male – n (%)	782 (72.9)	223 (89.9)*	412 (73.7)	360 (87.2)*	28 (42.4)*	73 (63.5)*
Age (years)	47.8 (5.7)	48.8 (5.7)*	48.8 (5.6)*	49.6 (5.8)*	47.5 (5.5)	48.8 (5.5)
Non-white ethnicity – n (%)	61 (5.7)	29 (11.7)*	34 (6.1)	37 (9)*	10 (15.2)*	9 (7.8)
Systolic blood pressure (mmHg)	115.4 (11.5)	124.9 (13.8)*	118.5 (10.3)*	126.4 (13.1)*	119.5 (13.6)*	129.2 (12.2)*
Diastolic blood pressure (mmHg)	75.9 (8.0)	82.9 (8.8)*	79.3 (7.6)*	85.6 (8.6)*	79.2 (7.8)*	85.9 (8.2)*
Fasting glucose (mmol/l)	5.1 (0.4)	5.6 (0.6)*	5.1 (0.4)	5.5 (0.6)*	5.0 (0.4)	5.6 (0.6)*
HOMA insulin resistance	1.0 (1.0)	1.9 (1.1)*	1.3 (0.7)*	2.5 (1.9)*	1.7 (1.0)*	3.3 (1.5)*
Triglycerides (mmol/l)	1.0 (0.4)	2.0 (1.1)*	5.1 (0.4)*	2.2 (1.2)*	1.1 (0.4)	2.2 (1.1)*
HDL cholesterol (mmol/l)	1.5 (0.4)	1.2 (0.3)*	1.5 (0.3)*	1.2 (0.3)*	1.5 (0.4)	1.2 (0.3)*
Body mass index (kg/m²)	22.6 (1.5)	23.5 (1.2)*	26.7 (1.3)*	27.2 (1.4)*	32.2 (2.7)*	33.0 (3.1)*
Range	18.56-24.99	18.53-24.00	25.00-29.99	25.04-29.98	30.11-41.84	30.01-45.52

Data are mean (standard deviation) unless otherwise noted. *Different from healthy normal-weight ($p<0.05$) based on linear (continuous variables) or logistic regression (binary variables).

Among the 66 healthy obese adults at baseline, 21 (31.8%) were unhealthy obese after 5 years, and 27 (40.9%), 23 (34.8%), and 34 (51.5%) were unhealthy obese after 10, 15, and 20 years respectively (**Table 22 and Table 23**). The proportion of healthy obese adults who were healthy normal-weight after 5, 10, 15, and 20 years was 1.5%, 0%, 1.5%, and 1.5% respectively.

In contrast, among 1073 healthy normal-weight adults at baseline, 3 (0.3%) were unhealthy obese at the 5-year follow-up, and 9 (0.8%), 14 (1.3%), and 19 (1.8%) were unhealthy obese at 10-, 15-, and 20-year follow-ups, respectively. The age-, sex-, and ethnicity-adjusted incidence of unhealthy obesity after 5 years was 102.66 (95% CI=30.88-341.30) times higher in initially healthy obese compared with initially healthy normal-weight adults. The corresponding incidence ratio for unhealthy obesity among initially healthy obese vs. initially healthy normal-weight adults was 45.27 (21.61, 94.81) at 10 years follow-up, 25.36 (13.37, 48.09) at 15 years follow-up, and 26.61 (15.85, 44.69) at 20 years follow-up.

Table 23 Changes, % (n), in metabolic and obesity statuses over 20 years among adults aged 39-62 years at baseline (n=2474)

	Status at follow-up						
	Healthy normal-weight	Unhealthy normal-weight	Healthy overweight	Unhealthy overweight	Healthy obese	Unhealthy obese	**Incidence ratio for unhealthy obesity at follow-up*** (95% CI)
			5-year follow-up				
Status at baseline							
Healthy normal-weight (n=1073)	68.5% (735)	7.6% (82)	18.1% (194)	5.5% (59)	0% (0)	0.3% (3)	1.00 (reference)
Unhealthy normal-weight (n=248)	36.3% (90)	30.2% (75)	11.7% (29)	21.8% (54)	0% (0)	0% (0)	NA[a]
Healthy overweight (n=559)	7.5% (42)	0.5% (3)	59.7% (334)	16.1% (90)	9.3% (52)	6.8% (38)	25.46 (7.94, 81.69)
Unhealthy overweight (n=413)	2.7% (11)	2.4% (10)	28.3% (117)	46.5% (192)	5.8% (24)	14.3% (59)	58.12 (18.60, 181.59)
Healthy obese (n=66)	1.5% (1)	0% (0)	4.5% (3)	0% (0)	62.1% (41)	31.8% (21)	102.66 (30.88, 341.30)
Unhealthy obese (n=115)	0.9% (1)	0% (0)	7% (8)	7.8% (9)	17.4% (20)	67% (77)	NA[a]
			10-year follow-up				
Healthy normal-weight (n=1073)	56% (601)	9.9% (106)	23.6% (253)	9.4% (101)	0.3% (3)	0.8% (9)	1.00 (reference)
Unhealthy normal-weight (n=248)	26.2% (65)	27% (67)	12.5% (31)	33.9% (84)	0% (0)	0.4% (1)	0.54 (0.07, 4.23)
Healthy overweight (n=559)	3.6% (20)	0.5% (3)	50.3% (281)	20.4% (114)	13.1% (73)	12.2% (68)	15.22 (7.69, 30.13)
Unhealthy overweight (n=413)	2.4% (10)	2.2% (9)	21.5% (89)	45.5% (188)	3.4% (14)	24.9% (103)	33.99 (17.67, 65.38)
Healthy obese (n=66)	0% (0)	1.5% (1)	4.5% (3)	0% (0)	53% (35)	40.9% (27)	45.27 (21.61, 94.81)
Unhealthy obese (n=115)	0% (0)	0% (0)	8.7% (10)	7.8% (9)	18.3% (21)	65.2% (75)	NA[a]

*Models exclude unhealthy obese individuals at baseline (remaining n=2359), and are adjusted for age, sex, and ethnicity. [a] Not applicable

Table 24 Changes, % (n), in metabolic and obesity statuses over 20 years among adults aged 39-62 years at baseline (n=2474)

	Status at follow-up						
	Healthy normal-weight	Unhealthy normal-weight	Healthy overweight	Unhealthy overweight	Healthy obese	Unhealthy obese	**Incidence ratio for unhealthy obesity at follow-up*** (95% CI)
			15-year follow-up				
Status at baseline							
Healthy normal-weight (n=1073)	59.8% (642)	7% (75)	22.7% (244)	8.7% (93)	0.5% (5)	1.3% (14)	1.00 (reference)
Unhealthy normal-weight (n=248)	27.4% (68)	29% (72)	14.9% (37)	27.8% (69)	0% (0)	0.8% (2)	0.69 (0.16, 3.00)
Healthy overweight (n=559)	6.3% (35)	1.1% (6)	49% (274)	17.7% (99)	13.8% (77)	12.2% (68)	9.89 (5.63, 17.36)
Unhealthy overweight (n=413)	4.6% (19)	2.2% (9)	25.7% (106)	39% (161)	5.6% (23)	23% (95)	20.17 (11.77, 34.58)
Healthy obese (n=66)	1.5% (1)	1.5% (1)	4.5% (3)	3% (2)	54.5% (36)	34.8% (23)	25.36 (13.37, 48.09)
Unhealthy obese (n=115)	0% (0)	0.9% (1)	10.4% (12)	2.6% (3)	19.1% (22)	67% (77)	NA[a]
			20-year follow-up				
Healthy normal-weight (n=1073)	54.6% (586)	9.4% (101)	20.4% (219)	13.1% (141)	0.7% (7)	1.8% (19)	1.00 (reference)
Unhealthy normal-weight (n=248)	25.8% (64)	28.6% (71)	14.5% (36)	29.8% (74)	0% (0)	1.2% (3)	0.77 (0.23, 2.59)
Healthy overweight (n=559)	7.7% (43)	2% (11)	42.8% (239)	20.6% (115)	12.3% (69)	14.7% (82)	8.82 (5.44, 14.31)
Unhealthy overweight (n=413)	4.1% (17)	4.8% (20)	20.3% (84)	41.4% (171)	4.8% (20)	24.5% (101)	16.06 (10.02, 25.73)
Healthy obese (n=66)	1.5% (1)	0% (0)	9.1% (6)	0% (0)	37.9% (25)	51.5% (34)	26.61 (15.85, 44.69)
Unhealthy obese (n=115)	0.9% (1)	0.9% (1)	7.8% (9)	12.2% (14)	18.3% (21)	60% (69)	NA[a]

*Models exclude unhealthy obese individuals at baseline (remaining n=2359), and are adjusted for age, sex, and ethnicity. [a] Not applicable

As shown in **Table 24** and **Table 25**, results based on maximum samples were similar to those of main analyses which were based on complete cases. Among 389 healthy obese adults with 5-year data, 35.2% were unhealthy obese at 5 years follow-up. This proportion was 34.7% at 10 years follow-up (healthy obese sample n=317), 37.9% at 15 years follow-up (healthy obese sample n=224), and 48.1% at 20 years follow-up (healthy obese sample n=106). Once again, these proportions were lower for baseline healthy normal-weight adults. Among 1955 healthy obese adults with 5-year data, 0.2% were unhealthy obese at 5 years follow-up, 0.7% were unhealthy obese at 10 years follow-up (healthy normal-weight sample n=2215), 1.2% were unhealthy obese at 15 years follow-up (healthy normal-weight sample n=2043), and 1.7% were unhealthy obese at 20 years follow-up (healthy normal-weight sample n=1664).

Table 25 Changes, % (n), in metabolic and obesity statuses over 20 years among adults based on maximum samples

	Status at follow-up					
	Healthy normal-weight	Unhealthy normal-weight	Healthy overweight	Unhealthy overweight	Healthy obese	Unhealthy obese
			5-year follow-up			
Status at baseline						
Healthy normal-weight (n=1955)	64.8% (1266)	9.4% (184)	19.1% (374)	6.5% (127)	0.1% (1)	0.2% (3)
Unhealthy normal-weight (n=659)	37.6% (248)	33.8% (223)	9.7% (64)	18.5% (122)	0.3% (2)	0% (0)
Healthy overweight (n=1744)	11% (192)	1.4% (24)	55.3% (964)	20.5% (357)	5.9% (103)	6% (104)
Unhealthy overweight (n=1565)	4% (62)	3.9% (61)	23.3% (364)	40.2% (629)	2.1% (33)	26.6% (416)
Healthy obese (n=389)	0.8% (3)	0% (0)	10.8% (42)	3.3% (13)	49.9% (194)	35.2% (137)
Unhealthy obese (n=618)	0.5% (3)	0.2% (1)	5.3% (33)	10.4% (64)	16.3% (101)	67.3% (416)
			10-year follow-up			
Healthy normal-weight (n=2215)	53.7% (1189)	10.6% (235)	23.2% (514)	11.4% (252)	0.5% (10)	0.7% (15)
Unhealthy normal-weight (n=652)	33.9% (221)	29.6% (193)	10.3% (67)	25.9% (169)	0% (0)	0.3% (2)
Healthy overweight (n=1691)	9.4% (159)	1.8% (31)	47.3% (799)	21.7% (367)	9.2% (155)	10.6% (180)
Unhealthy overweight (n=1287)	4.3% (55)	4% (51)	22.5% (289)	47.2% (607)	3.3% (43)	18.8% (242)
Healthy obese (n=317)	0.9% (3)	0.3% (1)	13.6% (43)	4.7% (15)	45.7% (145)	34.7% (110)
Unhealthy obese (n=538)	0% (0)	0% (0)	6.9% (37)	10.4% (56)	15.8% (85)	66.9% (360)

Table 26 Changes, % (n), in metabolic and obesity statuses over 20 years among adults based on maximum samples

	Status at follow-up					
	Healthy normal-weight	Unhealthy normal-weight	Healthy overweight	Unhealthy overweight	Healthy obese	Unhealthy obese
			15-year follow-up			
Status at baseline						
Healthy normal-weight (n=2043)	55.8% (1140)	8% (163)	24.1% (493)	10.1% (207)	0.7% (15)	1.2% (25)
Unhealthy normal-weight (n=527)	32.4% (171)	28.5% (150)	13.9% (73)	24.5% (129)	0% (0)	0.8% (4)
Healthy overweight (n=1366)	9.7% (132)	1.7% (23)	45.3% (619)	20.6% (281)	10.7% (146)	12.1% (165)
Unhealthy overweight (n=976)	4.3% (42)	4.7% (46)	23.3% (227)	42.1% (411)	5.3% (52)	20.3% (198)
Healthy obese (n=224)	1.3% (3)	0.4% (1)	10.7% (24)	5.4% (12)	44.2% (99)	37.9% (85)
Unhealthy obese (n=362)	0.8% (3)	0.6% (2)	6.6% (24)	6.6% (24)	19.6% (71)	65.7% (238)
			20-year follow-up			
Healthy normal-weight (n=1664)	53.2% (885)	9.7% (161)	21.9% (365)	12.5% (208)	1% (16)	1.7% (29)
Unhealthy normal-weight (n=359)	28.1% (101)	27.6% (99)	13.9% (50)	28.4% (102)	0% (0)	1.9% (7)
Healthy overweight (n=880)	7.6% (67)	2.2% (19)	42% (370)	20.6% (181)	11.7% (103)	15.9% (140)
Unhealthy overweight (n=612)	4.4% (27)	4.9% (30)	19.6% (120)	42.5% (260)	4.4% (27)	24.2 (148)
Healthy obese (n=106)	1.9% (2)	0% (0)	7.5% (8)	2.8% (3)	39.6% (42)	48.1% (51)
Unhealthy obese (n=177)	1.7% (3)	0.6% (1)	5.1% (9)	11.3% (20)	16.4% (29)	65% (115)

Objective 2: Incidence of individual metabolic risk factors over 20 years among initially healthy obese adults using repeat clinical measures, and comparison of incidence with that of healthy normal-weight adults

Among 2878 adults with anthropometric and metabolic risk factor data at each time point, 1120 adults (aged 39-61 years; 68% male) were free of all metabolic risk factors at baseline. A flow chart illustrating the selection of the analytical sample is provided in **Figure 9**.

Figure 9 Selection of the analytical sample for the study of incidence of individual metabolic risk factors among initially healthy obese adults over 20 years

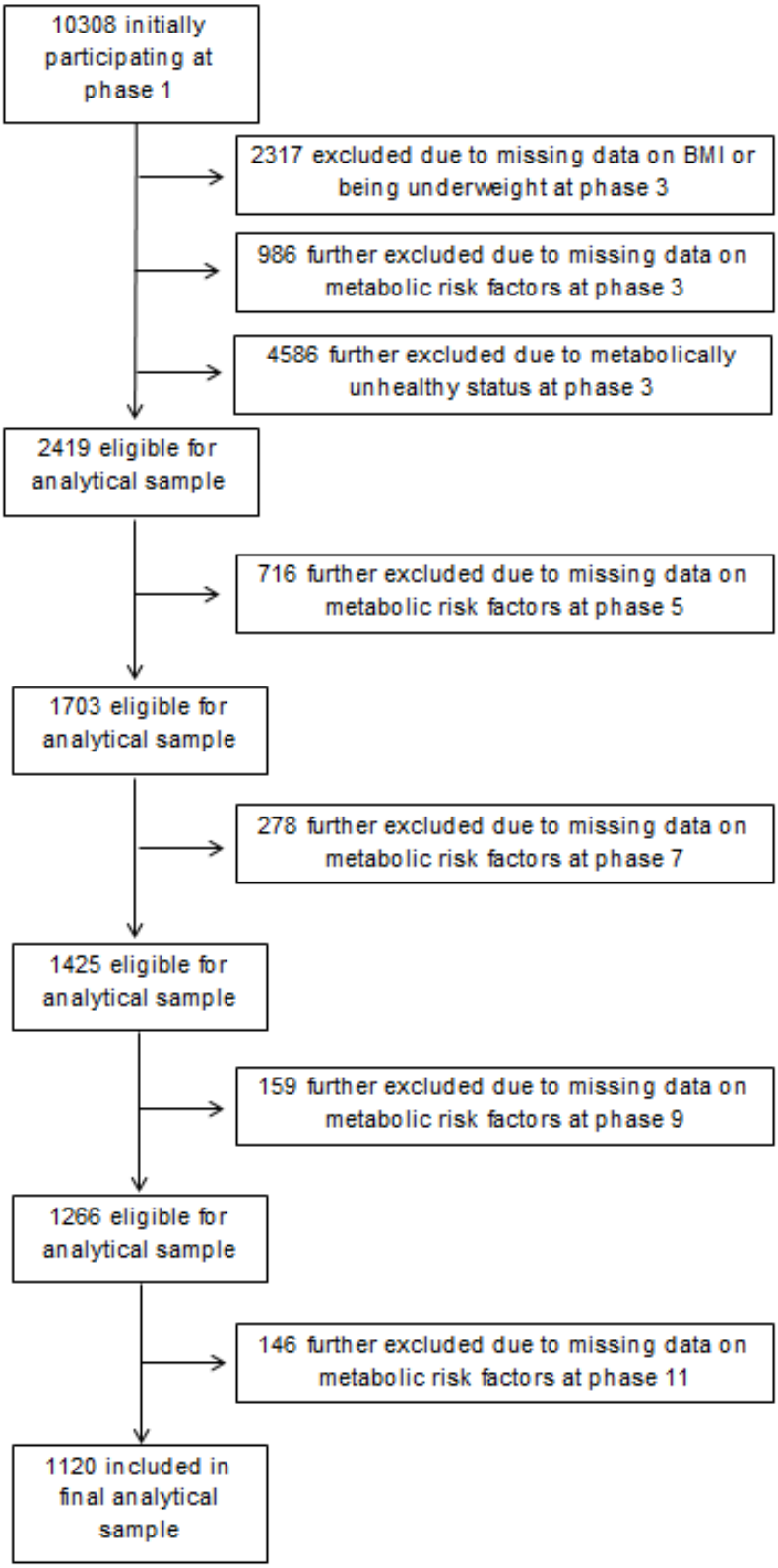


Table 26 shows descriptive characteristics of normal-weight, overweight, and obese adults who had none of the 5 metabolic risk factors of interest at baseline (1993/4), and were considered strictly healthy (n=1120). This strictly healthy status was rarer among higher BMI groups, representing 51.5%, 25.8%, and 13.4% of normal-weight, overweight, and obese adults in the wider cohort respectively. The proportion of healthy obese adults who were male was 32.1%, compared with 69.7% of healthy normal-weight adults ($p<0.05$). Healthy obese and healthy normal-weight adults did not differ in age. Just over 2% of healthy obese adults were of a non-white ethnicity, compared with 5% of healthy normal-weight adults ($p<0.05$). Healthy obese adults had higher insulin resistance and triglycerides than healthy normal-weight adults; other metabolic risk factors did not differ.

Compared with those included in the analytic sample (n=1120), those excluded (n=7695) did not differ by gender (33.2% female vs. 32.3% female, $p=0.55$), but were more likely to be of a non-white ethnicity (11.5% vs.6.3%, $p<0.001$), were more likely to be older (mean=50.1 years vs. 47.6 years, $p<0.001$), and were more likely to be obese at baseline (11.1% vs.2.5% respectively, $p<0.001$). All participants in this analysis were strictly metabolically healthy at baseline (0 metabolic risk factors) and so metabolic health status was not compared between included and excluded groups.

Table 27 Characteristics of the sample of initially healthy adults at phase 3 (1991/94) aged 39-61, 68% male, with healthy status defined as having 0 metabolic risk factors (n=1120)

	Healthy normal-weight (n=806)	**Healthy overweight (n=286)**	**Healthy obese (n=28)**
Baseline characteristics			
Male – n (%)	562 (69.7)	187 (65.4)	9 (32.1)*
Age (years)	47.4 (5.5)	48.3 (5.3)*	47.7 (5.6)
Non-white ethnicity – n (%)	40 (5)	25 (8.7)*	6 (2.1)*
Systolic blood pressure (mmHg)	111.7 (8.7)	113.5 (7.5)*	112.9 (8.0)
Diastolic blood pressure (mmHg)	73.5 (6.2)	75.4 (5.5)*	74.4 (6.3)
Fasting glucose (mmol/l)	5.0 (0.3)	5.0 (0.3)	5.0 (0.3)
HOMA insulin resistance	0.9 (0.5)	1.1 (0.6)*	1.4 (0.7)*
Triglycerides (mmol/l)	0.9 (0.3)	1.0 (0.3)*	1.01 (0.3)*
HDL cholesterol (mmol/l)	1.6 (0.4)	1.5 (0.3)*	1.6 (0.3)
Body mass index (kg/m²)	22.4 (1.6)	26.7 (1.3)*	32.3 (2.6)*
Range	18.56-24.99	25.00-29.99	30.15-41.84

Data are mean (standard deviation) unless otherwise noted. *Different from healthy normal-weight ($p<0.05$) based on linear (continuous variables) or logistic regression (binary variables).

The first set of results show the number of metabolic risk factors that were present at each follow-up (possible range being 0 to 5 risk factors) among normal-weight, overweight, and obese adults who initially had 0 metabolic risk factors. Of initially healthy obese adults, 57.1% had at least one metabolic risk factor at 5-years follow-up (**Table 27**); this corresponding proportion was 64.3% at 10- and 15-years follow-up and 78.6% at 20-years follow-up (**Table 28**). These proportions were smaller (32.8%, 46.7%, 44%, and 60.3%) among initially healthy normal-weight participants.

Incidence ratios indicated that initially healthy obese adults were 1.70 (95% CI=1.22, 2.36) times more likely to have at least 1 metabolic risk factor at 5 years follow-up compared with initially healthy normal-weight adults. This excess risk among initially healthy obese adults was 1.37 (95% CI=1.03, 1.82) times higher at 10 years follow-up, 1.46 (95% CI=1.10, 1.94) times higher at 15 years follow-up, and 1.30 (95% CI=1.07, 1.58) times higher at 20 years follow-up. Excess risk was also consistently observed among initially healthy overweight adults compared with initially healthy normal-weight adults, these being lower than that of the healthy obese.

Table 28 Changes in metabolic status over 20 years among adults aged 39-61 years (68% male) at baseline (n=1120), with baseline healthy status defined as having 0 metabolic risk factors

	Number of metabolic risk factors at follow-up						
	0	**1**	**2**	**3**	**4**	**5**	**Incidence ratio (95% CI) for having at least 1 risk factor at follow-up***
				5-year follow-up			
Status at baseline							
Healthy normal-weight (n=806)	67.2% (542)	25.3% (204)	5.8% (47)	1.5% (12)	0.1% (1)	0% (0)	1.00 (reference)
Healthy overweight (n=286)	51.7% (148)	33.6% (96)	10.8% (31)	3.5% (10)	0.3% (1)	0% (0)	1.45 (1.25, 1.70)
Healthy obese (n=28)	42.9% (12)	25% (7)	14.3% (4)	14.3% (4)	3.6% (1)	0% (0)	1.70 (1.22, 2.36)
				10-year follow-up			
Healthy normal-weight (n=806)	53.3% (430)	32.6% (263)	10.7% (86)	2.7% (22)	0.6% (5)	0% (0)	1.00 (reference)
Healthy overweight (n=286)	36% (103)	41.3% (118)	13.6% (39)	6.6% (19)	2.1% (6)	0.3% (1)	1.36 (1.21, 1.52)
Healthy obese (n=28)	35.7% (10)	32.1% (9)	17.9% (5)	10.7% (3)	3.6% (1)	0% (0)	1.37 (1.03, 1.82)

* Models adjusted for age, sex, and ethnicity. Risk factors include hypertension, low HDL cholesterol, high triglycerides, insulin resistance, and high blood glucose

Table 29 Changes in metabolic status over 20 years among adults aged 39-61 years (68% male) at baseline (n=1120), with baseline healthy status defined as having 0 metabolic risk factors

	Number of metabolic risk factors at follow-up						
	0	**1**	**2**	**3**	**4**	**5**	**Incidence ratio (95% CI) for having at least 1 risk factor at follow-up***
			15-year follow-up				
Status at baseline							
Healthy normal-weight (n=806)	56% (451)	31.4% (253)	9.2% (74)	3.1% (25)	0.4% (3)	0% (0)	1.00 (reference)
Healthy overweight (n=286)	40.9% (117)	36.7% (105)	12.6% (36)	8% (23)	1.4% (4)	0.3% (1)	1.33 (1.18, 1.51)
Healthy obese (n=28)	35.7% (10)	32.1% (9)	10.7% (3)	17.9% (5)	3.6% (1)	0% (0)	1.46 (1.10, 1.94)
			20-year follow-up				
Healthy normal-weight (n=806)	39.7% (320)	41.2% (332)	13.2% (106)	4.7% (38)	1% (8)	0.2% (2)	1.00 (reference)
Healthy overweight (n=286)	26.9% (77)	43.4% (124)	19.9% (57)	7% (20)	1.7% (5)	1% (3)	1.20 (1.10, 1.31)
Healthy obese (n=28)	21.4% (6)	28.6% (8)	17.9% (5)	28.6% (8)	3.6% (1)	0% (0)	1.30 (1.07, 1.58)

* Models adjusted for age, sex, and ethnicity. Risk factors include hypertension, low HDL cholesterol, high triglycerides, insulin resistance, and high blood glucose

The proportion of initially healthy normal-weight, overweight, and obese adults who developed each metabolic risk factor at 5, 10, 15, and 20-years follow-up are shown in **Table 29** and **Table 30**. Among 28 initially healthy obese adults at baseline, 32.1% were insulin resistant at 5-years follow-up, while 21.4% had high blood glucose, 39.3% had hypertension, 7.1% had high triglycerides, and 10.7% had low HDL cholesterol. These proportions remained a similar magnitude after 10 and 15 years follow-up. At the 20-year follow-up, proportions increased for insulin resistance (46.4%), high blood glucose (42.9%), and hypertension (64.3%), while no incident cases of low HDL cholesterol and few cases of high triglycerides were evident.

The proportion of initially healthy normal-weight adults who developed each risk factor over time was small; I.e. 6.2% were insulin resistant at 5 years follow-up, rising to 12.4% at 20 years follow-up. Incident hypertension was highest among healthy normal-weight adults at all follow-up points, being 17.6% at 5 years follow-up, rising to 46.8% at 20 years follow-up. Incidence of each metabolic risk factor among initially healthy overweight adults was at an intermediate level between that of initially healthy normal-weight and obese adults.

Table 30 Incidence, % (n), of individual metabolic risk factors over 20 years among initially healthy adults aged 39-61 years (n=1120)

	Insulin resistance	High blood glucose	Hypertension	Low HDL	High triglycerides
			5-year follow-up		
Status at baseline					
Healthy normal-weight (n=806)	6.2% (50)	6.9% (56)	17.6% (142)	5.2% (42)	6% (48)
Healthy overweight (n=286)	10.1% (29)	9.8% (28)	25.9% (74)	8.7% (25)	12.6% (36)
Healthy obese (n=28)	32.1% (9)	21.4% (6)	39.3% (11)	7.1% (2)	10.7% (3)
			10-year follow-up		
Healthy normal-weight (n=806)	5.6% (48)	18% (145)	29.3% (236)	2.4% (19)	9.1% (73)
Healthy overweight (n=286)	18.2% (52)	22.4% (64)	37.4% (107)	5.9% (17)	14.7% (42)
Healthy obese (n=28)	28.6% (8)	25% (7)	39.3% (11)	3.6% (1)	17.9% (5)

Baseline healthy status defined as having 0 of 5 metabolic risk factors (hypertension, low HDL cholesterol, high triglycerides, insulin resistance, and high blood glucose)

Table 31 Incidence, % (n), of individual metabolic risk factors over 20 years among initially healthy adults aged 39-61 years (n=1120)

	Insulin resistance	High blood glucose	Hypertension	Low HDL	High triglycerides
			15-year follow-up		
Status at baseline					
Healthy normal-weight (n=806)	5.6% (45)	12% (97)	33.5% (270)	2.5% (20)	6.9% (56)
Healthy overweight (n=286)	13.3% (38)	20.3% (58)	42.3% (121)	3.8% (11)	13.6% (39)
Healthy obese (n=28)	32.1% (9)	21.4% (6)	46.4% (13)	3.6% (1)	17.9% (5)
			20-year follow-up		
Healthy normal-weight (n=806)	12.4% (100)	18.5% (149)	46.8% (377)	1.7% (14)	7.4% (60)
Healthy overweight (n=286)	22% (63)	23.4% (67)	57.3% (164)	4.9% (14)	8.7% (25)
Healthy obese (n=28)	46.4% (13)	42.9% (12)	64.3% (18)	0% (0)	10.7% (3)

Baseline healthy status defined as having 0 of 5 metabolic risk factors (hypertension, low HDL cholesterol, high triglycerides, insulin resistance, and high blood glucose)

Incidence ratios for individual metabolic risk factors between groups are shown in **Table 31, Table 32,** and **Figure 10**. At the 5-year follow-up, compared with initially healthy normal-weight adults, initially healthy obese adults were 4.41 (95% CI=2.33, 8.34) times more likely to be insulin resistant, 3.35 (95% CI=1.54, 7.30) times more likely to have high blood glucose, and 1.92 (95% CI=1.14, 3.22) times more likely to be hypertensive. Insulin resistance remained most commonly incident among all metabolic risk factors at subsequent follow-ups among initially healthy obese compared with initially healthy normal-weight adults. At the 20-year follow-up, compared with initially healthy normal-weight adults, initially healthy obese adults were 3.78 (95% CI=2.38, 5.99) times more likely to be insulin resistant, 2.27 (95% CI=1.43, 3.61) times more likely to have high blood glucose, and 1.35 (95% CI=1.03, 1.77) times more likely to be hypertensive. Differences between initially healthy obese and initially healthy normal-weight adults for low HDL cholesterol and high triglycerides were non-significant at all follow-ups, with the exception of high triglycerides among initially healthy obese adults at 15-years follow-up (IR=2.69, 95% CI=1.13, 6.43).

Table 32 Incidence ratios for individual metabolic risk factors over 20 years (n=1120)

	Insulin resistance	**High blood glucose**	**Hypertension**	**Low HDL**	**High triglycerides**
	Incidence Ratio (95% CI)	Incidence Ratio (95% CI)	Incidence Ratio (95% CI)	Incidence Ratio (95% CI)	Incidence Ratio (95% CI)
			5-year follow-up		
Status at baseline					
Healthy normal-weight (n=806)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Healthy overweight (n=286)	1.63 (1.06, 2.52)	1.43 (0.92, 2.21)	1.37 (1.08, 1.75)	1.57 (0.96, 2.55)	2.20 (1.46, 3.32)
Healthy obese (n=28)	4.41 (2.33, 8.34)	3.35 (1.54, 7.30)	1.92 (1.14, 3.22)	1.06 (0.30, 3.69)	2.15 (0.71, 6.55)
			10-year follow-up		
Healthy normal-weight (n=806)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Healthy overweight (n=286)	3.03 (2.09, 4.38)	1.26 (0.97, 1.63)	1.20 (1.00, 1.45)	2.56 (1.33, 4.96)	1.70 (1.19, 2.42)
Healthy obese (n=28)	4.90 (2.47, 9.74)	1.63 (0.85, 3.15)	1.11 (0.68, 1.82)	1.40 (0.20, 9.58)	2.08 (0.89, 4.83)

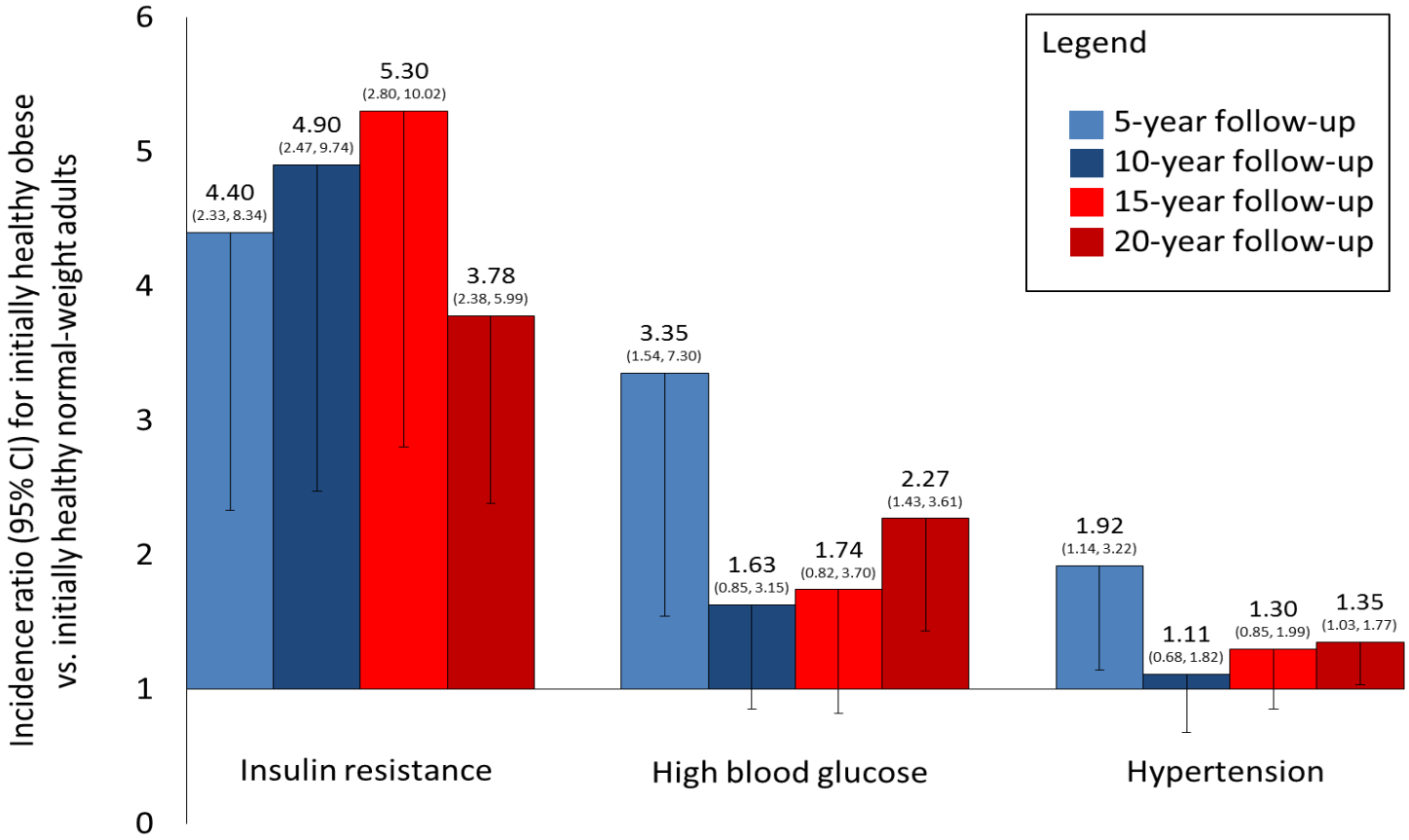
Models are adjusted for age, sex, and ethnicity. Baseline healthy status defined as having 0 of 5 metabolic risk factors (hypertension, low HDL cholesterol, high triglycerides, insulin resistance, and high blood glucose)

Table 33 Incidence ratios for individual metabolic risk factors over 20 years (n=1120)

	Insulin resistance	**High blood glucose**	**Hypertension**	**Low HDL**	**High triglycerides**
	Incidence Ratio (95% CI)	Incidence Ratio (95% CI)	Incidence Ratio (95% CI)	Incidence Ratio (95% CI)	Incidence Ratio (95% CI)
			15-year follow-up		
Status at baseline					
Healthy normal-weight (n=806)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Healthy overweight (n=286)	2.35 (1.56, 3.55)	1.69 (1.25, 2.28)	1.22 (1.03, 1.44)	1.57 (0.77, 3.22)	2.10 (1.44, 3.07)
Healthy obese (n=28)	5.30 (2.80, 10.02)	1.74 (0.82, 3.70)	1.30 (0.85, 1.99)	1.49 (0.23, 9.77)	2.69 (1.13, 6.43)
			20-year follow-up		
Healthy normal-weight (n=806)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Healthy overweight (n=286)	1.78 (1.34, 2.36)	1.27 (0.98, 1.64)	1.19 (1.05, 1.35)	2.78 (1.27, 6.11)	1.27 (0.82, 1.97)
Healthy obese (n=28)	3.78 (2.38, 5.99)	2.27 (1.43, 3.61)	1.35 (1.03, 1.77)	NA	1.39 (0.47, 4.13)

Models are adjusted for age, sex, and ethnicity. Baseline healthy status defined as having 0 of 5 metabolic risk factors (hypertension, low HDL cholesterol, high triglycerides, insulin resistance, and high blood glucose)

Figure 10 Incidence of metabolic risk factors among initially healthy obese compared with initially healthy normal-weight adults over 20 years (n=1120)



Baseline healthy status defined as having 0 metabolic risk factors (hypertension, low HDL cholesterol, high triglycerides, insulin resistance, and high blood glucose). Models are adjusted for age, sex, and ethnicity. Little difference in HDL-cholesterol or triglycerides was observed between groups, and these are not shown due to small case numbers.

As shown in **Table 33** and **Table 34**, results of metabolic risk factor incidence based on maximum samples were similar to results of main analyses which were based on complete cases. Among 80 healthy obese adults with 5-year data on all metabolic risk factors, at 5-years follow-up, 35% developed insulin resistance, 25% developed high blood glucose, 47.5% developed hypertension, 6.3% developed low HDL cholesterol, and 18.8% developed high triglycerides. Among 41 healthy obese adults with 20-year data on all metabolic risk factors, at 20-years follow-up, 41.5% developed insulin resistance, 36.6% developed high blood glucose, 65.9% developed hypertension, 0% developed low HDL cholesterol, and 7.3% developed high triglycerides.

Incidence of each metabolic risk factor tended to be lower among initially healthy normal-weight adults, with 11.7% developing insulin resistance, 17.6% developing high blood glucose, 44.7% developing hypertension, 2% developing low HDL cholesterol, and 7.4% developing high triglycerides after 20-years follow-up (sample n=1061).

Table 34 Incidence, % (n), of individual metabolic risk factors over 20 years among initially healthy adults using maximum samples

	Insulin resistance	High blood glucose	Hypertension	Low HDL	High triglycerides
			5-year follow-up		
Status at baseline					
Healthy normal-weight (n=1229)	9.2% (113)	16.4% (202)	37.3% (458)	6.5% (80)	10.3% (126)
Healthy overweight (n=618)	15% (93)	19.7% (122)	39.3% (243)	8.9% (55)	14.6% (90)
Healthy obese (n=80)	35% (28)	25% (20)	47.5% (38)	6.3% (5)	18.8% (15)
			10-year follow-up		
Healthy normal-weight (n=1304)	9.5% (124)	21.2% (276)	40.6% (529)	3.2% (42)	12.3% (160)
Healthy overweight (n=619)	19.9% (123)	22% (136)	45.7% (283)	6% (37)	14.9% (92)
Healthy obese (n=70)	32.9% (23)	25.7% (18)	47.1% (33)	2.9% (2)	12.9% (9)

Baseline healthy status defined as having 0 of 5 metabolic risk factors (hypertension, low HDL-cholesterol, high triglycerides, insulin resistance, and high blood glucose)

Table 35 Incidence, % (n), of individual metabolic risk factors over 20 years among initially healthy adults using maximum samples

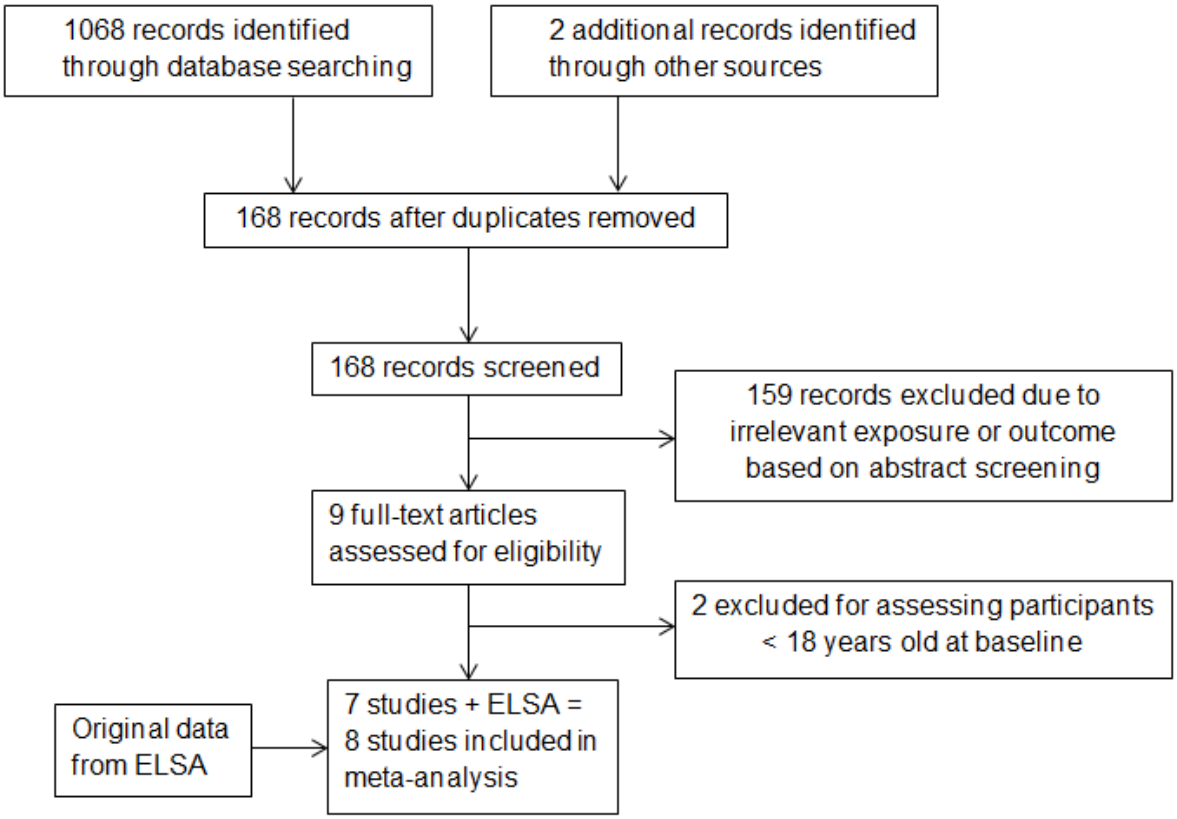
	Insulin resistance	High blood glucose	Hypertension	Low HDL	High triglycerides
			15-year follow-up		
Status at baseline					
Healthy normal-weight (n=1228)	8.6% (106)	15.6% (192)	40.9% (502)	3.2% (39)	7.6% (93)
Healthy overweight (n=536)	17.5% (94)	21.3% (114)	45.9% (246)	4.7% (25)	11.6% (62)
Healthy obese (n=62)	35.5% (22)	33.9% (21)	51.6% (32)	1.6% (1)	14.5% (9)
			20-year follow-up		
Healthy normal-weight (n=1061)	11.7% (124)	17.6% (187)	44.7% (474)	2% (21)	7.4% (79)
Healthy overweight (n=397)	23.4% (93)	22.9% (91)	54.9% (218)	4% (16)	9.8% (39)
Healthy obese (n=41)	41.5% (17)	36.6% (15)	65.9% (27)	0% (0)	7.3% (3)

Baseline healthy status defined as having 0 of 5 metabolic risk factors (hypertension, low HDL-cholesterol, high triglycerides, insulin resistance, and high blood glucose)

Objective 3: Systematic search of literature for published prospective studies on the risk of incident type 2 diabetes among obese adults who are metabolically healthy

As shown in **Figure 10**, the initial search of Medline and Embase retrieved 1068 results. Two additional studies were identified through other sources (51, 238). After removing duplications, 168 studies remained, 159 of which were excluded due to irrelevant exposure or outcome based on abstract screening. Nine studies were identified after screening as potentially relevant, and full-text articles were assessed for eligibility. Of these, 2 studies were excluded for assessing participants under 18 years of age at baseline (239, 240). Seven published studies therefore met our full criteria for inclusion (51, 167, 186, 187, 238, 241, 242). Hand-searching through reference lists within those 7 included studies identified 6 additional potentially relevant studies, but none of these met the full inclusion criteria. For instance one study assessed cross-sectional type 2 diabetes prevalence but not prospective incidence (243). A flow chart illustrating the systematic literature search for the meta-analysis is provided in **Figure 11**.

Figure 11 Outline of the systematic literature search for the meta-analysis



Including ELSA, a total of 8 studies contributed to the meta-analysis. Two studies reported effect estimates for type 2 diabetes separately by sex (238, 241), and were presented accordingly. The studies included in the meta-analysis represented a geographically diverse set of populations; however ethnic composition was not specifically reported in any study. Age at baseline ranged from 18 years in three studies (51, 167, 241), to 99 years in ELSA. All studies defined metabolic health based on metabolic clustering, with the least comprehensive measure considering only insulin resistance, triglycerides, and fasting glucose (167). All studies used an objective fasting blood or plasma glucose measure to diagnose incident type 2 diabetes except ELSA which used self-reported physician diagnosis. Average length of follow-up ranged from 5 years in Kim et al. (242) to 20 years in Arnlov et al. (187).

The reference category was a metabolically healthy normal-weight group in all studies; however specific BMI cut-offs varied, with one study using a broad 'non-obese' group as the reference (BMI < 30 kg/m^2) (167), while ELSA and others excluded overweight individuals from the reference group by setting the cut-off as BMI < 25 kg/m^2 (186, 187, 238, 242). Still others excluded both overweight and underweight adults in their reference group (51, 241). Overall, there appeared to be variability in effect estimates for type 2 diabetes, ranging from 2.09 (95% CI=0.87-5.03) in Appleton et al. (51), to 14.60 (95% CI=3.23-65.50) in Hwang at el. (women) (241). However, all relative risk estimates were positive and exceeded the reference value of one, and none reported a reduced risk of type 2 diabetes in healthy obese adults. Detailed characteristics of studies identified through the systematic literature search are described in **Table 35**.

Table 36 Characteristics of studies included in the meta-analysis

Study	Baseline sample	Baseline healthy obese n (% of obese)	Metabolically healthy obese criteria	Type 2 diabetes criteria	Follow-up length Diabetes cases for healthy obese	Estimate (95% CI)	Covariates	Quality score (/11)*
Meigs et al. 2006	N=2902 Mean 52 years (MHO group) 51.3% male (MHO group) Free of type 2 diabetes or CVD United States Community-based	236 (37%)	Criteria 1: ≤ 2 ATP3 metabolic syndrome criteria: fasting plasma glucose 5.6-6.9 mmol/L, waist circumference > 102 cm in men or > 88 cm in women, fasting triglycerides ≥ 1.7 mmol/L, HDL-cholesterol < 1.0 mmol/L in men or < 1.3 mmol/L in women, blood pressure ≥ 130/85 mmHg or current treatment for hypertension Criteria 2: HOMA-IR [(fasting glucose x fasting insulin)/22.5] < 75th percentile BMI ≥ 30 kg/m^2	Fasting plasma glucose ≥ 7.0 mmol/L or new use of hypoglycemic drug therapy	Mean 6.8 years 7 cases	Criteria 1 Model 1: RR=2.40 (0.94, 6.12) Model 2: RR=2.19 (0.85, 5.60) Reference: BMI < 25 kg/m^2 without metabolic syndrome Criteria 2 Model 1: RR=3.79 (1.66, 8.62) Model 2: RR=3.28 (1.44, 7.50) Reference: BMI < 25 kg/m^2 and insulin sensitive	Model 1: Age, sex Model 2: Further adjusted for family history of diabetes, IGT	5

Study	Baseline sample	Baseline healthy obese n (% of obese)	Metabolically healthy obese criteria	Type 2 diabetes criteria	Follow-up length Diabetes cases for healthy obese	Estimate (95% CI)	Covariates	Quality score (/11)*
Hadaegh et al. 2011	N=5250 ≥ 20 years 41.6% male Free of diabetes Tehran Nationally representative	452 (37.5%)	≤ 2 of: waist circumference ≥ 94.5 cm, HDL-cholesterol < 1.04 mmol/L in men and <1.03 mmol/L in women, triglycerides ≥ 1.7 mmol/L or lipid lowering drug use, blood pressure ≥ 130/85 mmHg or hypertension treatment, fasting glucose ≥ 5.5 mmol/L or previously diagnosed diabetes Obese BMI ≥ 30 kg/m^2	Fasting plasma glucose ≥ 7 mmol/L or 2 hour post-challenge plasma glucose ≥ 11.1 mmol/L or diabetes medication use	6.5 years 7 cases (men)[a] 11 cases (women)[a]	Men Model 1: OR=3.80 (1.70, 8.90) Model 2: OR=3.60 (1.50, 8.40) Women Model 1: OR=2.20 (1.00, 4.70) Model 2: OR=2.20 (1.00, 4.70) Reference: BMI < 25 kg/m^2, metabolically healthy	Model 1: Age Model 2: Further adjusted for family history of diabetes, history of cardiovascular disease, education, smoking, lifestyle intervention received	7

Study	Baseline sample	Baseline healthy obese n (% of obese)	Metabolically healthy obese criteria	Type 2 diabetes criteria	Follow-up length Diabetes cases for healthy obese	Estimate (95% CI)	Covariates	Quality score (/11)*
Arnlov et al. 2011	N=1675 50 years 100% male Free of type 2 diabetes Sweden Community-based	28 (31.8%)	Modified NCEP ATP3 ≤ 2 of: fasting blood glucose ≥ 5.6 mmol/L (corresponding to fasting plasma glucose ≥ 6.1 mmol/L), blood pressure ≥ 130/85 mmHg or treatment, triglycerides ≥ 1.7 mmol/L, HDL-cholesterol <1.04 mmol/L, body mass index ≥ 29.4 kg/m^2. BMI > 30 kg/m^2	Fasting blood glucose ≥ 6.1 mmol/L (corresponding to fasting plasma glucose ≥ 7.0 mmol/L) or use of antidiabetes medication	20 years 9 cases	Whole sample (n=1675) Crude OR=12.15 (5.10, 28.96) Adjusted OR=11.73 (4.88, 28.16) Sensitivity: Normal fasting glucose at baseline (n=1541) Crude OR=13.35 (5.55, 32.11) Adjusted OR=13.19 (5.42, 32.09) Reference: BMI < 25 kg/m^2 without metabolic syndrome	Age, smoking, physical activity	6

Study	Baseline sample	Baseline healthy obese n (% of obese)	Metabolically healthy obese criteria	Type 2 diabetes criteria	Follow-up length Diabetes cases for healthy obese	Estimate (95% CI)	Covariates	Quality score (/11)*
Kim et al. 2012	N=8748 20-79 years 65.2% male Free of self-reported history of physician diagnosed diabetes, or taking antihyperglycemic medication, fasting blood glucose ≥ 126 mg/dL, HbA1c ≥ 6.5% Korea Clinic-based	59 (41%)	≤ 2 of: fasting plasma glucose ≥ 100 mg/dL or antidiabetic treatment, blood pressure ≥ 130/85 mmHg, or antihypertensive treatment, plasma triglycerides ≥ 150 mg/dL, plasma HDL-cholesterol < 40 mg/dL in men and < 50 mg/dL in women, waist circumference ≥ 90 cm in men and ≥ 80 cm in women. BMI ≥ 30 kg/m^2 and repeated with Asian specific cut off – BMI ≥ 27.5 kg/m^2	Fasting plasma glucose ≥ 126 mg/dL, HbA1c > 6.5%, or on antihyperglycemic medication	5 years 5 cases	Crude OR=5.31 (2.08, 13.56) Adjusted OR=4.93 (1.90, 12.79) Reference: BMI < 25 kg/m^2 metabolically healthy Asian specific Crude OR=4.57 (2.57, 8.10) Adjusted OR=4.31 (2.36, 7.86) Reference: BMI < 23 kg/m^2 metabolically healthy	Age, sex, smoking, alcohol, physical activity	7

Study	Baseline sample	Baseline healthy obese n (% of obese)	Metabolically healthy obese criteria	Type 2 diabetes criteria	Follow-up length Diabetes cases for healthy obese	Estimate (95% CI)	Covariates	Quality score (/11)*
Hwang et al. 2012	N=1547 18-59 years 40.7% male Free of type 2 diabetes, hypertension, history of stroke, and metabolic abnormalities except central adiposity Taiwan Nationally representative	38 (28.5%)	AHA criteria modified for Asian populations ≤ 2 of: waist circumference ≥ 90cm for men and ≥ 80 cm for women, triglycerides ≥ 1.7 mmol/L, HDL-cholesterol <1.0 mmol/L for men and <1.3 mmol/L for women, systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or current use of antihypertensive drugs, and fasting plasma glucose ≥ 5.6 mmol/L or current use of antihyperglycemic drugs BMI ≥ 27 kg/m^2	Fasting plasma glucose ≥ 7.0 mmol/L or HbA1C > 6.5% or use of antihyperglycemic mediation	Mean 5.4 years 3 cases (men)[a] 5 cases (women)[a]	Men HR=14.30 (1.21, 168.00) Women HR=14.60 (3.23, 65.50) Total (men and women) HR=11.50 (3.38, 39.10) Reference: BMI 18.5 – 22.9 kg/m^2 metabolically healthy	Age, smoking status, alcohol intake, exercise, family history of diabetes or hypertension	8

Study	Baseline sample	Baseline healthy obese n (% of obese)	Metabolically healthy obese criteria	Type 2 diabetes criteria	Follow-up length Diabetes cases for healthy obese	Estimate (95% CI)	Covariates	Quality score (/11)*
Soriguer et al. 2013	N=1051 18-65 years 37.7 % male Free of type 2 diabetes Spain Nationally representative	105 (48.4%)	HOMA-IR < 90th percentile, triglycerides < 150 mg/dl, fasting glucose < 110 mg/dl BMI ≥ 30 kg/m^2	Fasting plasma glucose ≥ 7 mmol/L	6 and 11 years 17 cases (6-year follow-up) 11 cases (11-year follow-up)	After 6 years Model 1: OR=3.62 (1.83, 7.17) Model 2: OR=2.16 (1.07, 4.36) After 11 years Model 1: OR=6.76 (2.58, 17.69) Model 2: OR=4.12 (1.82, 9.34) Reference: metabolically healthy BMI < 30 kg/m^2	Model 1: Unadjusted Model 2: Age, sex, weight change, abnormal glucose regulation (IFG, IGT)	4
Appleton et al. 2013	N=3743 ≥ 18 years 39% male (MHO group) Free of CVD/stroke and not underweight Australia Nationally representative	454 (44.2%)	< 2 IDF metabolic syndrome criteria: triglycerides ≥ 1.7 mmol/L, HDL-cholesterol < 1 mmol/L in men or <1.3 mmol/L in women or lipid-lowering medication use, blood pressure ≥ 130/85 mmHg or antihypertensive medication use, fasting glucose ≥ 5.6 mmol/L or self-reported diabetes BMI ≥ 30 kg/m^2	Self-reported doctor diagnosis or fasting plasma glucose ≥ 7 mmol/L	Median 8.2 years 11 cases	OR=2.09 (0.87, 5.03) Reference: metabolically healthy BMI 18-5 - 24.9 kg/m^2)	Age, sex, household income, family history of diabetes	6

Study	Baseline sample	Baseline healthy obese n (% of obese)	Metabolically healthy obese criteria	Type 2 diabetes criteria	Follow-up length Diabetes cases for healthy obese	Estimate (95% CI)	Covariates	Quality score (/11)*
ELSA 2013	N=3066 Mean age 64.6 43.3% male Free from physician diagnosed diabetes England Nationally representative	308 (38.3%)	< 2 of: hypertension risk (clinic BP >130/85 mmHg, or hypertension diagnosis, or use of anti-hypertensive medication); diabetes risk (HbA1c > 6%); low grade inflammation (CRP ≥ 3mg/L); adverse HDL cholesterol profile (<1.03 mmol/l in men and <1.30 mmol/l women); adverse triglycerides (≥ 1.7 mmol/l). BMI ≥ 30 kg/m^2	Self-reported physician diagnosis, based on fasting plasma glucose ≥ 7 mmol/L	Mean 5.9 years 12 cases	Model 1: HR=9.30 (2.60, 32.70) Model 2: HR=8.60 (2.40, 30.40) Reference: metabolically healthy BMI < 25 kg/m^2)	Model 1: Age, sex Model 2: Further adjusted for cigarette smoking, frequency of alcohol intake, physical activity, wealth, depressive symptoms	7

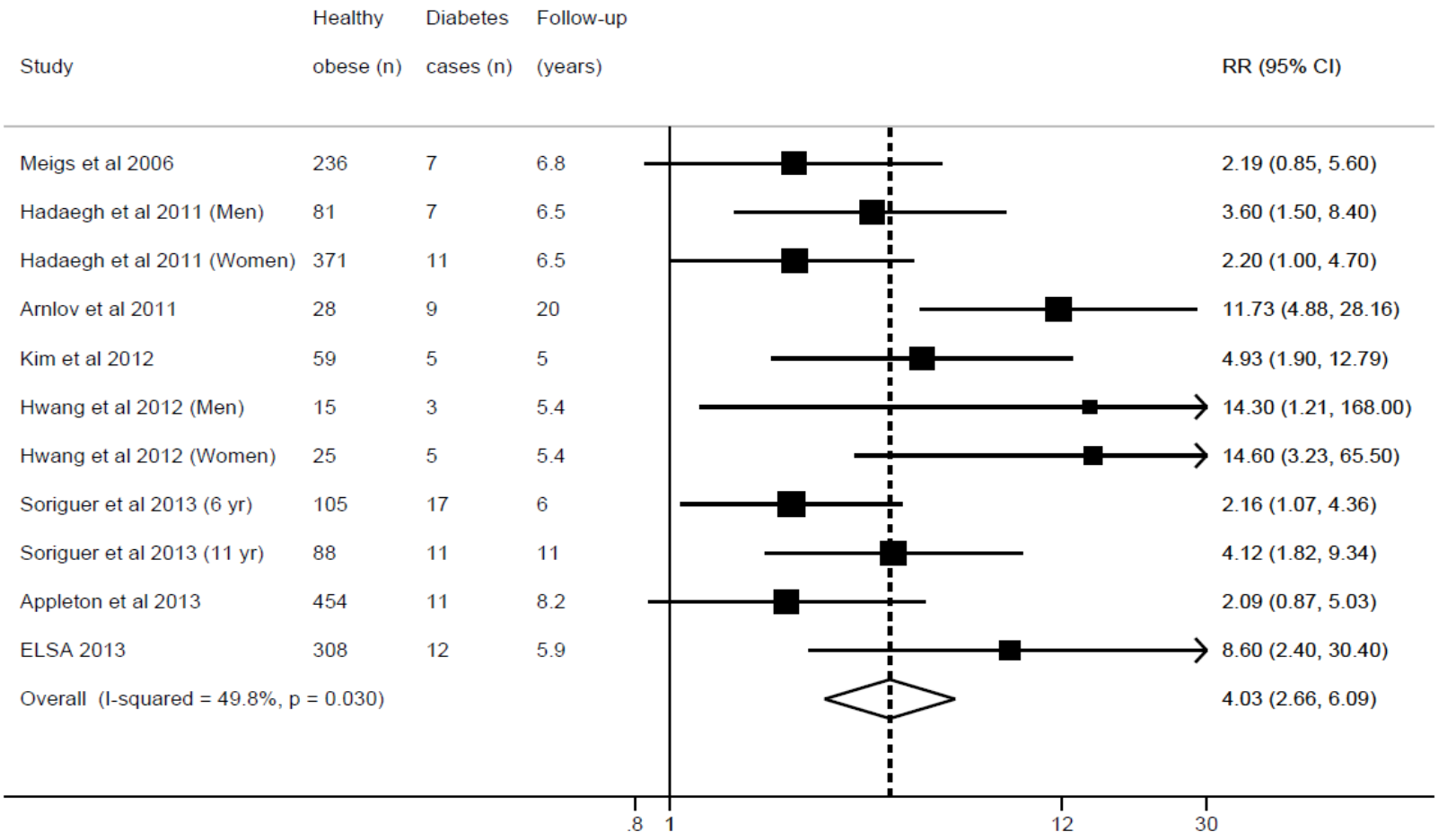
*Study quality assessed according to the rigor of study exposure, outcome, and model adjustment strategy. Points were assigned as follows: 2 points if the study considered metabolic clustering; 1 point if the study considered insulin profile alone. 2 points if diabetes diagnosis was based on objective clinical measurement (ie. blood glucose level); 1 point if diabetes diagnosis was based on self-report only.1 point if each of the following covariates were considered: family history of diabetes, ethnicity, alcohol consumption, smoking status, physical activity, dietary sugar intake, socioeconomic status. Studies were scored out of 11 possible points.

[a]Estimated from published cumulative incidence (%) figure.

Objective 4: Synthesis of estimates obtained from the literature using random-effects meta-analysis and examination of whether age, ethnicity, duration of follow-up, and study quality explain any observed between-study heterogeneity in effects

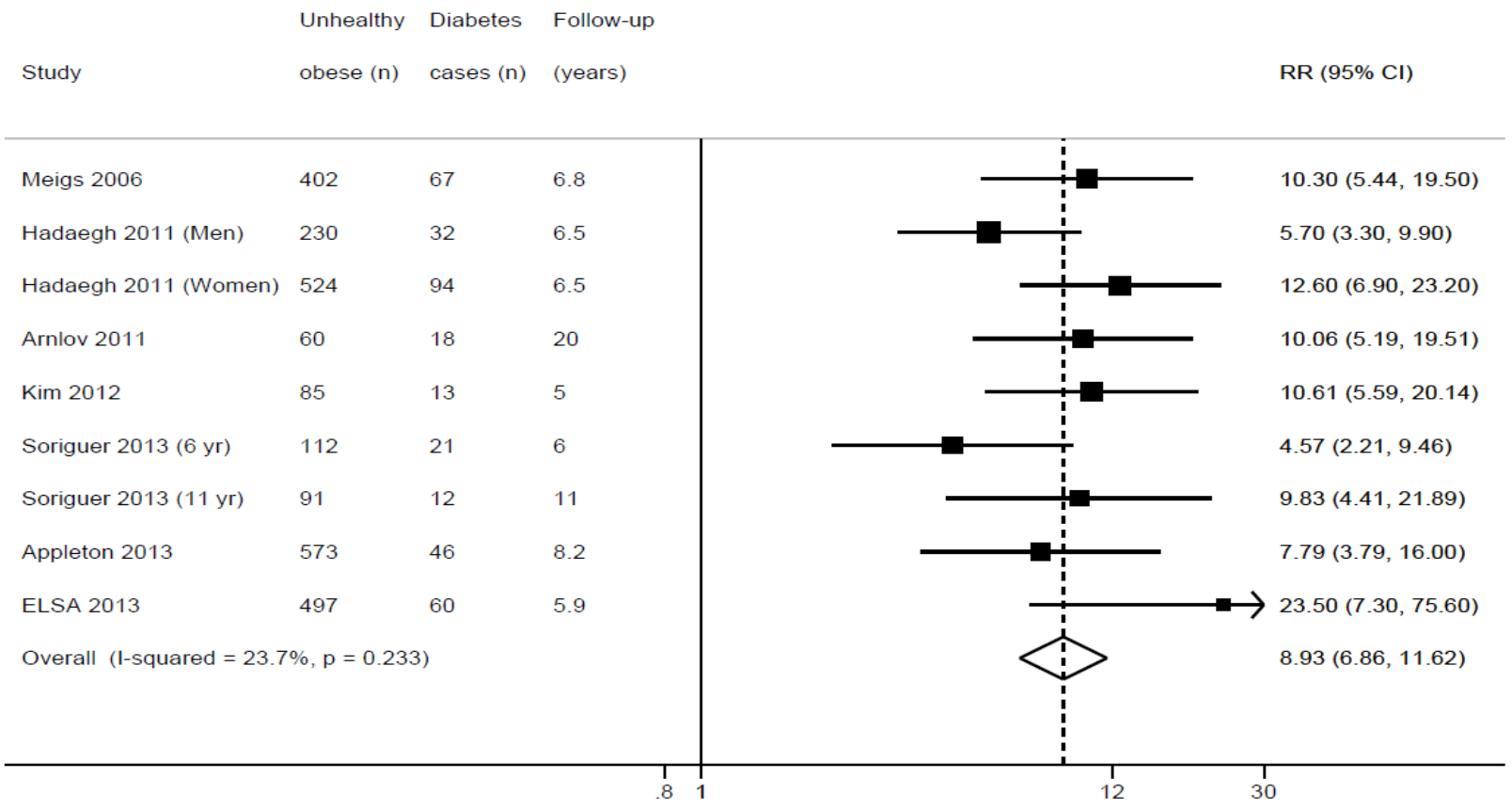
Figure 12 presents results of the random effects meta-analysis which modelled the log of odds ratios, risk ratios, hazard ratios, and confidence intervals pooled from respective studies. The summary relative risk for healthy obese adults was 4.03 (95% CI=2.66, 6.09), indicating over 4 times higher risk of incident type 2 diabetes than healthy normal-weight adults. In comparison, the corresponding pooled relative risk in the unhealthy obese group was 8.93 (95% CI=6.86, 11.62) (**Figure 13**) and the corresponding pooled relative risk in the unhealthy normal-weight group was 4.46 (95% CI=3.38, 5.88) (**Figure 14**). There was evidence of variability in effect sizes for the healthy obese group (I^2=49.8%; p=0.03), although relative risks were consistently positive and exceeded one in every study. Meta-regression was performed to test the extent to which specific study-level factors explained the between-study heterogeneity in effects, chosen *a priori* (244) as age, ethnicity, length of follow-up, and study quality. However no study reported the ethnic composition of their sample, preventing examination of that factor. Neither study quality (p=0.33), length of follow-up (p=0.29), nor age (p=0.97) significantly predicted heterogeneity in effect estimates, indicating that the variation in the strength of association observed between studies was not explained by these study-level factors. The summary relative risks of incident type 2 diabetes for each metabolic group relative to the healthy normal-weight group are illustrated in **Figure 15**.

Figure 12 Healthy obesity and adjusted relative risk of incident type 2 diabetes



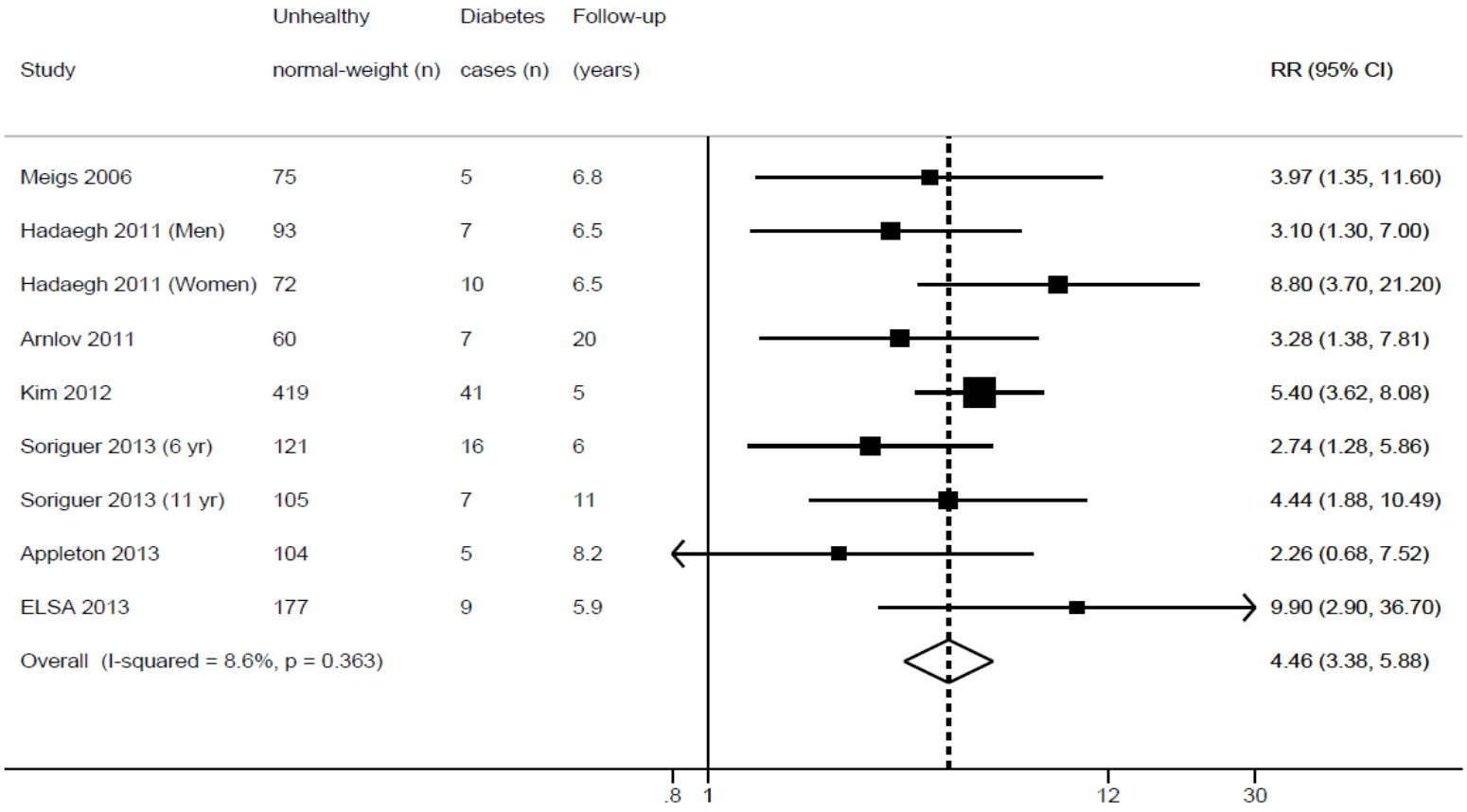
Reference group is healthy normal-weight

Figure 13 Unhealthy obesity and adjusted relative risk of incident type 2 diabetes



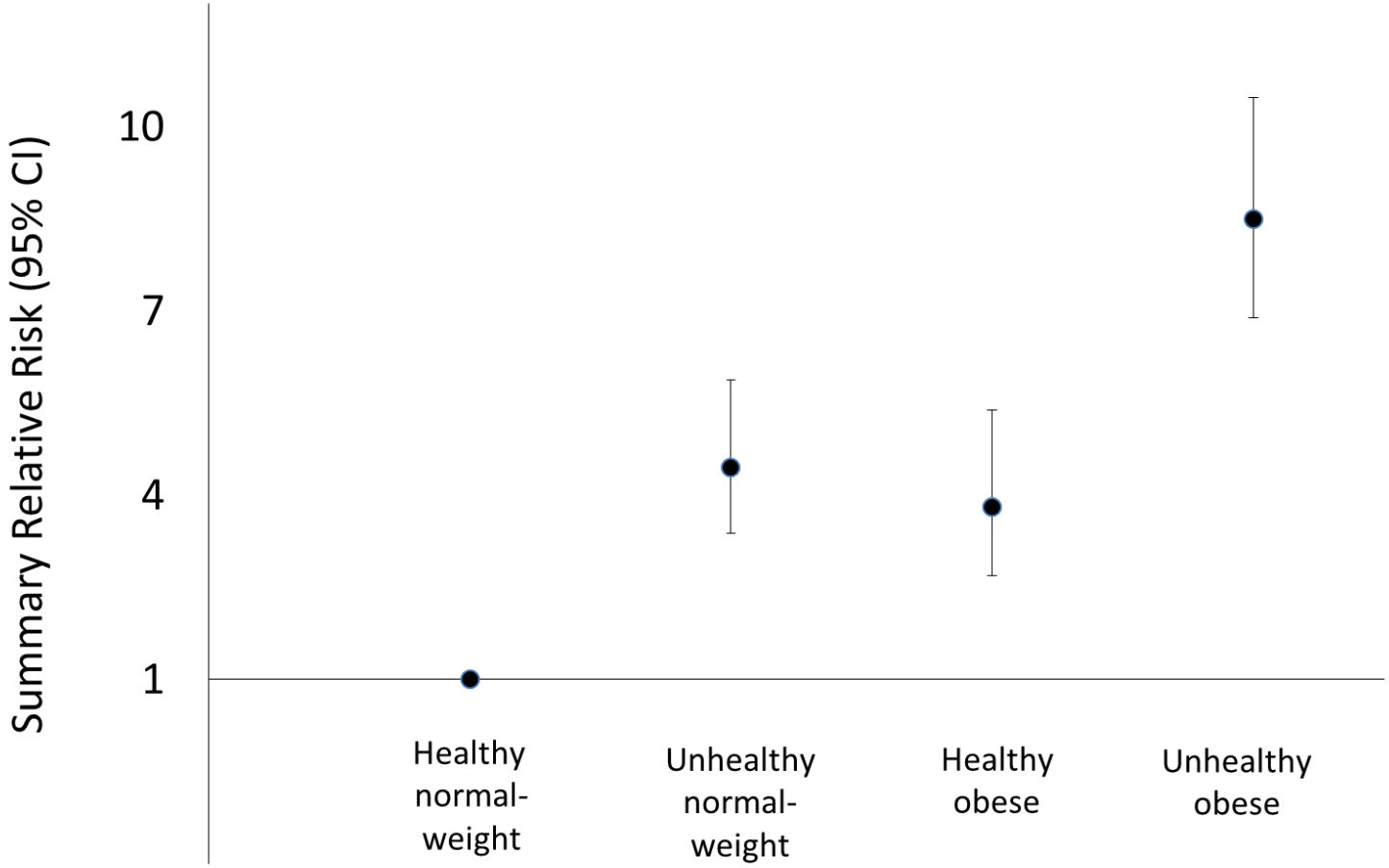
Reference group is healthy normal-weight. Analysis excludes Hwang et al. (2012) as authors considered metabolically healthy participants at baseline only.

Figure 14 Unhealthy normal-weight and adjusted relative risk of incident type 2 diabetes



Reference group is metabolically healthy normal-weight. Analysis excludes Hwang et al. (2012) as authors considered metabolically healthy participants at baseline only. Normal-weight considered BMI < 30 kg/m² in Soriguer et al. (2013).

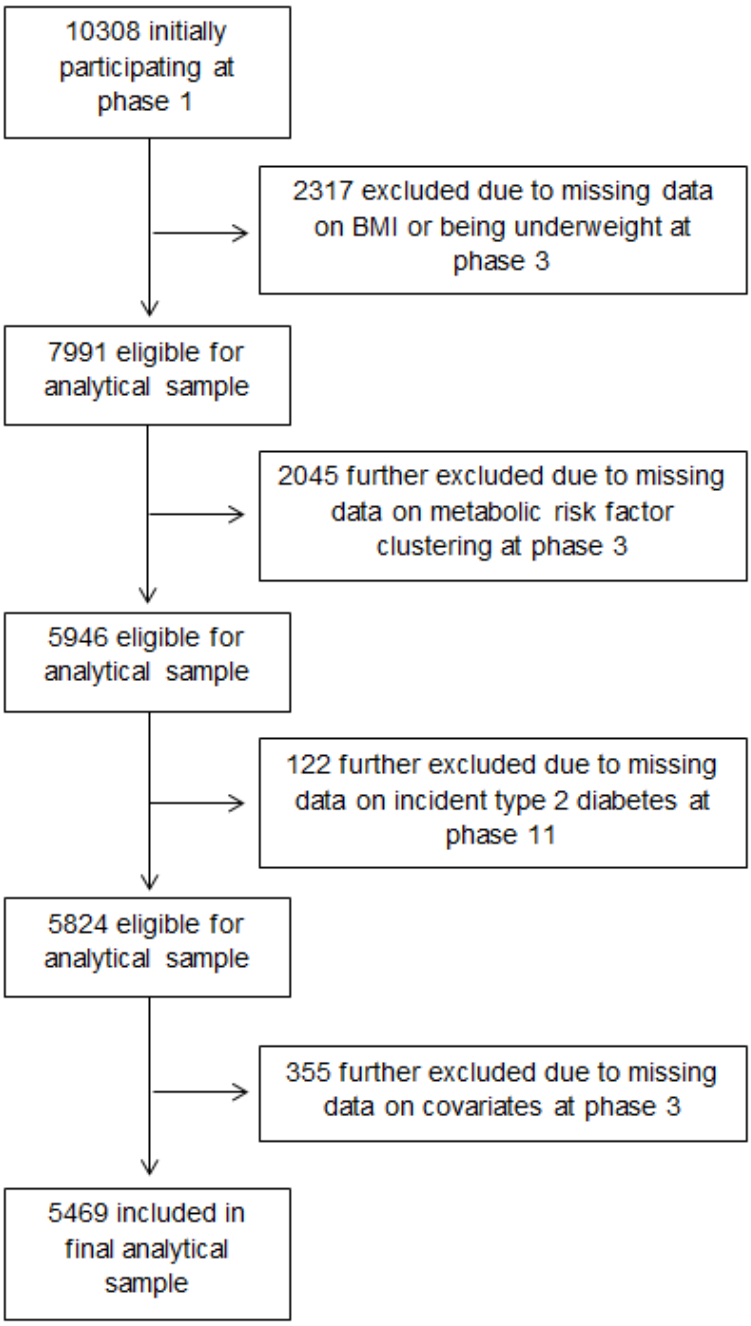
Figure 15 Metabolic and obesity groups and adjusted relative risk of incident type 2 diabetes based on summary estimates from meta-analyses



Objective 5: Original effect estimate for the risk of incident type 2 diabetes among obese adults who initially have 0 metabolic risk factors (a strictly healthy sample)

Phase 3 (1991/94) served as the baseline for this study with incident type 2 diabetes data extending to phase 11 (2012/13), affording a 20-year follow-up period. A flow chart illustrating the selection of the analytical sample is provided in **Figure 16**.

Figure 16 Selection of the analytical sample for the study of incident type 2 diabetes among obese adults who initially have 0 metabolic risk factors



Two sets of descriptive characteristics are provided for this sample; the first with health defined as having <2 metabolic risk factors, and the second with health defined as having 0 metabolic risk factors. Based on the first definition of health (**Table 36**), of 5469 adults in the sample, 167 were healthy obese, representing 36.5% of the obese. The proportion of normal-weight and overweight adults who were considered healthy was 82.2% and 57%, respectively. Over one-third of healthy obese adults were male (37.1%), compared with 68.2% of healthy normal-weight adults ($p<0.05$). Healthy obese adults were slightly older than healthy normal-weight adults (49.7 vs 48.6 years, $p<0.05$), and had a higher proportion being of a non-white ethnicity (15% vs 6.1%, $p<0.05$). Nearly one-quarter (24%) of healthy obese adults were of the lowest occupational class, compared with just one-tenth of healthy normal-weight adults (11.1%, $p<0.05$). Healthy obese adults reported a lower mean weekly duration of moderate-to-vigorous physical activity than healthy normal-weight adults (2.6 hours/week vs. 3.7 hours/week, $p<0.05$). Other health behaviours did not differ between groups. Healthy obese adults showed more adverse levels of all metabolic risk factors than healthy normal-weight adults (all $p<0.05$) with the exception of fasting glucose. 13.8% of initially healthy obese adults developed type 2 diabetes over a median follow-up time of 20.2 years, compared with 4.4% of initially healthy normal-weight adults, over a similar amount of time.

Compared with those included in the analytic sample (n=5469), those excluded (n=4839) were more likely to be female (38.7% vs. 28.2%, $p<0.001$), of a non-white ethnicity (14.7% vs. 7.6%, $p<0.001$), of an older age (mean=50.4 years vs. 49.4 years, $p<0.001$), of the lowest occupational position (24.4% vs. 12.8%, $p<0.001$), and had lower moderate to vigorous physical activity (3.3 hours/week vs. 3.6 hours/week respectively, $p=0.01$). Compared with those included in analyses, those excluded were also more likely to be obese (13.2% vs. 8.4% respectively, $p<0.001$) and were less likely to be metabolically healthy as defined as having <2 metabolic risk factors (60.6% vs. 68.8% respectively, $p<0.001$).

Table 37 Characteristics of the sample of adults at phase 3 (1991/94) by metabolic and obesity status who are initially free of type 2 diabetes (aged 39-63, 72% male), with baseline healthy status defined as having <2 metabolic risk factors (n=5469)

	Healthy normal-weight (n=2407)	Unhealthy normal-weight (n=522)	Healthy overweight (n=1186)	Unhealthy overweight (n=896)	Healthy obese (n=167)	Unhealthy obese (n=291)
Baseline characteristics						
Male – n (%)	1642 (68.2)	452 (86.6)*	827 (69.7)	757 (84.5)*	62 (37.1)*	187 (64.3)
Age (years)	48.6 (6)	50.1 (6.1)*	49.6 (5.9)*	50.7 (6.1)*	49.7 (5.7)*	49.8 (5.8)*
Non-white ethnicity – n (%)	147 (6.1)	57 (10.9)*	82 (6.9)	77 (8.6)*	25 (15)*	29 (10)*
Lowest occupational class – n (%)	268 (11.1)	49 (9.4)	178 (15)*	113 (12.6)	40 (24)*	54 (18.6)*
Consumes fruit and vegetables < daily – n (%)	792 (32.9)	205 (39.3)	444 (37.4)	381 (42.5)	48 (28.7)	128 (44)
Current smoker – n (%)	273 (11.3)	65 (12.5)	143 (12.1)	109 (12.2)	20 (12)	37 (12.7)
High alcohol consumption in previous week – n (%)	331 (13.8)	94 (18)*	205 (17.3)*	177 (19.8)*	29 (17.4)	49 (16.8)
Hours of moderate-to-vigorous activity per week	3.7 (4.2)	3.6 (3.9)	3.5 (4.0)	3.7 (4.1)	2.6 (2.9)*	2.9 (3.1)*
Has illness that greatly limits moderate or vigorous activity – n (%)	361 (15)	98 (18.8)*	208 (17.5)	184 (20.5)*	51 (30.5)*	100 (34.4)*
Systolic blood pressure (mmHg)	115.6 (11.8)	127.0 (14.1)*	118.4 (11.1)*	127.8 (12.9)*	121.8 (13.4)*	130.1 (12.0)*
Diastolic blood pressure (mmHg)	75.9 (8.2)	83.6 (9.0)*	78.9 (7.9)*	85.6 (8.4)*	80.5 (8.8)*	86.8 (8.3)*
Fasting glucose (mmol/l)	5.1 (0.4)	5.4 (0.5)*	5.1 (0.4)*	5.4 (0.5)*	5.0 (0.4)	5.5 (0.5)*
HOMA insulin resistance	1.5 (1.1)	2.7 (2.9)*	1.9 (1.4)*	3.5 (5.2)*	2.4 (1.2)*	6.5 (12.8)*
Triglycerides (mmol/l)	1.0 (0.4)	2.0 (1.1)*	1.2 (0.5)*	2.2 (1.2)*	1.2 (0.4)*	2.3 (1.2)*
HDL cholesterol (mmol/l)	1.6 (0.4)	1.2 (0.4)*	1.5 (0.3)*	1.2 (0.3)*	1.5 (0.3)*	1.2 (0.3)*
Body mass index (kg/m²)	22.6 (1.6)	23.5 (1.2)*	26.7 (1.3)*	27.2 (1.4)*	32.6 (2.7)*	33.2 (3.3)*
Range	18.50-25.00	18.53-24.99	25.00-29.99	25.00-29.99	30.00-41.99	30.00-48.48
Incident type 2 diabetes						
Cases – n (%)	106 (4.4)	84 (16.1)*	84 (7.1)*	202 (22.5)*	23 (13.8)*	109 (37.5)*
Median length of follow-up [a]	20.3	20.2*	20.3*	20.1*	20.2*	16.4*

Data are mean (standard deviation) unless otherwise noted. *Different from healthy normal-weight ($p<0.05$) based on linear (continuous variables) or logistic regression (binary variables). [a] Significance test based on mean

Table 37 presents descriptive characteristics of participants according to the strict definition of metabolic health (0 metabolic risk factors). The total sample size did not differ from that based on the previous definition of metabolic health (n=5469), however the proportion of obese adults who were now considered healthy at baseline according to this strict definition was lower, at 12.7% (n=58; compared with 36.5% based on the previous definition allowing for 1 metabolic risk factor). The proportion of normal-weight and overweight adults who were considered healthy based on this strict definition was 50.1% and 25.1%, respectively.

Over one-quarter of healthy obese adults were male (27.6%), compared with 64% of healthy normal-weight adults ($p<0.05$). Age did not differ between healthy obese and healthy normal-weight adults, while a higher proportion of healthy obese adults were of a non-white ethnicity (15.5% vs 5.9%, $p<0.05$). Twice as many healthy obese adults were of the lowest occupational class than were healthy normal-weight adults (20.7% vs 11.1%, $p<0.05$). One-quarter of healthy obese adults reported an illness which greatly limits their moderate or vigorous physical activity, compared with 13% of healthy normal-weight adults ($p<0.05$). Healthy obese adults on average reported 2.5 hours/week of moderate-to-vigorous physical activity, which was lower than for healthy normal-weight adults (3.7 hours/week, $p<0.05$). Other health behaviours did not differ between groups. Healthy obese adults did not show more adverse levels of any metabolic risk factor than healthy normal-weight adults at baseline. The proportion of initially healthy obese adults who developed type 2 diabetes over a median follow-up time of 20.2 years was 8.6%, compared with 3.2% of initially healthy normal-weight adults over a similar amount of time ($p>0.05$).

Included (n=5469) and excluded (n=4839) participants did not differ on their likelihood of being metabolically healthy as defined as having 0 metabolic risk factors (35.2% vs. 37.4% respectively, $p=0.30$). Comparisons on other variables were the same as for the previous sample when defining a healthy status as having <2 metabolic risk factors.

Table 38 Characteristics of the sample of adults at phase 3 (1993/4) by metabolic and obesity status who are initially free of type 2 diabetes (aged 39-63, 72% male), with baseline healthy status defined as having 0 metabolic risk factors (n=5469)

	Healthy normal-weight (n=1468)	Unhealthy normal-weight (n=1461)	Healthy overweight (n=522)	Unhealthy overweight (n=1560)	Healthy obese (n=58)	Unhealthy obese (n=400)
Baseline characteristics						
Male – n (%)	940 (64)	1154 (79)*	330 (63.2)	1254 (80.4)*	16 (27.6)*	233 (58.3)
Age (years)	48.1 (5.8)	49.7 (6.1)*	49.1 (5.9)*	50.4 (6)*	48.9 (5.5)	49.8 (5.8)*
Non-white ethnicity – n (%)	87 (5.9)	117 (8)*	36 (6.9)	123 (7.9)	9 (15.5)*	45 (11.3)*
Lowest occupational class – n (%)	163 (11.1)	154 (10.5)	80 (15.3)*	211 (13.5)*	12 (20.7)*	82 (20.5)*
Consumes fruit and vegetables < daily – n (%)	467 (31.8)	530 (36.3)*	201 (38.5)*	624 (40)*	15 (25.9)	161 (40.3)*
Current smoker – n (%)	161 (11)	177 (12.1)	66 (12.6)	186 (11.9)	8 (13.8)	49 (12.3)
High alcohol consumption in previous week – n (%)	193 (13.1)	232 (15.9)*	97 (18.6)*	285 (18.3)*	10 (17.2)	68 (17)*
Hours of moderate-to-vigorous activity per week	3.7 (4.1)	3.7 (4.1)	3.7 (4.4)	3.6 (3.9)	2.5 (2.4)*	2.9 (3.1)*
Has illness that greatly limits moderate or vigorous activity – n (%)	191 (13)	268 (18.3)*	85 (16.3)	307 (19.7)*	15 (25.9)*	136 (34)*
Systolic blood pressure (mmHg)	111.6 (8.9)	123.8 (13.7)*	113.6 (8.0)*	125.4 (12.7)*	113.5 (7.7)	129 (12.6)*
Diastolic blood pressure (mmHg)	73.3 (6.3)	81.3 (9.3)*	75.3 (5.5)*	84.0 (8.6)*	74.5 (5.5)	85.9 (8.5)*
Fasting glucose (mmol/l)	5.0 (0.3)	5.3 (0.5)*	5.0 (0.3)	5.3 (0.5)*	5.0 (0.3)	5.4 (0.5)*
HOMA insulin resistance	1.3 (0.6)	2.1 (2.2)*	1.6 (0.7)*	2.9 (4.2)*	2.1 (0.9)	5.4 (11.1)*
Triglycerides (mmol/l)	0.9 (0.3)	1.5 (0.9)*	1.0 (0.3)*	1.9 (1.1)*	1.1 (0.3)	2.0 (1.2)*
HDL cholesterol (mmol/l)	1.6 (0.4)	1.4 (0.4)*	1.5 (0.3)*	1.3 (0.4)*	1.6 (0.3)	1.2 (0.3)*
Body mass index (kg/m²)	22.3 (1.6)	23.1 (1.4)*	26.7 (1.3)*	27.0 (1.4)*	32.5 (2.7)*	33.1 (3.2)*
Range	18.51-25.00	18.50-25.00	25.01-29.99	25.00-29.99	30.04-41.84	30.00-48.48
Incident type 2 diabetes						
Cases – n (%)	47 (3.2)	143 (9.8)*	31 (5.9)	255 (16.3)*	5 (8.6)	127 (31.8)*
Median length of follow-up [a]	20.4	20.3*	20.3*	20.2*	20.2	19.2*

Data are mean (standard deviation) unless otherwise noted. *Different from healthy normal-weight ($p<0.05$) based on linear (continuous variables) or logistic regression (binary variables). [a] Significance test based on mean

Results of multivariable-adjusted analyses based on both definitions of metabolic health (<2 metabolic risk factors and 0 metabolic risk factors) are presented in **Table 38** and illustrated in **Figure 17**. When defining a healthy status as <2 metabolic risk factors, all groups showed increased risk for incident type 2 diabetes compared with healthy normal-weight adults after multivariable adjustment. This excess risk was 2.82 (95% CI=1.78, 4.46) times greater among healthy obese adults and 9.99 (95% CI=7.60, 13.14) times greater among unhealthy obese adults.

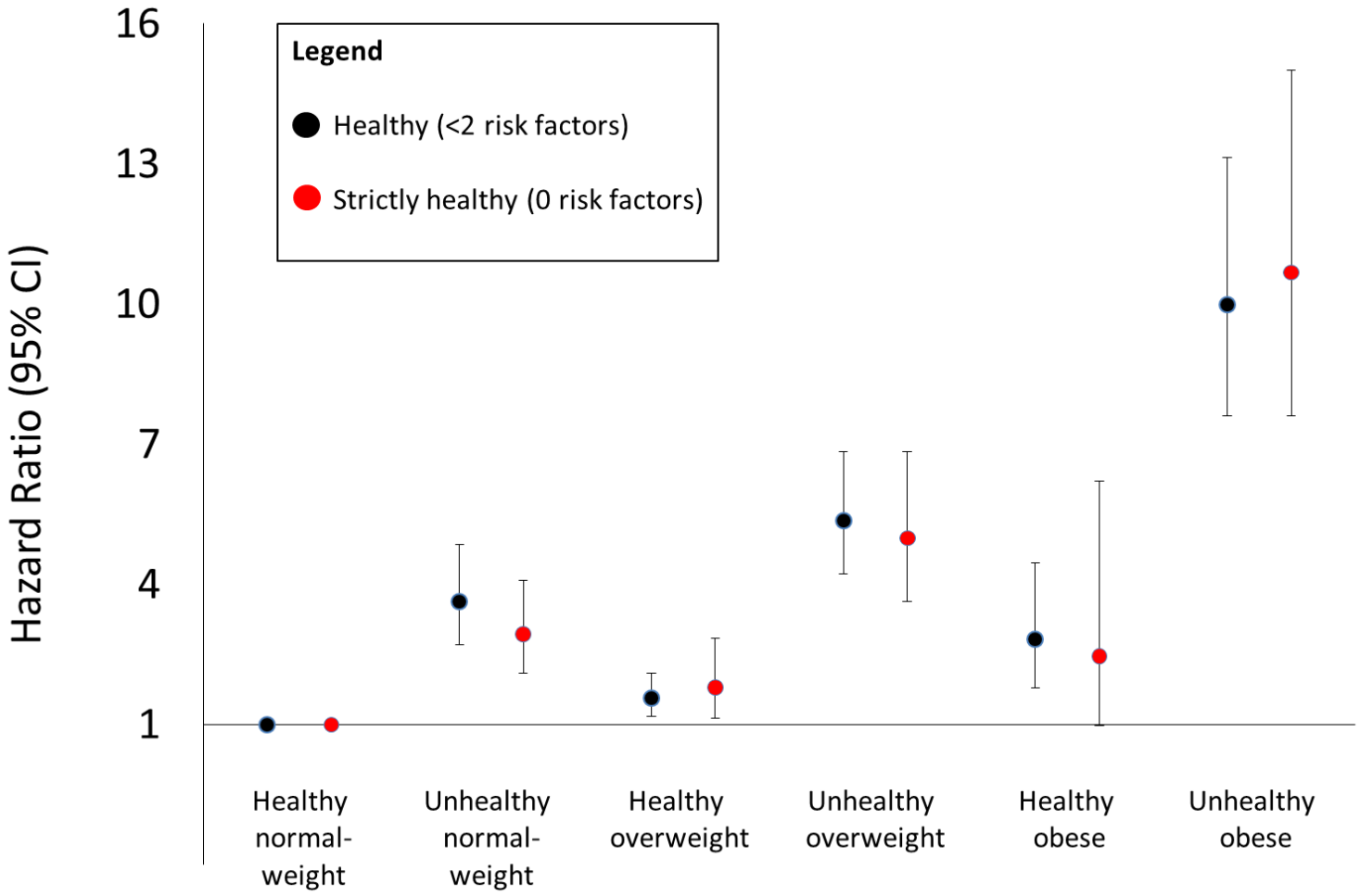
When defining a healthy status as 0 metabolic risk factors, all groups except the healthy obese showed increased risk for incident type 2 diabetes compared with healthy normal-weight adults after multivariable adjustment. The hazard ratio for strictly healthy obese adults adjusting for age, sex, and ethnicity was 2.51 (95% CI=0.99, 6.32), and was 2.46 (95% CI=0.98, 6.22) when additionally adjusting for occupational position, cigarette smoking, alcohol consumption, frequency of fruit and vegetable consumption, moderate-to-vigorous physical activity, and presence of an illness which limits moderate or vigorous physical activity. Excess risk among unhealthy adults increased steadily with higher BMI groups, with unhealthy obese adults showing the highest risk compared with healthy normal-weight adults (HR=10.68, 95% CI=7.60, 15.01 after multivariable adjustment).

Table 39 Risk of incident type 2 diabetes over 22 years among metabolic and obesity groups based on 2 definitions of metabolic health (n=5469)

	Healthy (<2 risk factors)			Strictly healthy (0 risk factors)		
	Cases/N	**Model 1** Hazard Ratio (95% CI)	**Model 2** Hazard Ratio (95% CI)	Cases/N	**Model 1** Hazard Ratio (95% CI)	**Model 2** Hazard Ratio (95% CI)
Healthy normal-weight	106/2407	1.00 (reference)	1.00 (reference)	47/1468	1.00 (reference)	1.00 (reference)
Unhealthy normal-weight	84/522	3.74 (2.80, 5.00)	3.63 (2.72, 4.86)	143/1461	3.05 (2.19, 4.24)	2.93 (2.10, 4.08)
Healthy overweight	84/1186	1.61 (1.21, 2.15)	1.57 (1.18, 2.10)	31/522	1.88 (1.20, 2.96)	1.80 (1.14, 2.84)
Unhealthy overweight	202/896	5.66 (4.46, 7.19)	5.37 (4.22, 6.84)	255/1560	5.31 (3.88, 7.26)	4.99 (3.64, 6.84)
Healthy obese	23/167	2.86 (1.81, 4.51)	2.82 (1.78, 4.46)	5/58	2.51 (0.99, 6.32)	2.46 (0.98, 6.22)
Unhealthy obese	109/291	10.74 (8.21, 14.04)	9.99 (7.60, 13.14)	127/400	11.54 (8.24, 16.15)	10.68 (7.60, 15.01)

Incident diabetes defined by fasting glucose ≥ 7 mmol/l or self-reported doctor diagnosis or diabetic medication use. **Model 1** adjusted for age, sex, and ethnicity. **Model 2** additionally adjusted for occupational position, cigarette smoking, alcohol consumption, frequency of fruit and vegetable consumption, moderate-to-vigorous physical activity, and presence of an illness which limits moderate or vigorous physical activity

Figure 17 Risk of incident type 2 diabetes over 22 years among metabolic and obesity groups based on 2 definitions of metabolic health (n=5469)



4.4 Summary of key findings on healthy obesity and metabolic decline

The second part of this thesis was concerned with the risk of future metabolic decline among healthy obese adults, specifically with regards to incident metabolic risk factor clustering and type 2 diabetes. Results showed that after 20 years, 52% of initially healthy obese adults were unhealthy obese, with initially healthy obese adults being 26.61 (95% CI=15.85, 44.69) times more likely to make this progression than initially healthy normal-weight adults. Analyses using a strict definition of metabolic health (having none of 5 metabolic risk factors) showed this to be rare among the obese at 13%, and to be highly susceptible to progressions to ill-health over time, with 78.6% of these strictly healthy obese becoming unhealthy at 20 years follow-up. Insulin resistance was most commonly incident among healthy obese compared with healthy normal-weight adults over time (IR=3.78, 95% CI=2.38, 5.99 at 20-years follow-up). A systematic review and meta-analysis of 8 prospective cohort studies indicated that healthy obese adults have 4.03 (95% CI=2.66, 6.09) times greater risk of incident type 2 diabetes compared with healthy normal-weight adults; this risk being half that of unhealthy obese adults. Original analyses of the Whitehall II cohort examining risk for incident type 2 diabetes among a strictly healthy obese group (those with 0 risk factors) indicated that this risk was not significantly elevated compared with strictly healthy normal-weight adults (HR=2.46, 95% CI=0.98, 6.22), but patterns of excess risk were otherwise the same across metabolic and obesity groups as when using the more common definition of metabolic health (<2 metabolic risk factors).

Section 5: Discussion

This section will begin by interpreting results on physical activity and sedentary behaviour in relation to healthy obesity in the context of previous research, followed by a discussion of their strengths and limitations. Findings from results on healthy obesity and future metabolic decline will then be interpreted in light of previous research, again followed by a discussion of their strengths and limitations. This section will end with an overall conclusion considering both parts of this thesis and with implications of results for public health and clinical practice.

5.1 Physical activity and sedentary behaviour in relation to healthy obesity: Interpretations of results in light of previous research

The first part of this thesis aimed to determine whether physical activity and sedentary behaviour are distinguishing features, and thus potential modifiable determinants, of healthy obesity. This aim was addressed by first examining whether durations in moderate-to-vigorous physical activity and leisure sitting, both measured by self-report using a questionnaire, were associated cross-sectionally with a higher likelihood of being metabolically healthy among obese adults. These associations were examined separately in mutually adjusted models to examine potential independent associations of each behaviour, as well as in combination using pairs of activity-sitting tertiles to examine whether associations are interactive in relation to healthy obesity.

Results suggested that higher moderate-to-vigorous physical activity was separately associated with a greater likelihood of being healthy among normal-weight and among overweight adults, but not among obese adults. Trends for effect estimates of physical activity were in the expected positive direction among the obese, but statistical significance was not reached.

In contrast, lower leisure sitting time was not separately associated with a greater likelihood of being healthy among normal-weight, overweight, or obese adults, and effect estimates did not show a clear pattern for any group. As discussed, sedentary behaviour is thought to represent a distinct state of muscle inactivity that may independently influence metabolic functioning through lipoprotein lipase or glucose pathways (78) or the expression of genes linked to inflammatory responses (132). Lower levels of sedentary behaviour were therefore hypothesised to help explain why some obese adults appear to be metabolically healthy, irrespective of their engagement in moderate-to-vigorous physical activity. This lack of association of sitting time among the obese does not support this hypothesis, and instead agrees with 2 previous studies finding no difference in self-reported sitting time between healthy and unhealthy obese adults (51, 65).

When viewing combined associations, having both high moderate-to-vigorous physical activity and low leisure sitting time was associated with a greater likelihood of being metabolically healthy among overweight adults after adjusting for basic demographic factors, but associations were not observed among normal-weight or among obese adults. The effect size for this combined effect among overweight adults was greater than that seen for the separate effect of moderate-to-vigorous physical activity, but the relative difference in prevalence was only modest. After additional adjustment for health behaviours, this association became marginally significant among the obese, and showed a larger effect size than among normal-weight and among overweight groups, suggesting that low sitting time could amplify a beneficial effect of high moderate-to-vigorous physical activity among the obese in particular. The direction of effects was in the expected direction, suggesting a higher likelihood of having a healthy profile among each BMI group including the obese with more favourable combinations of physical

activity and sitting, but the predictability of these self-reported behavioural measures were generally weak.

Next, this thesis aimed to build upon cross-sectional examinations and determine whether favourable levels of moderate-to-vigorous physical activity and leisure sitting were protective against becoming metabolically unhealthy over time among initially healthy obese adults. As discussed, favourable levels of moderate-to-vigorous physical activity and leisure sitting have each been associated prospectively with reduced incidence of metabolic ill-health in previous work (162), but it has not been known whether these behaviours exert independent or interactive effects on risk of adverse metabolic change, or how they relate to initially healthy obese adults specifically. Furthermore, a broad measure of leisure sitting time has not been used to examine prospective associations, as measures used in previous studies have been context-specific, considering activities such as TV viewing in isolation. Present results suggest that neither high moderate-to-vigorous physical activity nor low leisure sitting time were separately associated with reduced risk of becoming unhealthy over time among initially healthy obese adults. The same null result was seen among normal-weight and among overweight adults. Furthermore, in addition to being statistically non-significant, the magnitude of estimates were small-to-modest, and were not consistently in the expected direction, together suggesting a generally weak predictability of these behaviours for adverse metabolic change over time.

There was some evidence of a protective effect for intermediate levels of both moderate-to-vigorous physical activity and leisure sitting among overweight adults only; this apparent effect was robust to adjustment for potential confounders suggesting an advantage among overweight adults who avoid either too much or too little of both physical activity and leisure sitting. This was unexpected, and does not lead to obvious interpretations based on literature, and may therefore reflect a chance finding. Previous work using the Whitehall II cohort found that the same measures of high moderate-to-vigorous physical activity and low leisure sitting time interacted to greatly reduce risk of becoming obese over a 5 year period (245), while this combined effect on risk of developing metabolic risk factor clustering was unclear, again

suggesting a protective benefit of engaging in intermediate levels of both moderate-to-vigorous physical activity and leisure sitting. With regards to initially healthy obese adults in present analyses, the combination of high activity and low sitting did not confer a reduced risk of developing metabolic risk factor clustering compared with those combining low activity and high sitting (the least favourable combination), suggesting that incidence of ill-health among the obese may occur regardless of physical activity and sitting behaviour.

Given that associations of sitting time are known to be most pronounced when using TV viewing time as an indicator (147, 148), TV viewing was examined in further analyses in replace of the broader leisure sitting time measure. This was examined cross-sectionally at the most recent phase of the Whitehall II cohort study only, owing to limitations of sitting data as assessed at earlier phases. Results of these analyses suggest that TV viewing was not separately associated with the likelihood of being healthy among obese adults, but did interact with moderate-to-vigorous physical activity to produce a near doubling in likelihood of being healthy among those obese adults who report both high moderate-to-vigorous activity and low TV viewing, compared with those reporting both low activity and high TV viewing. However, this association was only observed when adjusting for age, sex, and ethnicity, and was attenuated to non-significance when additionally adjusting for health behaviours and the presence of a physically limiting illness, suggesting that this link may be partly explained by factors such as higher diet quality and the absence of a physically limiting illness which are associated with a higher engagement in moderate-to-vigorous activity and lower time spent viewing TV, rather than being due to the activity combination itself.

Further analyses examined differences in TV viewing across metabolic and obesity groups in the Whitehall II cohort study and found that unhealthy obese adults viewed nearly 4.5 hours more TV per week than healthy normal-weight adults after adjusting for covariates including duration in moderate-to-vigorous physical activity. However differences in TV viewing were only evident between healthy and unhealthy normal-weight adults, and not between healthy and unhealthy obese adults. This agrees with results of a previous study based on older adults from the English

Longitudinal Study of Ageing (ELSA), which found sizable differences in TV viewing time across metabolic and obesity groups with unhealthy obese adults viewing over 8 more hours of TV per week than healthy normal-weight adults (246); but differences in TV viewing time were again only evident between healthy and unhealthy normal-weight adults and not between healthy and unhealthy obese adults. Together, this suggests that TV viewing time plays a role in promoting health among normal-weight adults, but not among obese adults.

Thus, based on the current state of evidence drawn from studies in literature and results of this thesis, moderate-to-vigorous physical activity and sedentary behaviour have amassed little support as factors which distinguish or determine healthy obesity. Given the extensive literature reporting strong links between physical activity and sedentary behaviour with metabolic health among adults, a general lack of association of these behaviours in relation to prevalence and incidence of metabolic risk factor clustering observed in this thesis was unexpected, and could reflect several different possibilities.

The first possibility is that analyses which are stratified by BMI impose limited statistical power within each group, and that this may mask true associations among the obese group in particular. When considering all adults collectively in a series of subsidiary analyses, associations between moderate-to-vigorous physical activity and metabolic health status were evident irrespective of BMI group, with no evidence that these associations differed by BMI group. Likewise, high moderate-to-vigorous physical activity combined with low leisure sitting time was associated with an even greater likelihood of being healthy among all adults collectively, irrespective of BMI group. Null results on moderate-to-vigorous physical activity observed among obese adults in BMI-stratified analyses may therefore be more of an artefact of lower statistical power within the relatively small obese group than a true lack of association. Leisure sitting time was not associated with metabolic health status among all adults collectively in subsidiary analyses; although low TV viewing was separately associated with health among adults irrespective of BMI, suggesting that lower TV viewing time may indeed help differentiate metabolic health status among the obese. Stratification by BMI in main analyses was planned *a*

priori with the purpose of isolating obese adults as a population of interest, and results should be interpreted together with those obtained from alternative methodologies to more completely understand the nature of these associations.

A second possibility relates to the fact that both physical activity and sitting are behaviours which are subject to considerable change over time. A lack of discernible associations between membership in a certain physical activity or sitting group at baseline and metabolic health status at follow-up may reflect biases related to exposure misclassification – that is, participants may have changed their activity pattern over the duration of follow-up, and their baseline classification may no longer reflect their expected outcome. The risk of this bias may be especially high when examining long-term outcomes on the time scale of decades, as exposure groups may not track well into the distant future. This could result in regression dilution bias, in which regression lines fail to detect patterns and associations appear non-significant (247, 248). For example, those adults who began in the high activity-low sitting group may have reduced their usual activity and increased their usual sitting time, which would weaken any link this behaviour combination may otherwise have with incidence of ill-health over time. The outcome for incident metabolic risk factor clustering used in present analyses was cumulative, considering incidence 5 years later, or 10 years later, or 15 years later, and thus would have captured incidence at the shorter 5 year follow-up which is less prone to exposure misclassification. Still, the time unit of years is long when considering behaviours which are subject to change, especially given that participants advance their age considerably over the follow-up period and may change their lifestyles as they enter different life stages, such as retirement. However, this possibility would only be relevant to prospective analyses and would not explain null results of cross-sectional analyses.

A third possibility for a lack of cross-sectional and prospective associations is a confounding role of BMI in associations of physical activity, sedentary behaviour, and metabolic health. Present results are stratified by, and are in essence adjusted for, BMI group, and higher adiposity has known bidirectional associations with low physical activity and high sitting levels (245, 249, 250).

For example, a lower likelihood of developing metabolic risk factor clustering with higher physical activity shown in previous studies could partly reflect the fact that adults who engage in high physical activity also tend to be of a lower BMI, which is itself protective against ill-health (186).

Another possible reason for the apparent lack of associations is that participants of the Whitehall II cohort are relatively active compared with the general population, and such high underlying levels of physical activity could attenuate associations for both moderate-to-vigorous physical activity and leisure sitting time. Indeed, the proportion who report meeting national recommendations for moderate-to-vigorous activity is much higher among Whitehall II participants than among adults in the general population (58.2% of men and 33.9% of women in 1997/99 in the Whitehall II cohort compared with 32% of men and 21% of women in the general population in England in 1997 (251)). Results may be affected for moderate-to-vigorous physical activity if the difference in risk of metabolic risk factor clustering between the most and the least active is not sizable enough to reveal an association. Likewise, a high underlying level of moderate-to-vigorous physical activity may attenuate associations of higher sitting time on metabolic outcomes, as suggested in previous studies (69, 144, 145). Thus, associations for both physical activity and sitting may be underestimated by the selectively active nature of the population under study, and it may be expected that these behaviours have greater roles in promoting metabolic health in the general population.

A final and perhaps most likely explanation for a lack of associations is that the measures of moderate-to-vigorous physical activity and leisure sitting used in these analyses were both self-reported, which may underestimate true associations if they are imprecise. Indeed, stronger associations have been seen between physical activity and metabolic risk factors when using objective measures compared with self-reported measures (252), while other reports show low-to-moderate correlations between objective and self-reported assessments of physical activity (120); these correlations being lowest among the obese (123). Indeed, imprecision in behavioural measures are likely the greatest source of concern, as this may bias results

regardless of whether such results are examined among different BMI groups separately or among all adults collectively.

As mentioned, prior evidence on physical activity in relation to healthy obesity is based on self-reported measures of activity, which are prone to inaccuracies in recall and do not capture all movements which contribute to health. These are expected to be imprecise compared with objective accelerometer-based measures which monitor incidental movements in real-life settings. Thus, a further objective of this thesis was to examine differences in physical activity between healthy and unhealthy obese groups based on objective accelerometer assessments. Total physical activity serves as a useful starting point to assess differences in movement, as it captures the entire spectrum of physical activities, including those of light, moderate, and vigorous intensity, and also has practical advantages given that it is more normally distributed than moderate-to-vigorous physical activity, making it more suitable for standardisation and comparison with questionnaire-based measures.

In present analyses, differences in total physical activity between healthy and unhealthy obese groups were indeed evident when using an accelerometer, but not when using a questionnaire, providing the first objective evidence that healthy obese adults are more physically active than their unhealthy obese counterparts. A hip-worn counts-based accelerometer has been used in a previous study to show that total physical activity was lower among healthy overweight and obese adults compared with healthy normal-weight adults (253), but no comparisons were made with unhealthy overweight or obese groups. One other study using a pedometer (step count) did not find differences in total physical activity between healthy and unhealthy obese groups, but this was based on a small sample of obese women (N=39) (118), and thus was likely underpowered to detect true differences. There was a low-to-moderate correlation between self-reported and objectively assessed total physical activity among all adults in the sample, in line with 2 previous reports from the same cohort (120, 122). The correlation was found to be lower among obese adults than among normal-weight and overweight adults in the present study, with an even lower correlation observed among unhealthy obese than among healthy

obese adults suggesting differential measurement error and a higher degree of recall bias among obese adults who are unhealthy. This might explain weak and inconsistent associations previously observed with self-reported physical activity among obese adults, as previous reports have not distinguished between metabolic types of obesity when examining correlations. Differences in total physical activity between healthy and unhealthy normal-weight, overweight, and obese groups were also evident after controlling for health behaviours including a summary indicator of diet quality, supporting associations of physical activity with metabolic risk factors which are independent of diet.

As mentioned, total physical activity is a broad measure of overall body movement and is thus a good starting point for examining differences in objectively measured physical activity between obese groups. However, as a consequence, interpretations of present results are not straight-forward as the 24-hour monitoring of the wrist-worn accelerometer captured all light, moderate, and vigorous intensity activities, and also reflects differences in time spent sitting and sleeping. Given that light physical activity (125) and sitting (133) are both associated with metabolic risk factor clustering independently of moderate-to-vigorous activity, it seems plausible that higher total physical activity among healthy obese adults could reflect either or all of higher moderate-to-vigorous activity, higher light intensity activity, lower sitting time, or higher sleeping time. Teasing apart the contributions of each activity component is necessary to understand which component is driving these associations, and thus where efforts to intervene would be best directed.

To begin addressing this issue, differences in the likelihood of meeting moderate-to-vigorous physical activity recommendations based on accelerometer were compared between healthy and unhealthy obese adults. No clear differences were found, such that healthy obese adults were not more likely than unhealthy obese adults to meet recommendations for moderate-to-vigorous physical activity when this activity requires 10-minute bouts as currently stipulated (142). However, in sensitivity analyses, the healthy obese were more likely than the unhealthy obese to meet recommendations when measuring moderate-to-vigorous physical activity with a

more stringent cut-point (which captures activities in the more intense end of the moderate-to-vigorous distribution) and when also considering activity durations of at least 1 minute instead of at least 10 minutes. This suggests that healthy obese adults do engage in more moderate-to-vigorous activity, but this is done in shorter durations which are unrecognised by current guidelines. Attention to the way in which moderate-to-vigorous activity is accumulated may be important for accurately assessing activity patterns among obese adults. It is plausible that short bouts of movement may contribute to health among the obese, as it has been shown previously that moderate-to-vigorous physical activity which is accumulated sporadically is associated with the same reduced prevalence of metabolic risk factor clustering as moderate-to-vigorous activity which is accumulated in traditional 10-minute bouts – the total amount of activity being equal (254). However sporadic activity was defined in this previous study simply as being less than 10 minutes, and much of this activity may be just under the 10-minute mark and not of short (I.e. 1 or 2 minute) durations. By the same token, the shorter bouts examined in present analyses were defined as being 1 minute or more, and much of this activity may be close to the 10-minute mark and not exclusively short. Additional research is needed to confirm present findings and to examine bouts which are exclusively short in duration, i.e. 1-5 minutes, to clarify the role of short activity bouts in metabolic health and their implications for public health recommendations.

Given clear differences in total physical activity between healthy and unhealthy obese groups, and less clear differences in moderate-to-vigorous physical activity, it is possible that higher total activity among the healthy obese reflects more light intensity activity. As mentioned, there is some evidence that light activity, measured objectively, may reduce metabolic risk factor clustering independently of moderate-to-vigorous activity (125). A greater body of literature has examined the role of non-exercise activity thermogenesis (NEAT) which pertains to fidgeting-like activities that expend less energy than moderate intensity activities, but more energy than sedentary behaviour (255). Differences in NEAT are thought to explain a substantial proportion of daily movement and may help account for differences in the susceptibility to store fat in

humans (256), but NEAT has not been linked with reduced risk of having or developing metabolic risk factor clustering, and not among obese adults specifically. However recent studies examining breaks in sitting time may have revived this idea, with cross-sectional associations observed between breaking-up sitting time with lower plasma glucose and triglycerides in addition to lower waist circumference and BMI (257). An intervention study also recently demonstrated that breaking-up sitting every 20 minutes is associated with improved insulin and glucose responses to food (156). Such evidence supports the idea that energy expenditure and metabolic health may be promoted by simply 'keeping the machinery running' through frequent movement, rather than needing to segment activity into bouts of moderate-to-vigorous intensity. Such an idea seems attractive given data showing that that the largest proportion of the day for most adults is spent either sedentary or in light activities such as standing or slow walking, with a relatively small proportion being spent in moderate-to-vigorous activities (141, 258). This idea is also attractive given wider theories of evolution, such as those describing environments of evolutionary adaptedness which demanded frequent physical activity to meet basic survival needs; although the energy historically expended in hunting and gathering food was likely more moderate-to-vigorous than light (255). The benefits of light intensity physical activity relative to sedentary time on cardiometabolic outcomes in free-living humans are plausible, but are currently an area of debate as this form of activity is harder to assess using self-report and objective measures (125, 259).

Previous results of this thesis do not support sitting time as a factor related to the prevalence or incidence of metabolic risk factor clustering among the obese, and so lower sitting time seems an unlikely explanation for the observed difference in total physical activity between obese groups. However, as with physical activity, previous results were based on self-reported measures of sitting which are known to produce weaker associations with metabolic risk factors than objective measures (252). No objective measure of sitting time is currently available in the Whitehall II cohort, and so this could not be compared with self-reported measures. Future work could examine objectively measured leisure sitting time in relation to healthy obesity and its

contribution alongside moderate-to-vigorous activity in explaining total physical activity among obese adults.

The development and use of objective measures of physical activity are important advancements which allow for valuable comparisons with widely used self-reported measures; however it is important to address some conceptual issues that arise when making these comparisons. First, the amount of moderate-to-vigorous physical activity that is recommended in national and international guidelines, 150 minutes or more per week, is based on self-reported physical activity data. This guideline figure of 150 minutes therefore aims to summarise the amount of 'self-reported minutes' of moderate-to-vigorous physical activity that are required to reduce risk of morbidity and premature mortality. Given low-to-moderate correlations between self-reported and objective assessments of physical activity reported previously (120, 122) and again in this thesis, and given that the links between physical activity and health outcomes are based on self-reported physical activity data, it is not appropriate to assume that 150 'objective minutes' are required to provide the same health benefit as 150 'self-reported minutes'. These measures capture conceptually different dimensions of movement; self-reported measures quantify the perceived duration of time devoted to activity (i.e. a 1-hour sporting session), while objective measures quantify the amount of time the body physically moves, which is expected to be less than the total time devoted to activity (i.e. only physically moving for half of that 1-hour sporting session) (260). The amount of objective minutes required to bring about the same reduction in health risks as self-reported minutes may be lower, although these estimates are not yet available.

It is, however, appropriate to use both self-reported and objective measures of physical activity with the purpose of comparing the existence, magnitude, and patterning of associations as they relate to health indicators. Given that objective measures offer greater precision and reliability for the measurement of incidental movements which are not well-recalled from memory, objective measures can offer important insights into the role of physical activity to health outcomes that may otherwise go undetected. In this thesis, differences in total physical activity

between healthy and unhealthy obese groups are evident only when using objective assessments, indicating that physical activity has a greater role in healthy obesity than previously thought.

Although less precise, self-reported measures do have their advantages. For instance, accelerometers are designed to detect the intensity and duration of activity performed, but they do not inform the researcher of the type of activity this actually is (I.e. running versus swimming versus other sports). Self-reported measures provide insight into these activity types as well as the social preferences and perceptions of activities, all of which are essential for designing and evaluating public health programmes (261). Thus it is recommended that objective measures be used as a complement to, and not as a replacement for, self-reported measures (262).

5.1.1 Strengths and limitations in the study of physical activity and sedentary behaviour in relation to healthy obesity

Strengths of this section include its use of large sample sizes and its use of both cross-sectional and prospective designs with follow-up extending to 15 years. Objective measures of metabolic risk factors and anthropometrics were used to define metabolic and obesity phenotypes. Metabolic health was defined in this study according to comprehensive criteria used in previous work on the general United States population [2], which had the advantage of including insulin resistance which is excluded from other widely used criteria (27, 28). However C-reactive protein (CRP) was excluded as part of the current definition for the sake of consistency, as it was not measured at later follow-up points. Systemic inflammation may help define healthy obesity (32) and should be considered in future studies when possible.

The main self-reported measure of sitting was based on total leisure sitting time, which covers all types of sitting in a leisure setting and is thus more comprehensive than measures which

consider only specific activities such as TV viewing. However, as a consequence of this, there is the possibility that memory recall for total leisure sitting time is less accurate than recall for TV viewing time, resulting in greater recall bias and imprecision. Measures of sitting and physical activity used for prospective associations were self-reported, and thus may have introduced biases. In particular, self-reported sitting time tends to be only moderately correlated with objective assessments (263). However given that subjective measures of physical activity (264) and sitting have shown weaker and less consistent associations with metabolic risk factors compared with objective measures (252), associations observed in present analyses likely underestimate, rather than overestimate, true effects. Associations of moderate-to-vigorous physical activity and leisure sitting in relation to metabolic health among the obese were mainly inferred from BMI-stratified analyses, which as discussed, could limit statistical power among the relatively small obese group. Subsidiary analyses were performed which considered all adults collectively, providing contrasting results but ultimately interpretations which are based on more comprehensive methodology. This section used a tri-axial accelerometer device worn on the wrist to provide novel insights into the role of physical activity in healthy obesity based on precise effect estimates, and insights into the relative strength and utility of objective and self-reported assessments. Results pertaining to objective physical activity assessments are, however, based on a cross-sectional study design only, and future research is needed to examine prospectively whether increases in physical activity among unhealthy obese adults lead to a healthier status. Accelerometry results are subject to the specific brand and body placement used in the present study; however strong correlations have been found with VO^2 for both GeneActiv and Actigraph accelerometers and for both wrist and hip placements (221).

Participants were of an older age at later phases of data collection and results may not be readily generalisable to younger or middle-aged adults. The validity of BMI for assessing total body fat is known to be lower among older than among younger adults due to age-related changes in body composition including reductions in lean muscle mass (265, 266); subcutaneous fat also decreases while visceral fat becomes more prominent. Thus, although BMI is used in

present studies with the assumption that values indicate total body fat, differences in BMI between metabolic and obesity groups may also reflect differences in lean mass which may overestimate the role of body fat in metabolic health status (267).

Health behaviour and health status covariates were based on self-reported data and are subject to measurement inaccuracies. Diet quality was assessed via frequency of fruit and vegetable consumption, type of milk consumed, and type of bread consumed, and thus cannot eliminate the possibility of residual confounding by other aspects of diet such as sugar intake (178). Snacking behaviour was not specifically considered as a covariate in studies of leisure sitting and TV viewing, which is known to commonly occur in such scenarios (157). Previous work has shown that associations between TV viewing and metabolic abnormalities persist after controlling for frequency of unhealthy food consumption (268), but this behaviour may indeed confound associations if underreported. However given that differences in TV viewing were not evident between healthy and unhealthy obese groups even before additional adjustments for dietary factors, this is not likely an issue. The questionnaire item used to assess TV viewing in Whitehall II have not been validated against objective measures, although a recent review concluded that questions focusing on TV viewing have the strongest reliability and validity among non-occupational sedentary behaviour questions (158). Self-reported TV viewing is a proxy measure of sedentary time as it assumes participants are in a sedentary position while viewing TV. Analyses on TV viewing were cross-sectional and thus cannot determine whether viewing time contributes to or results from phenotype status; however adjustment for the presence of an illness which limits moderate-to-vigorous physical activity partly controlled for reverse causation. The indicator of baseline health status used in these studies as a covariate was a derived indicator of whether the participant reported an illness which limits moderate or vigorous physical activity, which is not widely used in previous studies. This indicator did vary significantly across metabolic and obesity groups, with a higher proportion of unhealthy obese adults reporting that they were greatly limited than healthy normal-weight adults, as expected. This indicator directly addresses the issue of having a physical activity-limiting illness as judged

by the participants themselves, and a similar derived measure could be used in future studies based on other cohorts to confirm its validity.

5.2 Healthy obesity and metabolic decline: Interpretations of results in light of previous research

The second part of this thesis investigated the risk of future metabolic decline among healthy obese adults. This aim was first addressed by describing progressions from healthy to unhealthy obesity and comparing the tendency for progression between initially healthy obese and initially healthy normal-weight adults. Results show that after 20 years, approximately half of initially healthy obese adults were unhealthy obese, while less than 2% were healthy normal-weight. Healthy obese adults were far more likely to progress to an unhealthy obese state at 20 years follow-up than were healthy normal-weight adults, and were consistently more likely to make this adverse transition than unhealthy normal-weight adults. The proportion of healthy obese adults who progressed to unhealthy obesity also increased steadily with increasing follow-up duration when using maximum samples of healthy obese adults. Previous studies in literature have attempted to examine the natural course of healthy obesity but were limited to shorter follow-up durations; the longest follow-up duration previously used being 10 years (170). Present results were based on follow-up durations which were up to a decade longer than previous studies, providing greater insight into the long-term nature of healthy obesity and more solid evidence to support the notion that healthy obesity is a temporary state which often progresses to ill-health. Long-term stability in healthy obesity does indeed exist, but this is now viewed as the exception, not the norm.

The main outcome of interest for these descriptive analyses was becoming unhealthy obese over time, as evidence clearly indicates that this state carries the highest risk for cardiometabolic disease and early death (201, 202) and thus represents the 'worst-case scenario'. To examine the issue of metabolic decline in depth, 2 definitions of 'healthy' were used for analyses; the first being the most common definition used in the literature, defined as having <2 metabolic risk

factors, thus allowing for 1 metabolic risk factor to be present; the second being a strict definition defined as having no metabolic risk factors at all. One key observation relates to the prevalence of healthy obesity according to these different definitions. While present results suggest that about 1 in 3 obese adults are considered healthy when defined as having <2 metabolic risk factors, only about 1 in 10 obese adults are considered healthy when defined as having 0 metabolic risk factors. Interestingly, this latter prevalence is the same as the prevalence of obese adults in the general population who have a high level of cardiorespiratory fitness (113) (the so-called 'fat and fit'), suggesting that there may be a considerable degree of overlap in these phenotypes.

A second important observation relates to the rate of progression to ill-health based on these different definitions of 'healthy'. If an initially healthy status is defined as having less than 2 metabolic risk factors then about 50% of these initially healthy obese adults progress to ill-health over a period of 20 years. However, if restricting the definition of 'healthy' to have 0 metabolic risk factors at baseline, then about 80% of these initially healthy obese adults progress to ill-health over the same period of time. Together, this suggests that a strictly healthy type of obesity is exceptionally rare, and that maintenance of this strictly healthy obese state is rarer still. The tendency for metabolic decline was much higher among strictly healthy obese adults compared with their strictly healthy normal-weight counterparts, supporting the notion that healthy obesity is a transient phase and a high risk state for future decline.

When examining incidence of specific metabolic risk factors among a subset of obese adults who are strictly healthy, the risk of developing insulin resistance, high blood glucose, and hypertension was 2-to-5 times higher among initially healthy obese compared with initially healthy normal-weight adults over 20 years follow-up, with incidence being evident after only 5 years of follow-up. There was little difference in incidence of low HDL cholesterol or high triglycerides, suggesting that a strictly healthy type of obesity is fairly robust against the development of dyslipidaemia. However, as the use of lipid-lowering drugs was not considered in this set of analyses, it is unclear to what extent this observation represents a true lack of

incidence or widespread use of prescription drugs among this group. This is particularly an issue given that participants had reached an advanced age at the final measurement phase, when contact with medical services and prescription drug use is most common. Insulin resistance was consistently most common among healthy obese adults over time, both in terms of the magnitude and of the significance of the difference compared with healthy normal-weight adults. Insulin resistance is therefore supported as a key factor explaining the long-term decline of healthy obesity, and one which likely drives long-term progressions to an unhealthy obese state over time.

The approach used in this section was descriptive, the aim being to describe the natural course of healthy obesity (whether it remains stable or gets progressively worse) and not to identify modifiable determinants of this progression. The only covariates considered in models comparing risk of unhealthy obesity and incidence of individual metabolic risk factors between initially healthy obese and initially healthy normal-weight adults were age, sex, and ethnicity. These factors were chosen as they are relevant to natural differences in the rate of metabolic decline and are expected to remain constant over time, or in the case of age, progress at a constant rate for all participants. Other factors such as social circumstances and health behaviours including physical activity may be hypothesised to modify the tendency to progress to ill-health among obese adults; however, these are subject to considerable change over the duration of follow-up, and simple baseline adjustments for these factors are not likely sufficient to capture their involvement. Examining behaviour patterns in stratified analyses would also likely introduce more missing data and reduce statistical power when using complete case analyses, ultimately reducing the validity of results. Furthermore, given earlier results of this thesis which provided no evidence for an association of either self-reported moderate-to-vigorous physical activity or self-reported leisure sitting time with risk of becoming unhealthy among initially healthy obese adults, these factors are not strong candidates as modifiers of phenotype progression. Although physical activity was later associated with metabolic health among obese adults when measured objectively, objective measures of physical activity are not

available at earlier phases of the Whitehall II cohort; any prospective analyses would necessarily reply upon imprecise self-reported measures.

This thesis next aimed to determine whether healthy obese adults face an excess risk for incident type 2 diabetes: a type of metabolic decline with high clinical importance. This aim was first addressed by systematically searching the literature on incident type 2 diabetes risk among healthy obese adults, and by synthesizing these estimates in a meta-analysis. Findings from the systematic literature search showed that healthy obese adults have, with few exceptions, a substantially increased risk for developing type 2 diabetes compared with healthy normal-weight adults. When prospective evidence was synthesised in a random effects meta-analysis (average length of follow-up ranging from 5 years in Kim et al. (242) to 20 years in Arnlov et al. (187)), healthy obese adults demonstrated over 4.0 times greater risk of developing type 2 diabetes; albeit this risk was approximately half that of unhealthy obese adults. The pooled relative risk for healthy obese adults was comparable to that for unhealthy normal weight adults (Summary RR=3.81, 95% CI=2.69, 5.39 for healthy obese vs. Summary RR=4.46, 95% CI=3.38, 5.88 for unhealthy normal-weight).

Type 2 diabetes is often regarded as a state of chronic energy oversupply (194), and as such, dietary factors are expected to play a central role in disease risk. Despite this, no studies considered the influence of dietary factors, such as sugar intake, on the risk of type 2 diabetes for healthy obese adults. Likewise, only half of the studies considered any indicator of physical activity or cardiorespiratory fitness, which are also important protective factors against type 2 diabetes development (180, 181). The healthy obese group is often defined according to use of drugs such as antihyperglycemic or antihypertensive medications, however a limited range of additional prescription drugs were considered in statistical adjustments, with the use of statins considered in only 2 studies (51, 238).

Heterogeneity in excess risk for healthy obesity was observed between studies, with estimates ranging from about 2.0 times greater in Appleton et al. (51), to nearly 15.0 times greater in Hwang at el. (women) (241), and meta-regression provided no evidence to suggest that this was

explained by differences in participant age, duration of follow-up, or study quality. Such heterogeneity might stem from variations in phenotype criteria used across studies including inconsistencies in specific metabolic factors and their cut-points, statistical adjustment strategies, as well as differences inherent to populations such as ethnicity or participation in obesity management strategies such as lifestyle interventions or prescription drug use. However, with the small number of studies currently available, and with each measuring a different population, numbers within each factor group would likely be too small to draw meaningful conclusions about the source of heterogeneity. A standard definition of what constitutes 'health' within obese populations would aid efforts to understand differences in effects due purely to specific demographic or lifestyle factors. It is important to note, however, that heterogeneity in this case refers only to the magnitude of effects, as all estimates exceeded the reference value of 1.0 and were in the positive direction, with no studies reporting a reduced risk of incident type 2 diabetes for healthy obese adults. Thus, the overall message is consistent – healthy obese adults are far more likely than healthy normal-weight adults to become diabetic over time.

Results of previous meta-analyses indicate that healthy obese adults have greater risk for developing cardiovascular disease than healthy normal-weight adults, at a magnitude of about 1.2 to 2.0 (201, 202). Present results therefore also suggest that the risk among healthy obese adults for developing type 2 diabetes is much greater than for developing cardiovascular disease (relative risk of about 4.0 vs 1.2-2.0). The multistage model of type 2 diabetes development discussed previously, where elevated blood glucose and type 2 diabetes diagnosis is preceded by a long period of insulin resistance (191), is indeed likely relevant to healthy obesity given that initially healthy obese adults show a consistently higher risk of developing insulin resistance over time, with this being evident even at relatively short follow-up periods. This strong tendency to become insulin resistant likely explains the substantially increased risk for future type 2 diabetes among healthy obese adults.

All studies identified in the literature search allowed for at least 1 metabolic risk factor to be present when defining healthy obesity. This 1 metabolic risk factor may well be insulin resistance or high blood glucose which is elevated just below the clinical cut-point for type 2 diabetes but still qualifying as prediabetic (193). To examine the potential for this definition to bias estimates of type 2 diabetes risk and to provide novel evidence on diabetes risk among obese adults who have a strictly healthy metabolic profile, original analyses of the Whitehall II cohort study were conducted which defined healthy obesity as having no metabolic risk factors at baseline. Analyses based on the more common definition of health (<2 metabolic risk factors) were also performed to allow comparison of results based on different definitions within the same population. Original results based on the common definition of health are in agreement with literature – a substantially increased risk of type 2 diabetes was found among healthy obese compared with healthy normal-weight adults, with the magnitude of this effect being high at nearly 4.0. Results based on the strict definition of health were less clear, with no significant difference in risk observed among strictly healthy obese compared with strictly healthy normal-weight adults over the same 20-year follow-up period. The confidence interval boundary on this estimate was, however, only marginally crossing the reference point, and this should be interpreted in light of the smaller sample size and lower statistical power afforded by this strict definition of health. Additionally, when estimates for each metabolic and obesity group according to different health definitions are illustrated together, a consistent pattern across groups is visually evident. This should also be interpreted in light of previous results showing that after as little as 5 years, initially healthy obese adults have a substantially increased risk for developing insulin resistance, a known pre-curser to impaired glucose control (191), as well as high fasting glucose itself. Taken together, this single null finding on diabetes risk does not provide strong evidence that obese adults who are strictly healthy are really protected against developing type 2 diabetes in the long-term.

A core assumption when modelling associations between exposure and outcome variables in standard regression models is that values of the exposure variable remain stable for the

duration of follow-up; if they do not, exposures can be misclassified, which can bias results. Given the strong tendency for healthy obesity to progress to unhealthy obesity over time, several recent studies have stratified analyses of healthy obesity and disease risk into those healthy obese adults who are stable for the duration of follow-up versus those who are not stable. For example, at least 2 studies have examined the risk of incident type 2 diabetes separately among those healthy obese adults who maintain their healthy status and those who progress to unhealthy obesity, both showing that increased diabetes risk is evident only among those who transition into unhealthy obesity over the follow-up period (51, 269). This seems obvious, as one would expect those who develop metabolic abnormalities over time to be the ones who eventually develop disease. There is therefore a conceptual concern with this stratification approach, as in the case of type 2 diabetes, progressions to ill-health in the form of insulin resistance and high blood glucose are part of the disease process itself, and would therefore be considered a mediator of disease and not a source of bias to be addressed as such. Given that the process of metabolic decline among healthy obese adults over time is now better known, this stratification approach seems less meaningful and may be less supported in future work. There are also practical challenges of working with small case numbers in analyses, as sub-dividing an already small group to view stratified risk estimates may not yield reliable results due to low statistical power. This also requires consistent data on anthropometrics and metabolic risk factors for phenotype criteria at both baseline and follow-up, which may not always be available.

Descriptive analyses from this as well as the previous section indicated that healthy obese adults had more adverse levels of individual metabolic risk factors than healthy normal-weight adults at respective baselines, an early sign that the healthy obese may progress to ill-health over time. Likewise, within the healthy obese group, it is possible that those unstable healthy obese adults who later progress to ill-health may have started with more adverse levels of metabolic risk factors at baseline than those who are stable, although this was not specifically tested in analyses. Although these differences may exist, these are viewed more as explanations of results

than sources of bias to be addressed as such. Indeed, it would be expected that healthy obese adults who later develop disease would show signs of such disease at an earlier point in time, and likewise, those healthy obese adults who progress to ill-health are expected to show more adverse levels of risk factors at baseline than those who do not progress. Differences in pre-clinical disease burden may indicate that progressions are already in motion at the first measurement occasion.

It is important to acknowledge however, that a sizable proportion, just over one-third, of healthy obese adults did remain healthy over the full 20-year period, appearing remarkably resistant against the progression to ill-health. This begs the question – what are they doing right? What is special about them? As previously discussed, a great deal of human metabolism has to do not just with the total amount of fat, but with where the fat is located. Maintenance of a favourable fat distribution may help explain stability among a subset of healthy obese adults, based on what is known at the 'adipose tissue expandability' theory. According to this theory, individuals differ in the robustness of their subcutaneous fat cells when accommodating for excess energy intake (195, 270). Incoming energy is initially stored in relatively safe subcutaneous stores as a matter of intention and if these subcutaneous stores are robust, they continue expanding as energy intake increases (271, 272). Adipose tissue is prevented from accumulating in visceral and ectopic sites, and tissues therefore remain insulin sensitive, affording such adults the appearance of a metabolically healthy profile. In adults whose subcutaneous fat stores are not robust, however, accumulating adipose tissue 'spills over' into sites such as the liver, muscle, arteries, and other vasculature, which contribute to visceral fat and increase the resistance of tissues to insulin, ultimately contributing to the classification of an unhealthy profile.

Recent experimental evidence among healthy obese adults supports this view. In one study, obese adults who were considered metabolically healthy at baseline were protected from the short-term adverse effects of diet-induced weight gain by a superior ability to partition triglycerides and other lipids into subcutaneous stores, while those defined as unhealthy obese at the study outset were unable to partition fat in this manner, instead showing signs of visceral

fat accumulation (273). This subset of the healthy obese who are stable over time may also be expected to have robust pancreatic beta-cells which are able to compensate for minor impairments in insulin sensitivity (194, 195), which together with robust subcutaneous fat stores may help explain an ability to maintain a healthy status even after 20 years and avoid insulin resistance and subsequent pathology.

As discussed, healthy obese adults have a more favourable fat distribution characterised by lower abdominal and visceral fat (56) along with favourable adipose tissue function and morphology (274). This has led some to investigate the extent to which fat distribution modifies a healthy obese adults' risk of incident disease, with Appleton et al., 2013 (51) reporting that lower waist circumference was associated with maintaining metabolic health over time and protection against developing type 2 diabetes or cardiovascular disease. Higher waist circumference has also been associated with progressing from healthy to unhealthy obesity over a period of 8 years (169), while a more recent study reported that lower visceral and higher lower-body fat among obese adults significantly lowered the 10-year risk of incident cardiovascular events (275). A range of metabolic and cellular risk factors including inflammation and inefficient mitochondrial transcription are known to be closely aligned with the presence of liver fat (276), and recently, the presence of liver fat has been shown to modify the risk of incident type 2 diabetes among healthy obese adults, with increased risk found only among those healthy obese adults who had signs of liver fat, and not among those who did not (277). This protection was evident after adjusting for age, sex, parental history of diabetes, smoking, alcohol consumption, and self-reported engagement in physical activity.

Although there is certainly heterogeneity in associated disease risk within the healthy obese group, a key contribution of this thesis is to provide a uniquely long-term view of the natural course of healthy obesity over time. Findings revealed a strong tendency for metabolic decline among the majority of healthy obese adults, indicating that for most, health gets worse over time. Although some healthy obese adults do remain healthy, the increasing proportion of healthy obese adults who decline over time indicates that the absolute number of obese adults

who can maintain an optimal balance of fat stores in the long-term is not high. An early implication of these findings is that weight loss is of paramount importance for obese adults, even those who appear to be metabolically healthy. However it is interesting to note that standard weight-loss interventions among healthy obese adults have so far experienced limited success. For example, healthy obese adults showed no improvement in blood lipids, inflammatory markers (278), and insulin sensitivity (279) in response to a diet and physical activity-based intervention, while other studies reported detrimental effects such as decreased insulin sensitivity (280). In another study, healthy obese adults who lost fat mass up to the point of resistance to further weight-loss experienced adverse physiological effects including worsened appetite regulation, decreased energy expenditure, and increased depressive symptoms (281); all of which may promote weight regain. It remains unknown whether such adverse physiological effects persist over time or whether weight-loss itself is more easily maintained among healthy compared with unhealthy obese adults. Targeted fat loss, focusing on reductions in abdominal and ectopic fat, may therefore be more appropriate for healthy obese adults. Indeed, several interventional studies report reductions in visceral fat among healthy obese men and women (279, 282, 283), while others show increased levels of cardiorespiratory fitness (282), improved insulin sensitivity, and improved fasting insulin levels (283).

Importantly, physical activity has the potential to improve fat distribution by reducing visceral fat even in the absence of weight-loss (97), and such reductions in visceral fat, together with increases in muscle mass, may be key reasons why regular physical activity helps promote insulin sensitivity (1). As discovered earlier in this thesis, total physical activity, measured objectively, was higher among healthy than among unhealthy obese adults, and higher total physical activity was also most strongly associated with a reduced likelihood of having insulin resistance. Physical activity may therefore be a key target for promoting stability of healthy obesity and for protecting against the onset of disease, but further research is needed with objective physical

activity measures and large samples to determine if physical activity truly reduces risk of future metabolic decline among healthy obese adults.

Furthermore, although physical activity is important, previous studies suggest that it is not sufficient to remove the health risks of obesity completely. Previous studies of middle-aged women from the US Nurses' Health Study examined interactive effects of physical activity and obesity status and reported that both physical activity and obesity are independently associated with risk of incident type 2 diabetes (284) and cardiovascular disease (285), with the excess risk attributed to obesity being much greater than attributed to low physical activity for both disease outcomes. Obesity and low physical activity were also independent predictors of all-cause and cardiovascular mortality in that same cohort (286). Results of this thesis go further to suggest that disease risks are cumulative with regards to obesity and metabolic ill-health, with having both obesity and metabolic ill-health conferring substantially greater risk than either component on its own. Conversely, having only one component, either obesity or metabolic ill-health, was not sufficient to protect against disease as excess risks are still evident among adults who are healthy obese or unhealthy normal-weight. This suggests that these components are inseparable and that focusing solely on promoting a normal-weight or a healthy metabolic profile is insufficient – both are required for optimal health.

5.2.1 Strengths and limitations in the study of healthy obesity and metabolic decline

This section examined the natural course of healthy obesity using consistent metabolic risk factor measures over the longest follow-up duration to date, 20 years, providing greater insights into long-term trends within and between groups than were previously possible. This section also included the first meta-analysis to summarise the risk of incident type 2 diabetes among

healthy obese adults and was the first to establish whether this apparently healthy group faces an increased risk for metabolic disease. This meta-analysis was supplemented with an original unpublished estimate from a nationally representative sample of older adults in England, affording a larger sample size and a more complete view of diabetes risk across adulthood. This meta-analysis also explored the impact of potential confounding factors of age, duration of follow-up, and study quality using meta-regression.

The need for a standardised definition of 'metabolically healthy' obesity has been emphasised repeatedly, most recently in the World Obesity Forum's 2013 Stock Report (287). A consistent definition of a 'healthy' metabolic profile was used throughout this thesis, data permitting, except for analyses of individual metabolic risk factor incidence and sensitivity analyses of incident type 2 diabetes, which was necessary to address current research objectives. The definition used in this thesis was based on independently proposed criteria which was used previously in the US NHANES study to determine national prevalence and correlated of healthy obesity (25). This criteria considers core metabolic risk factors of hypertension, blood lipids, and blood glucose, but additionally includes insulin resistance, which is excluded in widely used Adult Treatment Panel III criteria (27). Waist circumference was not considered for inclusion in this criteria as it is highly correlated with BMI (288), and would introduce an upward bias for the presence of metabolic risk factor clustering, given that most adults who are considered obese by BMI would also show a high waist circumference, and would therefore be automatically assigned 1 metabolic risk factor without consideration of the other 5 risk factors of interest.

Phenotype reference groups are not always consistent across published studies on healthy obesity, and within this thesis, reference groups used for analyses were consistently defined as healthy normal-weight based on a BMI range of 18.5-24.9 kg/m^2, which isolates normal-weight from overweight adults. This is expected to improve precision in effect estimates for disease risk, as differences between overweight and obese adults are likely smaller than differences between normal-weight and obese adults. Adults within this narrower BMI range are considered the

theoretically healthiest group based on large-scale individual-level analyses showing the lowest all-cause and cause-specific mortality risk (4, 5).

BMI may be seen as a crude measure of adiposity as it does not distinguish fat from muscle, and it does not characterise the distribution of fat within the body. These are valid and important limitations, and when fat distribution is of special interest, complementary indicators of adiposity such as waist circumference are available, which estimate the amount of visceral fat in the abdominal region (37, 38). Given that BMI is most widely used in the literature to define healthy obesity, BMI was used throughout this thesis in order to make results comparable with previous studies. A meta-analysis previously concluded that the predictability of BMI for incident type 2 diabetes was comparable to waist circumference and the waist-to-hip ratio (172), while BMI has been found to better predict incident coronary heart disease over 3 years than waist circumference among adults under the age of 65 years at baseline (289). Although not perfect, BMI remains a suitable indicator of obesity and its metabolic consequences and one which will likely continue to be used in future.

The definition of incident type 2 diabetes used in the Whitehall II cohort study was based on fasting blood glucose as recommended by both the World Health Organization in 2006 (224) and the American Diabetes Association in 2010 (225). Other diagnostic components do exist and have since been added to recommendations for diabetes diagnosis including oral glucose tolerance tests (OGTT) and glycated hemoglobin (HbA1c); however debate over the most effective and clinically appropriate method of diagnosis is on-going. Fasting glucose was recently shown to predict type 2 diabetes prevalence at a comparable level as fasting glucose combined with OGTT in a pooled analysis of 96 cohort studies (290), while HbA1c alone was found to underestimate diabetes prevalence. It is possible that some incident cases of type 2 diabetes are not captured by fasting glucose alone, however the number of such cases which are captured by other means and are not captured by fasting glucose is expected to be small, and any such bias introduced is expected to be minimal given that this small number of missed cases would be included in the relatively large control group. Fasting blood glucose was measured over all

clinical follow-up periods in the Whitehall II cohort and thus afforded a consistent definition of diabetes and a maximum follow-up duration, which is of greatest value for epidemiological investigations into the long-term clinical consequences of healthy obesity.

Results are based on complete case analyses, which include only those participants who have observed data on all variables required to conduct respective analyses. This raises two issues. First, unless data are missing completely at random such that no systematic differences exist between observed and missing data, results may be biased due to the selective nature of participants being considered (281). Differences between observed and missing data on important characteristics were examined in present analyses, with results suggesting that participants excluded from analytical samples were less likely than those included to be metabolically healthy. There was also evidence of selective drop-out from analytical samples according to BMI, with obese adults being more likely than normal-weight adults to be excluded. Thus, while these differences may result in estimates of associations which are biased, given that participants included in analyses were a relatively healthy subset of obese adults in the wider cohort, the direction of this bias is expected to be towards the null, producing estimates which are, if anything, conservative.

In addition to describing differences in characteristics between included and excluded participants in analytical samples, analyses in the first part of this thesis on physical activity and sedentary behaviour used a 'last observation carried forward' approach to fill in missing covariate data, while analyses in the second part of this thesis used a 'participant observation' approach to examine the natural course of healthy obesity over time using maximum samples. Both approaches yielded results which replicated patterns observed in complete cases analyses, building confidence that initial results were valid. Another method of handling missing data which was not attempted is multiple imputation, which aims to replace missing data values with values estimated from a distribution which is predicted by a range of other factors which are associated with the factor of interest. This approach assumes that any systematic differences between missing and observed data can be fully explained by differences in other observed data

(281), which, although a slightly more flexible assumption, is still not likely to hold given that missing metabolic risk factor data is likely systematically due to obesity and to adverse levels of metabolic risk factors among excluded participants themselves. Furthermore, given that missing data pertain mostly to clinical outcome variables and not to exposures or covariates, as well as given that the amount of missing data involved and the range of factors which may prevent participation in clinical assessments over a period of decades are both large, there is concern that imputation may induce biases in results which are at least as big as those induced from complete case analyses (281).

The second issue arising from the use of complete case analyses is a reduction in statistical power to detect associations among limited numbers of participants remaining in samples; an issue amplified by the requirement of data on several long-term follow-up occasions. However, associations were observed in the latter part of this thesis and these were large in magnitude, with healthy obese adults showing a substantial excess risk for progressing to ill-health (at over 20 times greater) and for developing type 2 diabetes (at over 4 times greater) compared with healthy normal-weight adults. The large magnitude of associations increases confidence that effects are genuine and not due largely to some form of bias, as this is expected to be more the case with smaller effect sizes which are closer to null reference values.

Results from this thesis are based on an occupational cohort and not a nationally representative sample of the general population. However, there is evidence that traditional metabolic risk factors and health behaviours measured in occupational cohorts predict cardiovascular disease risk at a level comparable to nationally representative studies; a recent comparison between the Whitehall II occupational cohort study and the British Regional Heart Study, a nationally representative cohort (291), illustrated this clearly. Given that present results pertain to biological processes and common health behaviours, and not to social phenomena, they are likely sufficiently generalizable and useful to the population at large.

Section 6: Conclusions & Implications

This final section will provide concluding remarks on the results and contributions of this thesis, ending with their implications for public health and clinical practice. This is followed by a list of outputs generated from this thesis and full-text copies of peer-reviewed publications.

6.1 Overall conclusions

There has been considerable interest and confusion in recent years over an apparently healthy subset of the obese population – those who present without metabolic risk factor clustering and may therefore be protected from the adverse cardiometabolic consequences traditionally associated with obesity. This thesis first aimed to determine whether physical activity and sedentary behaviour are factors which distinguish healthy from unhealthy obesity, and which may therefore be modified to promote it. Results suggest that neither high moderate-to-vigorous physical activity nor low leisure sitting time related to a higher likelihood of being healthy among obese adults; nor did they influence risk of becoming unhealthy among initially healthy obese adults over time. However, these measures were self-reported and may be imprecise. Total physical activity was later found to be higher among healthy versus unhealthy obese adults when measured objectively. Objective assessments also indicate that healthy obese adults engage in more moderate-to-vigorous intensity physical activity, but this is done in durations which are shorter than those recognised in current UK and international physical activity guidelines, and thus may have previously gone unnoticed. Thus, it is concluded that physical activity is a distinguishing feature of healthy obesity and may therefore be a modifiable factor for its promotion.

This thesis next aimed to further clarify the natural course of healthy obesity over time, and revealed that healthy obesity is a highly temporary state which often progresses to ill-health in the long-term. This declining metabolic status is likely driven by a strong tendency to become insulin resistant, which subsequently induces metabolic pathology. It was also established that healthy obese adults have a substantially increased risk for future type 2 diabetes compared with healthy normal-weight adults, and this excess risk is also likely present among obese adults who are strictly healthy, initially showing no signs of metabolic dysfunction. Interpreted together with previous work revealing a significantly increased risk of developing cardiovascular disease among healthy obese adults compared with healthy normal-weight adults, this firmly supports healthy obesity as a high risk state for future decline. There are exceptions, possibly explained by maintenance of higher physical activity and maintenance of a favourable fat distribution; however these cases are exceptionally rare.

The foremost contribution of this thesis is to provide a more realistic view of healthy obesity, one which is informed by the long-term tendencies of healthy obese adults over time. Given the strong tendency for future decline and their intermediate disease risk, healthy obesity is now best regarded not as a state of *absolute* health – but one of *relative* health. Although health risks for this group may not be eliminated, sizable benefits may still be realised by promoting transitions from unhealthy obesity into its relatively healthy counterpart. This may be particularly important for individuals who are genetically predisposed to a high BMI, and for whom weight loss has not proved successful. However it should be understood that healthy obesity is still not ideal, and that both a healthy profile and a normal BMI are required for optimal health.

There is more to understand on the topic of healthy obesity, such as how different types of physical activity contribute to health among the obese and how these different types may modify risk of metabolic decline, how the presence of obesity affects the maintenance of physical activity over time, and how long-term risk of non-metabolic health outcomes such as functional impairment, chronic pain, and cancer among healthy obese adults compares with that

of healthy normal-weight adults. Although these questions are worth pursuing, the core recommendation stemming from this thesis is that these pursuits should not distract from continued efforts to develop more effective and sustainable weight-loss solutions.

6.2 Implications for public health and clinical practice

Physical activity is currently being promoted aggressively in England, as outlined in several recent national strategy documents (142, 292). Given the limited success of weight-loss interventions, physical activity is likely viewed as a 'winnable battle', and one which is more politically neutral than tackling obesogenic food environments through taxation and market regulation of processed foods. Physical activity is certainly important for normal-weight and obese adults alike, and increasing political will is welcomed; however results of this thesis indicate that obesity itself should not be ignored, even when it exists alongside an apparently healthy metabolic profile, and that an equally high priority should be placed on promoting a healthy body weight as placed on increasing physical activity. Results of this thesis also demonstrate that disease risks are cumulative with regards to obesity and metabolic-ill health, with having both obesity and metabolic ill-health conferring substantially greater risk than having either component on its own. Conversely, having only one component, either obesity or metabolic ill-health, was not sufficient to protect against disease as excess risks are still evident among adults who are healthy obese or unhealthy normal-weight. The public health message therefore, is that attention should not be focused solely on promoting high physical activity or a normal BMI - both are required for optimal health.

The benefits of physical activity are undoubtedly great, but they are also short lived – physical activity needs to be done on a regular basis for its benefits to last. It is a common sense view that physical activity is more easily performed and more easily maintained if BMI is lower, and

that carrying excess weight is a barrier to realising the full benefits of an active lifestyle; although this issue was not specifically examined in this thesis and requires further study. However, given that the tendency for decline among the healthy obese gets stronger over time, it may be speculated that if physical activity does has a role in promoting health among this group it is likely not well-maintained over time.

When focusing their efforts and resources, clinicians and public health practitioners should be aware of the long-term tendencies for metabolic decline among healthy obese adults, and that these tendencies are much greater than among healthy or unhealthy normal-weight adults. This inseparable link between excess body fat and excess type 2 diabetes risk is becoming better appreciated by public health practitioners in England, as indicated by plans for a national Diabetes Prevention Programme delivered by the National Health Service (NHS) in collaboration with NHS England and Public Health England. Although still under development as of late 2015, this programme aims to identify patients seen routinely in primary care who have blood glucose within the prediabetic range, and to provide intensive and sustained behaviour change support to these patients in an effort to delay the onset of or entirely prevent type 2 diabetes (293). The programme's components are said to be informed by findings of a recent systematic review and meta-analysis conducted by academics on behalf of Public Health England on the effectiveness of behavioural interventions in primary care settings for reducing incidence of type 2 diabetes among high-risk individuals (294). Recommendations from this review include the measurement of blood glucose, weight, physical activity, and other metabolic risk factors both at baseline and at least 9 months follow-up, with at least 16 hours of contact with a professional counsellor included in the interim. Weight-loss is therefore identified as a core priority in addition to increased physical activity, which is encouraging given results of this thesis. Maintenance of both weight loss and high physical activity among high-risk patients is crucial to the long-term success of this programme, and it is therefore important for both factors to be monitored for as long as feasible.

A separate but complementary public health programme in England is the NHS Health Check, a free screening service offered through primary care to adults aged 40-74 (295). This screening involves fairly routine examinations of blood and anthropometric factors including BMI, which aim to inform individuals of their risk of developing type 2 diabetes, cardiovascular diseases including stroke, kidney disease, and dementia (295). Given previous discussions, it would be ideal if one's level of insulin resistance was also measured alongside blood glucose, as this may provide an even earlier indication of future risk of type 2 diabetes. Nevertheless, this programme is useful for identifying middle aged adults who may not be aware of their prediabetic or overweight status, and who could then be directed into the Diabetes Prevention Programme once it is rolled out nationally. There is, however, some concern that the lower age threshold for automatic enrolment into the Health Checks programme is high, at 40, given that obesity and type 2 diabetes are developing increasingly early in life, in adolescence and even childhood, and given that contact with health services tends to be lower among these younger groups. Furthermore, although components of both programmes are informed by scientific evidence, the programmes themselves are still new, and their effectiveness will undoubtedly depend on how they are delivered; namely what practical and financial challenges arise and how they are overcome. Research should therefore not just measure the health conditions of interest but also the process of programme delivery, as good intentions are simply not enough to improve the public's health.

Public health practitioners are encouraged to maintain a focus on obesity prevention and management, and clinicians who encounter healthy obese adults in practice are likewise encouraged to make weight-loss a continued priority; however discretion and common sense should still be applied at the individual-level. For instance, it may be clear for some patients that BMI is elevated due to large muscle mass and not excess fat, and if these patients maintain an active lifestyle with a balanced diet, then weight-loss is likely not a suitable target for that patient. Ultimately, it is understood that lasting success in obesity prevention and management will come from improvements to the food system which determines which forms of energy are

accessible, affordable, and convenient, as well as from improvements to built and social environments which determine the level of physical activity required to support daily living. These are beyond the scale of individual-level interventions and require national and international cooperation together with bold public health initiatives.

Thesis publications

Bell, J.A., Hamer, M., Batty, G.D., Singh-Manoux, A., Sabia, S., Kivimaki, M. (2014) Combined effect of physical activity and leisure-time sitting on long-term risk of incident obesity and metabolic risk factor clustering. **Diabetologia** 57: 2048-2056.

Bell, J.A., Hamer, M., van Hees, V., Singh-Manoux, A., Kivimaki, M., Sabia, S. (2015) Healthy Obesity and Objective Physical Activity. **Am J Clin Nutr** 102: 268-275.

Bell, J.A., Hamer, M., Sabia, S., Singh-Manoux, A., Batty, G.D., Kivimaki, M. (2015) The Natural Course of Healthy Obesity Over 20 Years. **J Am Coll Cardiol** 65(1): 101-102.

Bell, J.A., Hamer, M., Singh-Manoux, A., Batty, G.D., Sabia, S., Kivimaki, M. Incidence of Metabolic Risk Factors Among Healthy Obese Adults: 20-Year Follow-Up. **J Am Coll Cardiol** 66(7): 871-873.

Bell, J.A., Kivimaki, M., Hamer, M. (2014) Metabolically healthy obesity and risk of incident type 2 diabetes: a meta-analysis of prospective cohort studies. **Obes Rev** 15 (6): 504-515.

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Appendices

Appendix 1 Original questionnaire items forming the self-reported assessment of total and moderate-to-vigorous physical activity (Page 20 of Phase 5 Questionnaire)

We would like to know about your activities at work and in your free time that involve physical activity.

4.1 Getting about in the **PAST WEEK**.

a. On average, for how many minutes did you **walk** outside your home/workplace?

on each weekday TWLKOUTA — on each weekend day TWLKOUTB

b. On average, for how many minutes did you **pedal cycle**?

on each weekday TPEDCYCA — on each weekend day TPEDCYCB

c. On average, how many **flights of stairs** did you climb?

on each weekday TSTAIRSA — on each weekend day TSTAIRSB

4.2 Other physical activities in the **PAST FOUR WEEKS**. *Please indicate the number of **occasions** and **total** time spent on each of the activities listed. Write in other types of activity not listed, as applicable.*

a. SPORTS AND GAMES

		Occasions in the past 4 weeks							Total hours in past 4 weeks						
		None	1-2	3-4	5-10	11-15	16-20	21+	None	½	1-1½	2-3	4-5	6-10	11+
SOCCERF	Football (including coaching etc.)														TSOCCERH
TGOLFF	Golf														TGOLFH
TSWIMF	Swimming														TSWIMH
	Other activities e.g. aerobics, ballroom dancing, keep fit, jogging, tennis *(please specify)*														
TSPORT1															TSPORT1H
TSPORT2															TSPORT2H

TSPORT1F TSPORT2F

b. GARDENING

		Occasions in the past 4 weeks							Total hours in past 4 weeks						
		None	1-2	3-4	5-10	11-15	16-20	21+	None	½	1-1½	2-3	4-5	6-10	11+
TWEEDF	Weeding, hoeing, pruning etc.)														TWEEDH
TMOWF	Manual lawn mowing														TMOWH
	Other gardening e.g. digging, planting, clearing ground etc. *(please specify)*														
TGARDN1															TGARDN1H

TGARDN1F

c. HOUSEWORK

		Occasions in the past 4 weeks							Total hours in past 4 weeks						
		None	1-2	3-4	5-10	11-15	16-20	21+	None	½	1-1½	2-3	4-5	6-10	11+
ARRYHF	Carrying heavy shopping														TCARRYHH
TCOOKF	Cooking														TCOOKH
HANGWF	Hanging out washing														THANGWH
	Other housework e.g. dusting, ironing, hoovering *(please specify)*														
HOUSW1															THOUSW1H
HOUSW2															THOUSW2H

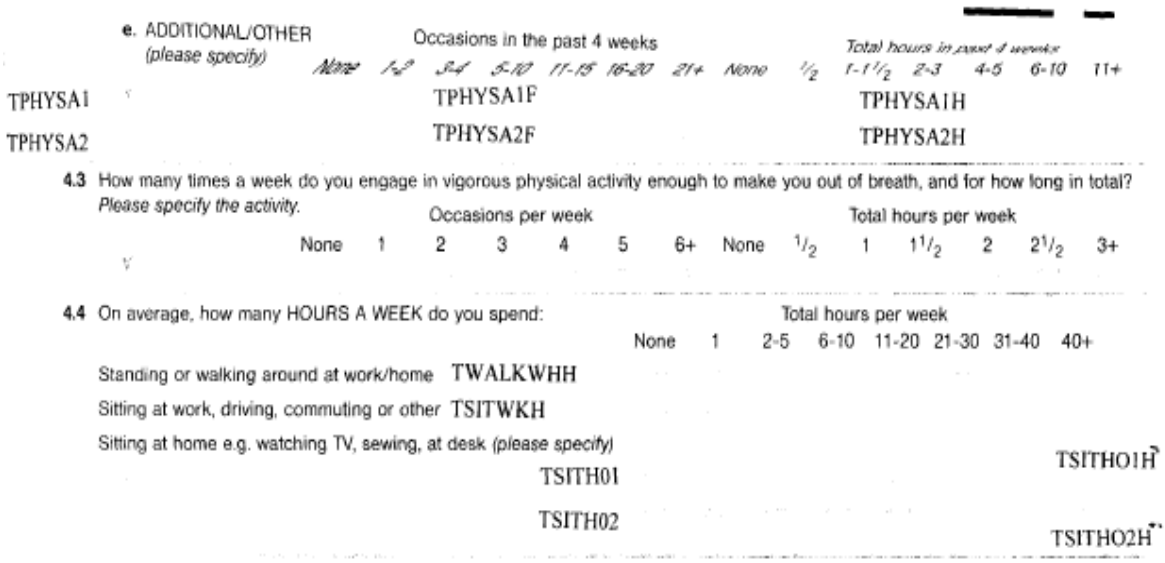
THOUSW1F THOUSW2F

d. DO-IT-YOURSELF

		Occasions in the past 4 weeks							Total hours in past 4 weeks						
		None	1-2	3-4	5-10	11-15	16-20	21+	None	½	1-1½	2-3	4-5	6-10	11+
ARWASF	Manual car washing														TCARWASH
AIDECF	Painting/decorating														TPAIDECH
	Other DIY e.g. household repairs, woodwork, bricklaying *(please specify)*														
TDIY1															TDIY1H

TDIY1F

Appendix 1 (Continued): Original questionnaire items forming the self-reported assessment of total and moderate-to-vigorous physical activity (Page 21 of Phase 5 Questionnaire)



e. ADDITIONAL/OTHER *(please specify)*

Occasions in the past 4 weeks: None | 1-2 | 3-4 | 5-10 | 11-15 | 16-20 | 21+

Total hours in past 4 weeks: None | ½ | 1-1½ | 2-3 | 4-5 | 6-10 | 11+

TPHYSA1 TPHYSA1F TPHYSA1H

TPHYSA2 TPHYSA2F TPHYSA2H

4.3 How many times a week do you engage in vigorous physical activity enough to make you out of breath, and for how long in total? *Please specify the activity.*

Occasions per week: None | 1 | 2 | 3 | 4 | 5 | 6+

Total hours per week: None | ½ | 1 | 1½ | 2 | 2½ | 3+

4.4 On average, how many HOURS A WEEK do you spend:

Total hours per week: None | 1 | 2-5 | 6-10 | 11-20 | 21-30 | 31-40 | 40+

Standing or walking around at work/home TWALKWHH

Sitting at work, driving, commuting or other TSITWKH

Sitting at home e.g. watching TV, sewing, at desk *(please specify)*

TSITH01 TSITHO1H

TSITH02 TSITHO2H

Appendix 2 Examples of reported physical activities and associated MET values (based on *Ainsworth et al. Med Sci Sports Exerc. 2011*) as part of the self-reported assessment of total and moderate-to-vigorous physical activity

Reported physical activity	**2011 MET value**
Walking (general)	2.9
Bicycling (general for leisure)	5
Swimming (general)	6
Football (general)	8
Golf (general)	4.8
Mowing lawn, walk, power mower	4.5
Gardening (general)	3.8
Weeding, cultivating the garden	4.5
Painting, decorating	3.3
Carrying	4.8
Cooking	2
Washing the car	4
Do-it-yourself activity (other)	3

Appendix 3 Separate associations of moderate-to-vigorous physical activity and leisure sitting with health among adults aged 45-69 at baseline (n=4177)

	Prevalence of being healthy	
	Model 1 Prevalence Ratio (95% CI)	**Model 2** Prevalence Ratio (95% CI)
Moderate-to-vigorous physical activity level*		
Lowest	1.00 (reference)	1.00 (reference)
Intermediate	1.06 (1.01, 1.11)	1.05 (1.00, 1.10)
Highest	1.12 (1.06, 1.17)	1.10 (1.04, 1.15)
p-interaction with BMI group	0.77	0.58
Leisure sitting time level*		
Highest	1.00 (reference)	1.00 (reference)
Intermediate	1.02 (0.97, 1.06)	1.01 (0.96, 1.05)
Lowest	1.01 (0.96, 1.06)	1.00 (0.95, 1.05)
p-interaction with BMI group	0.05	0.05

* Associations are mutually adjusted. **Model 1** adjusted for age, sex, and ethnicity, and BMI group. **Model 2** additionally adjusted for occupational position, alcohol, smoking, diet quality, and presence of an illness which limits moderate or vigorous physical activity

Appendix 4 Separate associations of moderate-to-vigorous physical activity and leisure sitting with health among adults aged 45-69 (n=4177), based on continuously measured behaviours

	Prevalence of being healthy	
	Model 1 Prevalence Ratio (95% CI)	**Model 2** Prevalence Ratio (95% CI)
Moderate-to-vigorous physical activity (per 1 hr/wk)*	1.01 (1.01, 1.02)	1.01 (1.01, 1.02)
p-interaction with BMI	0.34	0.26
Leisure sitting time (per 1 hr/wk)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
p-interaction with BMI	0.09	0.10
p-interaction (moderate-to-vigorous physical activity X leisure sitting)	0.62	0.66

* Associations are mutually adjusted. **Model 1** adjusted for age, sex, and ethnicity, and BMI. **Model 2** additionally adjusted for occupational position, alcohol, smoking, diet quality, and presence of an illness which limits moderate or vigorous physical activity

Appendix 5 Combined associations of moderate-to-vigorous physical activity and leisure sitting with health among adults aged 45-69 at baseline (n=4177)

	Prevalence of being healthy		
	Model 1 Prevalence Ratio (95% CI)		
	Leisure sitting time level		
Moderate-to-vigorous physical activity level	Highest	Intermediate	Lowest
Lowest	1.00 (reference)	1.01 (0.93, 1.10)	1.02 (0.93, 1.11)
Intermediate	1.07 (0.99, 1.16)	1.10 (1.02, 1.19)	1.03 (0.95, 1.12)
Highest	1.11 (1.02, 1.20)	1.12 (1.03, 1.21)	1.17 (1.08, 1.27)
p-interaction		0.58	
p-interaction with BMI group		0.15	
	Model 2 Prevalence Ratio (95% CI)		
	Leisure sitting time level		
Moderate-to-vigorous physical activity level	Highest	Intermediate	Lowest
Lowest	1.00 (reference)	1.01 (0.93, 1.09)	1.01 (0.92, 1.10)
Intermediate	1.06 (0.98, 1.15)	1.09 (1.00, 1.18)	1.01 (0.93, 1.09)
Highest	1.09 (1.01, 1.18)	1.08 (1.00, 1.17)	1.14 (1.05, 1.24)
p-interaction		0.61	
p-interaction with BMI group		0.12	

Model 1 adjusted for age, sex, and ethnicity, and BMI group. **Model 2** additionally adjusted for occupational position, alcohol, smoking, diet quality, and presence of an illness which limits moderate or vigorous physical activity

Appendix 6 Separate associations of moderate-to-vigorous physical activity and leisure sitting with incident metabolic risk factor clustering among initially healthy adults aged 45-69 at baseline (n=2128)

	Risk of incident metabolic risk factor clustering over 15 years	
	Model 1 Incidence Ratio (95% CI)	**Model 2** Incidence Ratio (95% CI)
Moderate-to-vigorous physical activity level*		
Lowest	1.00 (reference)	1.00 (reference)
Intermediate	0.96 (0.87, 1.05)	0.97 (0.89, 1.07)
Highest	1.01 (0.93, 1.11)	1.04 (0.95, 1.14)
p-interaction with BMI group	0.48	0.53
Leisure sitting time level*		
Highest	1.00 (reference)	1.00 (reference)
Intermediate	0.90 (0.82, 0.98)	0.91 (0.83, 0.98)
Lowest	0.97 (0.89, 1.06)	0.98 (0.89, 1.07)
p-interaction with BMI group	0.09	0.16

* Associations are mutually adjusted. Follow-up duration is cumulative, considering incidence after 5, 10, or 15 years. **Model 1** adjusted for age, sex, and ethnicity, and BMI group. **Model 2** additionally adjusted for occupational position, alcohol, smoking, diet quality, and presence of an illness which limits moderate or vigorous physical activity

Appendix 7 Separate associations of moderate-to-vigorous physical activity and leisure sitting with incident metabolic risk factor clustering among adults aged 45-69 at baseline (n=2128), based on continuously measured behaviours

	Incident metabolic risk factor clustering	
	Model 1 Incidence Ratio (95% CI)	**Model 2** Incidence Ratio (95% CI)
Moderate-to-vigorous physical activity (per 1 hr/wk)*	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
p-interaction with BMI	0.74	0.67
Leisure sitting time (per 1 hr/wk)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
p-interaction with BMI	0.19	0.30
p-interaction (moderate-to-vigorous physical activity X leisure sitting)	0.42	0.54

* Associations are mutually adjusted. Follow-up duration is cumulative, considering incidence after 5, 10, or 15 years. **Model 1** adjusted for age, sex, and ethnicity, and BMI. **Model 2** additionally adjusted for occupational position, alcohol, smoking, diet quality, and presence of an illness which limits moderate or vigorous physical activity

Appendix 8 Combined associations of moderate-to-vigorous physical activity and leisure sitting with incident metabolic risk factor clustering over 15 years among initially healthy adults aged 45-69 at baseline (n=2128)

	Risk of incident metabolic risk factor clustering over 15 years		
	Model 1 Incidence Ratio (95% CI)		
	Leisure sitting time level		
Moderate-to-vigorous physical activity level	Highest	Intermediate	Lowest
Lowest	1.00 (reference)	0.94 (0.80, 1.09)	0.98 (0.84, 1.15)
Intermediate	1.03 (0.90, 1.19)	0.85 (0.73, 1.00)	0.90 (0.76, 1.06)
Highest	1.00 (0.87, 1.14)	0.93 (0.81, 1.07)	1.05 (0.91, 1.22)
p-interaction		0.48	
p-interaction with BMI group		0.27	
	Model 2 Incidence Ratio (95% CI)		
	Leisure sitting time level		
Moderate-to-vigorous physical activity level	Highest	Intermediate	Lowest
Lowest	1.00 (reference)	0.94 (0.81, 1.10)	0.99 (0.85, 1.16)
Intermediate	1.05 (0.92, 1.20)	0.87 (0.75, 1.02)	0.92 (0.78, 1.09)
Highest	1.02 (0.90, 1.17)	0.96 (0.83, 1.10)	1.09 (0.93, 1.26)
p-interaction		0.50	
p-interaction with BMI group		0.34	

Follow-up duration is cumulative, considering incidence after 5, 10, or 15 years. **Model 1** adjusted for age, sex, and ethnicity, and BMI group. **Model 2** additionally adjusted for occupational position, alcohol, smoking, diet quality, and presence of an illness which limits moderate or vigorous physical activity

Appendix 9 Separate associations of moderate-to-vigorous physical activity and TV viewing with health among adults aged 45-69 (n=4141)

	Prevalence of being healthy	
	Model 1 Prevalence Ratio (95% CI)	**Model 2** Prevalence Ratio (95% CI)
Moderate-to-vigorous physical activity level*		
Lowest	1.00 (reference)	1.00 (reference)
Intermediate	1.08 (1.00, 1.17)	1.07 (1.00, 1.16)
Highest	1.18 (1.09, 1.27)	1.16 (1.07, 1.25)
p-interaction with BMI group	0.12	0.08
TV viewing level*		
Highest	1.00 (reference)	1.00 (reference)
Intermediate	1.06 (0.98, 1.15)	1.06 (0.97, 1.14)
Lowest	1.13 (1.05, 1.21)	1.12 (1.04, 1.20)
p-interaction with BMI group	0.28	0.25

* Associations are mutually adjusted. **Model 1** adjusted for age, sex, and ethnicity, and BMI group. **Model 2** additionally adjusted for occupational position, alcohol, smoking, diet quality, and presence of an illness which limits moderate or vigorous physical activity

Appendix 10 Separate associations of moderate-to-vigorous physical activity and TV viewing with health among adults aged 45-69 (n=4141), based on continuously measured behaviours

	Prevalence of being healthy	
	Model 1 Prevalence Ratio (95% CI)	**Model 2** Prevalence Ratio (95% CI)
Moderate-to-vigorous physical activity (per 1 hr/wk)*	1.02 (1.01, 1.03)	1.02 (1.01, 1.02)
p-interaction with BMI	0.20	0.12
TV viewing time (per 1 hr/wk)*	1.00 (0.99, 1.00)	1.00 (1.00, 1.00)
p-interaction with BMI	0.63	0.55
p-interaction (moderate-to-vigorous physical activity X TV viewing time)	0.92	0.77

* Associations are mutually adjusted. Follow-up duration is cumulative, considering incidence after 5, 10, or 15 years. **Model 1** adjusted for age, sex, and ethnicity, and BMI group. **Model 2** additionally adjusted for occupational position, alcohol, smoking, diet quality, and presence of an illness which limits moderate or vigorous physical activity

Appendix 11 Combined associations of moderate-to-vigorous physical activity and TV viewing with health among adults aged 45-69 (n=4141)

	Prevalence of being healthy		
	Model 1 Prevalence Ratio (95% CI)		
	TV viewing level		
Moderate-to-vigorous physical activity level	Highest	Intermediate	Lowest
Lowest	1.00 (reference)	1.10 (0.95, 1.27)	1.13 (0.98, 1.29)
Intermediate	1.12 (0.98, 1.29)	1.13 (0.98, 1.29)	1.23 (1.09, 1.40)
Highest	1.16 (1.00, 1.34)	1.28 (1.11, 1.46)	1.35 (1.19, 1.53)
p-interaction		0.75	
p-interaction with BMI group		0.29	
	Model 2 Prevalence Ratio (95% CI)		
	TV viewing level		
Moderate-to-vigorous physical activity level	Highest	Intermediate	Lowest
Lowest	1.00 (reference)	1.09 (0.94, 1.27)	1.12 (0.98, 1.29)
Intermediate	1.12 (0.97, 1.29)	1.11 (0.97, 1.28)	1.21 (1.06, 1.38)
Highest	1.15 (0.99, 1.33)	1.25 (1.09, 1.43)	1.31 (1.15, 1.49)
p-interaction		0.84	
p-interaction with BMI group		0.28	

Model 1 adjusted for age, sex, and ethnicity, and BMI group. **Model 2** additionally adjusted for occupational position, alcohol, smoking, diet quality, and presence of an illness which limits moderate or vigorous physical activity