Sedentary Behaviour and Health

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I certify that all material in this thesis which is not my own work has been identified and that no material has previously been submitted and approved for the award of a degree by this or any other University.

Signature: ……..

Abstract

The term sedentary refers to a distinct class of activities which involve sitting or reclining and which do not cause an increase in energy expenditure above resting levels. Observational studies have reported positive associations between both sedentary time and the number of hours spent sitting per day, with risk for a number of health outcomes that are independent of moderate to vigorous physical activity (MVPA). The total time spent sitting can be amassed in different patterns (long and short bouts) and different types (watching TV, driving, working at a computer) that may have differential associations with health outcomes as well as different confounders that have yet to be properly explored. Further, limitations in current measures used to quantify sedentary behaviour and the possibility of residual confounding, mean that it is unclear whether the posture of sitting itself represents a risk to health or whether sitting is actually a proxy for low energy expenditure. This thesis aimed to examine; the associations between five separate sitting types with health risk, the prevalence of sitting behaviour in England, and the biological mechanisms which might underpin the observed negative health consequences of sitting.

Using data from the Whitehall II cohort study the first four studies of this thesis examined prospective associations between sitting at work, TV viewing, non-TV leisure time sitting, total leisure time sitting (TV and non-TV leisure sitting combined) and total sitting from work and leisure, with four health outcomes; mortality, cardiovascular disease, type II diabetes and obesity. No association between any of the sitting indicators with risk for mortality or incident cardiovascular disease was found. TV viewing and total sitting were

associated with an increase in risk for type II diabetes following adjustment for sociodemographic covariates and MVPA, but were attenuated following further adjustment for body mass index. None of the five sitting indicators were associated with incident obesity but being obese prior to the measurement of sitting was associated with the number of reported hours of daily TV viewing. The final study of this thesis examined the acute effect of sustained versus interrupted sitting on glucose and insulin metabolism. Interrupting sitting with repeated short bouts of light intensity walking significantly improved insulin sensitivity while repeated short bouts of standing did not.

Sitting is a prevalent behaviour in English adults and varies by socio-demographic characteristics. Previously reported associations between sitting time and health risk may be confounded by light intensity physical activity and obesity. The absence of an effect of repeated standing bouts (a change in posture without a change in energy expenditure) suggests that promoting reductions in sitting without also promoting increases in movement are not likely to lead to improvements in metabolic health. New measures of sedentary behaviour are required that can be used in population studies, and can discriminate between the posture of sitting, standing and very low levels of physical activity of a light intensity. This would permit further studies that are needed to clarify the precise nature of the association between sitting and health.

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Definitions

Throughout this thesis the terms physical activity and sedentary behaviour will be defined as follows:

Physical activity:

'any bodily movement produced by skeletal muscle that results in energy expenditure above resting level' Caspersen 1985'[1] (pp126)

Sedentary behaviour:

'activities requiring seated or reclining postures which do not require an energy expenditure substantially above resting levels, typically 1-1.5 METs' Pate 2008'[2] (pp174)

Glossary of epidemiological terms

Correlates: Each of two or more variables which are mutually or reciprocally related.

Determinants: A variable that has an established reproducible association, or predictive relationship with an outcome variable; a correlate but not necessarily a confirmed cause.

Causal direction: the temporal sequence of an event and second event, where the second event is understood as a consequence of the first.

Confounding: The distortion of the apparent effect of an exposure or risk brought about by association with other factors that can influence the outcome.

Residual confounding: Occurs when all potential confounders are not adequately measured or analysed or when adjustments are not made for confounders that change across time.

Occult disease: Undiagnosed disease or disease not accompanied by readily discernible signs or symptoms.

Chapter 1

Sedentary behaviour and health: An introduction

1.1. Physical activity and health: historical context and the evolving definition of sedentary

Learned scholars have written about the protective effects of exercise and associations of impaired health and reduced longevity with 'sedentary living' for many centuries.[2]

Hippocrates wrote extensively about the benefits of exercise for a variety of ailments including both physical and mental illnesses. Claudius Galenus, whose writings from the first and second centuries continued to be studied by medical students and practitioners well into the nineteenth century, believed that exercise could be used to treat virtually any condition.[2] In his 1713 work '*Morbis Artificum Diatriba'* (Diseases of Workers) Bernardino Ramazzini also observed that differences in disease risk between workers were not only due to exposure to different working environments (including chemical and physical agents), but also to differences in the physical demands and postures associated with their occupations, and suggested physical activity as a remedy.

In referring to 'the clerks, the cobblers, the learned men' (whom he describes as 'chair workers') Ramazzini states;

…'These workers suffer from general ill-health ….caused by their sedentary life….It follows that when occasion offers we must advise men employed in these trades to interrupt when they can by walking or exercising the body in some way'.[3]

The last 60 years has seen a wealth of observational and experimental evidence which supports the conclusions of these early scholars by demonstrating the plethora of physiologic benefits and reductions in disease risk associated with regular physical activity. In the modern era this began with the pioneering work of Dr Jeremy Morris in the 1950's. In a seminal epidemiologic study of London transport workers Dr Morris observed that bus conductors who stood and climbed stairs during their working day had a significantly reduced risk of cardiovascular events than bus drivers who remained seated.[4] In a subsequent investigation titled 'Coronary Heart Disease and the Physical Activity of Work' published in the British Medical Journal in 1958 Dr Morris examined the presence of ischaemic myocardial fibrosis in 3800 middle aged men who had died of causes other than coronary heart disease in relation to the relative physical activity involved in their occupations. There was clear evidence of a positive association in both presence and severity of the condition across categories of decreasing occupational activity (occupations were classified based on their physicality as being heavy, active or light).[5] Observations of the beneficial effects of physical activity were not limited to studies of occupational behaviour. In 1978 Dr Ralph Paffenbarger published data from the Harvard Alumni Study in which 16936 participants provided a self-report of activities including walking, stair climbing and all sporting activities. It

was observed that risk of myocardial infarction was inversely associated with both sporting activity and total daily energy expenditure.[6]

Since these relatively early investigations, physical activity of a moderate or vigorous intensity (MVPA) has been demonstrated to have a protective effect against a range of non-communicable conditions including cardiovascular diseases,[7] metabolic conditions,[8] obesity,[9] and some cancers.[10 11] The terms moderate and vigorous refers to activities which elicit an energy expenditure of greater than three and six metabolic equivalents (METS), respectively. One metabolic equivalent represents a basal metabolic value and is equal to the utilisation of 3.5mL/Kg/min of oxygen in adults.[12] Therefore, 3 METs represents three times the energy cost of rest. The wealth of evidence for a protective effect of MVPA has allowed the formulation of public health guidelines for improving or maintaining health and traditionally these guidelines have focussed on physical activity of at least moderate intensity. The Chief Medical Officers' Physical Activity Guidelines[13] state that adults should aim to achieve at least 150 minutes of moderate intensity physical activity per week in bouts of 10 minutes or more, or 75 minutes of vigorous intensity activity. Current recommendations also advise that adults should undertake exercise to strengthen muscles and to improve flexibility on at least two days of the week although in order to maintain physical function and support this physical activity behaviour.

From these historical observations, through the early examinations of physical activity by Morris, Paffenbarger and their contemporaries, right up until

the last decade, the term sedentary was used by researchers variously to describe, non-exercisers,[14] those who did not adhere to physical activity recommendations,[15] or to the least active members of a population,[16] rather than any specific measured behaviour or activity. In the Harvard Alumni Study, men who expended less than an estimated 2000 kcal/wk through walking, cycling, stair climbing and playing sports were classified as sedentary.[17] The criteria outlined in the Five Cities Study (a comparative population based study of five large Indian cities) considered a participant to be sedentary if they walked <14.5 km a week, climbed fewer than 20 flights of stairs a week during household or occupational activities and performed no moderate or vigorous leisure time physical activity on five days a week.[18] Sedentary behaviour and MVPA were viewed as opposite ends of the same continuum and accordingly, the health risks associated with 'being sedentary', or having a 'sedentary lifestyle' were attributed exclusively to the absence of the documented protective effects of moderate to vigorous physical activity.[19 20]

This idea was first challenged by Owen and colleagues[21] who reported that the determinants of sedentary behaviours (those involving sitting) and MVPA might be distinct and importantly that they may have independent and qualitatively different influences on human metabolism.[22-25] Put simply, too much sitting is very different from too little exercise.[26]

1.2. Sedentary behaviour as an exposure: current definitions and its importance as an independent health determinant

In the 13 years since Owen and colleagues first postulated that sedentary behaviour is a separate and distinct entity to MVPA, research into sedentary behaviour has proliferated[26] and there is now widespread conceptual and empirical support that it exerts an independent influence on health.[2 19 26-30]

The English word sedentary is derivative of the Latin verb 'sedere' meaning 'to sit' and sedentary behaviours are defined both in terms of this postural topography and their low energy expenditure. This is in contrast to light, moderate and vigorous intensity activities which are defined exclusively by their energy requirements and can involve a range of postures.

Typically sedentary behaviours are defined as:

'activities requiring seated or reclining postures which do not require an energy expenditure substantially above resting levels, typically 1-1.5 METs'[2 20]

and include; sitting at home i.e. while watching television, working or reading; sitting at work; or sitting while commuting in motorised transportation.

The idea that high volumes of sitting behaviours can represent a risk to health is a very significant one. In contemporary society, technological advancement affecting all areas of life has allowed prolonged sitting to become a feature of day to day living across a range of contexts.[31] While the population

level prevalence of sitting across the UK is unclear, such data is available from the US. Analysis of data from over 6000 participants (aged ≥20yrs) in the 2003-2006 US National Health and Nutrition Examination Survey (NHANES) found that mean daily sedentary time (measured using accelerometers and classified as time spent below a predetermined movement threshold [this method will be addressed in chapter 2]) ranged between 7.3 and 9.3 hrs per day.[32] Proportionally this represented between 51% and 68% of adults' total waking hours. In contrast, moderate to vigorous physical activity accounted for around 5% of time across the sample[33] with the remainder logically consisting of light intensity day to day activities. Similar volumes of daily sedentary time were observed in a sample of participants from the Australian Diabetes and Lifestyle (AusDiab) study where the sample mean was 8.4 hrs per day while moderate or vigorous activity accounted for only around 30 minutes.[34]

In addition to their prevalence, if sedentary behaviours are not a displacement of MVPA then it is possible for someone to engage in high volumes of daily sitting while also engaging in moderate or vigorous intensity physical activity sufficient to meet public health recommendations. It follows that any health risks associated with high volumes of sitting could potentially affect both those who do and those who don't achieve 150 mins per week of MVPA. Indeed significant metabolic disturbance has been associated with high volumes of sitting in adults who report to undertake at least the recommended 150 minutes per week of MVPA.[35]

Nevertheless, the focus of current physical activity guidelines remains MVPA. The most recent UK guidelines,[13] while recognising that sedentary behaviour or inactivity could potentially be damaging and therefore should be minimal, were unable make any specific recommendations regarding healthy or unhealthy volumes of sitting.[36] Likewise the recently updated recommendation for adults on physical activity and public health from the American College of sports Medicine (ACSM) and the American Heart Association (AHA) states only that the 'the recommended amount of physical activity (whether of a moderate or vigorous intensity) is in addition to the routine activities of daily living, which are of light intensity.' These activities include self-care, casual walking and household tasks.[37] Changes in the patterns of these day to day light intensity activities could lead to reductions in sitting but again the recommendations do not specifically mention sitting per se. The inability to make specific recommendations stems simply from the relative recentness of research interest into sitting as an exposure and therefore the paucity of observational and experimental evidence of its effects relative to physical activity which has been the subject of detailed examination for well over half a century.

With sitting representing such a large component of day to day life in developed countries and if it does represent a unique and independent health risk then an understanding of its prevalence in the UK, its correlates and its determinants, and the biological mechanisms underpinning the deleterious effect on health outcomes is essential. However, there are many outstanding research questions which must be addressed before it can be said with a high degree of certainty that these adverse health consequences are uniquely

caused by too much sitting, or if what has been observed to this point is attributable to a low volume of light, moderate or vigorous intensity physical activity.[26] The aim of this thesis is to address a number of these outstanding questions.

1.3. Thesis overview

The questions addressed in this thesis follow the first three of the five phases of research outlined in the behavioural epidemiology framework proposed by Sallis, Owen and Fotheringham.[38] Central to the development of knowledge regarding sitting behaviour and its effect on health outcomes is the measurement of the exposures in observational studies. Chapter 2 addresses the application, strengths and limitations of the various self-report and objective device-based measures used to quantify sitting or sedentary behaviours within the published literature.

In order to determine the outstanding research questions within the field of sedentary behaviour research it is necessary to review the current evidence. To this end, Chapter 3 features a series of systematic reviews which aim to evaluate existing evidence and frame the research questions which become the focus of the subsequent chapters. These reviews examine literature regarding the associations between sedentary behaviour and the four most commonly investigated health outcomes; mortality, cardiovascular disease, metabolic disease and obesity. Alongside these themed systematic reviews the case for a causal association between sitting and health risk will be evaluated using the

nine criteria for causality outline by Sir Austin Bradford-Hill[39]. From this systematic review of the published literature, six separate research questions were identified and these fall under three more general headings; what is the risk?, who is at risk?, and what causes the risk?

1.3.2. What is the risk?

The initial questions addressed in this thesis fall under the broader question 'what is the risk?' Are high volumes of sitting time associated with an increased risk to health? Due to growing evidence that the pattern or number of interruptions during a given period of sitting is a significant factor in the magnitude of the observed deleterious effects on health, the following chapters take the novel approach of examining the potentially differential associations of five indicators of sitting time (sitting at work, sitting while watching TV, leisure time sitting excluding TV viewing, total leisure time sitting, and total sitting from both work and leisure time) with health. The four major health outcomes in these analyses have been selected as they are the focus of the early literature reviews of the negative effects of sedentary behaviour; mortality, cardiovascular disease, metabolic disease – specifically type II diabetes, and obesity. Chapter 4 will introduce the Whitehall II cohort study and provide some historical background for the source of data for these analyses. Chapters 5, 6 and 7 will examine the prospective associations of the five sitting exposures with mortality risk, risk of incident cardiovascular disease, and the development of type II diabetes respectively.

It is logical that obesity could be a cause or a consequence of high volumes of sitting. Consequently the causal direction of this association requires further examination. Chapter 8 therefore addresses the cross-sectional associations of sitting with prevalent obesity, the prospective associations with incident obesity and the prospective associations of prior obesity with baseline sitting time.

1.3.3. Who is at risk?

Chapter 9 will then address the question ‘who is at risk?’ It is necessary to examine the prevalence of sitting in a representative sample of the English population in order to determine potential differences in exposure between population subgroups which would infer a greater or lesser degree of risk and potentially provide a useful basis for targeted public health interventions aimed at reducing this risk.

1.3.4. What causes the risk?

In Chapter 3 it will be evident that there is a growing body of evidence for an association between high volumes of sitting and adverse health consequences. A fundamental next step in this field is to examine the biological mechanisms which underpin these associations. Chapter 10 will focus on an experimental investigation into the acute metabolic effects of sustained and interrupted sitting. The aim of this study is examine one of the potential biological pathways which may be affected by different patterns of sitting.

In Chapter 11 the findings, conclusions and evaluations of these six investigations are then discussed in the context of the existing literature. This chapter will then go on to outline the practical and theoretical applications of these findings and to outline the research questions which must be addressed in order to continue to develop this field.

Chapter 2

The measurement of sedentary behaviour

A comprehensive population-health research agenda for sedentary behaviour involves; identifying and quantifying associations with health outcomes, estimating the population prevalence of sedentary behaviour, understanding the relevant correlates and determinants of sedentary behaviours, developing interventions to alter the determinants in order to reduce the health burden associated with sedentary time and to evaluate the effectiveness of the interventions.[40] The accurate measurement of sedentary behaviour is crucial in all stages of this agenda. The development of precise measurement tools which can be used to examine sedentary behaviour on a large scale is also essential for future population surveillance, and for identifying changing trends.[41]

The variation in measurement techniques used to examine sedentary behaviour and its association with health has led to uncertainty about the true nature of the exposure. Self-report measures can assess sitting behaviour while objective measures (i.e. those which are independent of the influence of those being measured) such as heart rate monitors and accelerometers assess low levels of movement or energy expenditure (which are often features of sitting). In addition each technique has its own limitations and can introduce misclassification and bias in different ways, which adds to this uncertainty. The most precise method of assessing sedentary behaviour is direct observation although this is impractical in free-living settings and not feasible in large-scale

population studies.[42] The following chapter will examine methods that have been used to measure sedentary behaviours in adult populations. Both self-report measures (including diaries, logs and questionnaires) and objective measurement tools (devices such as heart rate monitors and accelerometers) will be discussed in terms of their reliability, validity, strengths and limitations. The discussion will then progress to newer and developing methodologies which may improve the measurement of sedentary behaviour for future research.

2.2. Self-report measures of sedentary behaviour

As discussed previously, population based research into physical activity is rooted in the research of Professor Jerry Morris in the 1950s[43] with his examination of differences in incident cardiovascular disease of bus conductors and drivers according to the physical activity demanded by their occupations. Over the next two decades there were a number of studies examining the associations between physical activity, classified solely by occupation, and a range of health outcomes.[44-50] These studies were conducted at a time when a substantial proportion of the workforce routinely performed sustained periods of moderate to vigorous physical activity as part of their working day,[43] a feature which is far less true of today's society. No self-report information of physical activity or sedentary behaviour was included in these studies.

In 1964 an article published in the Journal of the National Cancer Institute reported on the association between self-reported physical activity and

risk of death from all causes.[51] A questionnaire item simply asked *'how much physical activity do you get at work or play?'* with the possible responses: '*none', 'slight,' moderate', and' heavy'.* Following this publication there was a major shift away from using occupational classification as a physical activity exposure, towards the use of self-report measures which were able to identify and quantify the frequency, duration, intensity and type of physical activities during both work and leisure.[43]

Over the last 50 years data collected using various self-report measures have been critical in establishing the strong inverse relationship between volume of habitual physical activity and disease morbidity and mortality and in the development of physical activity guidelines.[13] More recently self-report measures have been used to examine associations between sedentary behaviour and health outcomes in population based research. Such methods include behavioural logs,[52] and questionnaires.[53-56]

2.2.2. Diaries and behavioural logs

Activity diaries require participants to record specific activities (for example different sitting behaviours or sitting in different contexts) as they occur during a predetermined measurement period. In contrast behavioural logs require participants to record the time spent in broad categories of activity, usually defined by intensity (sedentary, light intensity, moderate intensity and vigorous intensity). An example of this type of measure is the log proposed by Bouchard et al[57] which requires participants to record their activity intensity at

15 minute intervals throughout the day. Examples of activities for each intensity classification are provided for reference. Similarly Ainsworth et al[58] developed an activity log book which requires participants to record time spent in 48 different activities (7 resting/light intensity, 25 moderate, 16 hard/very hard) which are organised as home, transport, occupation, conditioning, or sports and leisure activities. Participants were instructed to record only activities with a duration of 10 minutes or more. Ecological Momentary Assessment (EMA) diaries can also be effective in capturing sedentary behaviours. Ecological Momentary Assessment involves participants recording the main behaviour that they are involved in every 15 minutes throughout the measurement period. At the same time they respond to two questions relating to where they are and who they are with.[59] These methods have the advantage of being able to provide information on a range of specific sedentary behaviours in the contexts in which they occur[41] (for example sitting while watching television or while at work) as well as overall sedentary time per day/week etc. The real time recording of these behaviours may also reduce the measurement error associated with difficulties in recalling or summarising behaviours over a prolonged period.[41 59] This is of particular importance when you consider the numerous opportunities for sitting and the intermittent and sporadic nature of sitting.

2.2.3. Questionnaires

The majority of studies which have employed self-report measures to quantify time spent in sedentary behaviours have done so using questionnaires which have either been completed by participants or administered by

interviewers. Questionnaires are a popular method[41] because they can be implemented on a large scale, are relatively inexpensive and do not alter the behaviour under investigation as they involve recalling and recording behaviours after they have happened.[60] [61] Questionnaire items have asked respondents to classify (see example *a*. below) or to quantify (example *b*. below) total habitual sedentary behaviour or to recall the amount of time spent engaged in sedentary behaviours over a given period (see example *c*. below).

Example *a.* from the Canadian Fitness Survey[62]

'*how much time do you spend sitting during the course of most days of the week?'* Responses include: *1) almost none of the time, 2) approximately one fourth of the time, 3) approximately half of the time, 4) approximately three fourths of the time, or 5) almost all of the time*.

Example *b.* from the Australian Longitudinal Study of Women's Health.[63]

'think about all the time you spend sitting each day while at home, at work, while getting from place to place or during your spare time. How many hours each day do you typically spend sitting down while doing things like visiting friend, driving, reading, watching television, or working at a desk or computer on a usual weekday and b) a weekend day'.

Example *c*. from the International Physical Activity Questionnaire (IPAQ) as used in the Azorean Physical Activity and Health Study (APAHS).[64]

'*Now think about the time you spent sitting on week days during the last 7 days. Include time spent at work, at home, while doing course work, and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television.*

During the last 7 days, how much time did you usually spend sitting on a week day?'

Other questionnaire items have sought to quantify time spent in specific individual sitting behaviours including; TV viewing,(as in the Australian Diabetes and Lifestyle study, the 1958 British Birth cohort study, and the EPIC-Norfolk study)[53 65 66] screen time (usually comprising TV viewing time and computer use – as described in the Scottish Health Survey),[67] leisure-time sitting (as in the American Cancer Society's Cancer prevention Study II),[68] occupational sitting[69] or a number of these (as in the Whitehall II study and US National Institute for Health – American Association of Retired Persons Diet and health Study).[68 70] Like other self-report measures questionnaires have the flexibility to obtain information on frequency and duration of individual bouts of sedentary behaviour and the context in which they occur as well as the total volume of daily or weekly sedentary time.

As a very prevalent leisure-time activity in developed countries[71] TV viewing is commonly examined in studies looking to assess the associations between sedentary behaviour and health. Pate et al[2] highlight inconsistencies in some of these studies that report findings solely on TV viewing time and yet discuss these findings in terms of overall sedentary behaviour. Television

viewing is one of a range of sedentary behaviours which adults engage in and should not be used as a proxy or indicator of a broader pattern of sedentary behaviour. Clark et al observed only a fair correlation (Spearman ρ=0.22 95% CI 0.20 to 0.25) between self-reported TV viewing time and total sedentary time across all age and ethnic groups although further analysis showed the level of agreement to vary significantly between population subgroups.[72] For example there were no significant correlations in people of working age who were in either part time or full time employment. This is logical when considering the possible contribution of a full time office-based job to total sedentary time. In addition, sedentary behaviours which take place in different contexts and fulfil different purposes are likely to have different determinants, and their individual relationships with health are likely to be influenced by a range of unique confounding factors.[73] For example TV viewing has been demonstrated to alter eating patterns through both food advertising and because of snacking during TV viewing itself,[74] and the association between occupational sitting and health may be confounded by work-related stress.[73] By focussing on total sitting time or solely on sitting in one domain, different and important associations between various sitting behaviours and health will be missed. Therefore, while examining total volume of sitting remains useful, it is also necessary to separately consider sitting behaviour in all contexts as this may assist hypotheses about potential mechanisms and the appropriate selection of potential confounding factors. Self-report measures are able to provide this vital contextual information.

2.2.3. Reliability and validity of self-report measures

Ultimately the usefulness of a self-report measure is dictated to a large extent by properties of its test-retest reliability and criterion validity.[75] Test-retest reliability pertains to the consistency or repeatability of a measure i.e. the extent to which repeated measurements would yield the same results.[76] A number of studies have sought to examine the reliability of self-report measures of overall or domain specific sedentary time. The self-report measures used in these reliability studies have varied in terms of recall period from three days[77-80] to three months,[81] in administration method (telephone or interview) and target population. This makes the comparison of findings between studies problematic. Accordingly a recent review demonstrated that the correlation between test and retest measures varied widely.[61] Studies examining single items for total sedentary time or composite measures of sitting from multiple domains reported correlational coefficients (intra-class correlation, Spearman's rho, or Pearson's r, depending on the information available) for repeated tests of between 0.37 and 0.97.[61] Domain specific measures of sedentary behaviours including TV viewing, computer use, sitting at work and while commuting were similar with correlation coefficients ranging between 0.32 and 0.93.[61] Overall the majority of self-reported sedentary time measures showed moderate to high correlations with magnitudes similar to those reported for physical activity measures,[82] and indicating acceptable to good test-retest reliability.[61] Healy et al also comment that stronger reliability was generally observed for sedentary behaviours that tend to be undertaken on a regular basis and for prolonged periods of time, than for more sporadic or less regularly performed behaviours.[61] This is consistent with another review which reported that the strongest reliability outcomes were from questions regarding TV viewing and

leisure time computer use where intra-class correlation coefficients were moderate to high, while the poorest were from leisure-time telephone use which might occur less regularly and for shorter durations.[41] It is also possible that the different types of sedentary behaviour are more or less habitual and that low correlation coefficients represent actual variations over time rather than a weakness in the measure.

Studies seeking to validate self-report measures of sedentary time most commonly examine criterion validity relative to sedentary time measured using accelerometers,[83] heart rate monitors[84] or behavioural logs.[52] Most studies have shown low to moderate correlations with accelerometer derived sedentary time for both single items relating to total sedentary time,[80 82 85 86] and for composite measures of sitting in a number of domains.[87-90] Although direct comparison between validation studies is difficult due to differences in criterion measures, correlations tend to be higher for domain specific measures[61] particularly TV viewing, computer use and work related sitting. However caution must be taken when interpreting these findings. Criterion validity refers to the extent to which a self-report measure is related to a recognised or standardised criterion, usually a gold standard measure.[76] However, the criterion measures used in these validation studies (accelerometers) are not gold standard measures of sedentary time and are subject to their own errors and biases[61] that will be discussed in greater detail below.

Results from studies examining the reliability and validity of self-report measures of sedentary time suggest that perhaps the measurement of domain

specific behaviours is preferable. The better test-retest reliability and validity associated with these measures is logical when it is considered that recalling a specific behaviour which occurred for a substantial and more sustained period of time (for example sitting and watching a particular TV programme/film or at work for a number of hours) is easier than trying to recall total sedentary time which would include a mixture of sedentary behaviours that vary in frequency, duration and pattern. In light of these differences if a measure of total sedentary behaviour is required then all sedentary behaviours will need to be assessed rather than relying on a single behaviour as a proxy of the total.

2.2.4. Strengths and limitations of self-report measures

As discussed, self-report measures are relatively inexpensive and are suitable for population surveillance as they can be easily implemented on a large scale. In addition the reliability and validity of self-reported measures of sedentary time, while very variable, are comparable to self-reported measures of physical activity,[61] with most studies demonstrating acceptable test-retest reliability and moderate agreement with criterion measures. The ability to obtain information on a range of different sitting behaviours at the same time is also a fundamental advantage of using self-report methods. Although the postural topography and biomechanical aspects of sitting do not change between contexts, the next chapter will refer to evidence which suggests that the pattern of sitting, in terms of the number of interruptions or breaks in a sustained period may be important in understanding the association with health outcomes. Therefore, the pattern of each sedentary behaviour within each day may also be required in addition to total daily duration and weekly frequency.

2.2.4.2. Limitations of self-report measures.

There are a number of limitations of the use of self-report measures to assess sedentary behaviour. These include the potential for exposure misclassification, the costs of data processing and the potential participant burden of various self-report measures.

The participant burden associated with self-report measures of physical activity and sedentary behaviour is dependent on the specific measure employed. Questionnaires generally require estimates of typical sedentary behaviour or the recall of sedentary behaviours over a specific time period (a week or a month is common). Participants are administered the questionnaire at one time point for a given measurement period (there may be more than one measurement period if repeated measures are used to track changes in behaviour over time), and therefore the participant burden is fairly small. Conversely, there is considerable participant burden associated with the use of activity logs as most require the recording of behaviour at very short intervals for the duration of the measurement period. This may be particularly burdensome when assessing behaviours as ubiquitous as sitting. This burden may affect response rates and compliance[41] to measurement protocol which may lead to selection bias in the sample if those who complete the log are different from those who do not. However behavioural logs differ in their specific requirements. The log developed by Ainsworth et al[58] requires participants to record physical activity and sedentary behaviours only at the end of each day, so is perhaps less burdensome than others.

The cost and complexity of data processing must also be considered when selecting a method to measure sedentary behaviour. As discussed an advantage of using self-report measures is the ability to collect detailed information on specific behaviours in the contexts in which they occur. However the volume and detail of this data can make it complicated to reduce, and analyse. This is especially true considering the range of specific sedentary behaviours that occur in a variety of contexts, sometimes for short periods.

While questionnaires may be relatively inexpensive to produce and distribute the administration costs of using behavioural logs for large scale studies can also be prohibitive,[91] although a number of new approaches and technologies have the potential to reduce costs. The US National Cancer Institute has recently developed and tested an internet based method for recording physical activity and sedentary behaviours.[91] While it must be acknowledged that not all members of a given population will be familiar with internet use or have routine access to the internet this approach certainly holds promise. The ease of distributing and retrieving data on sedentary behaviour for a vast number of people both nationally and internationally is an obvious advantage over sending hard-copy activity logs via post that then require data entry and processing. The ease of altering digital content both over time and for cultural relevance also allows a great deal of flexibility at relatively little expense.[91]

As discussed above it is likely that some sedentary behaviours are easier to recall than others depending on their regularity or duration, and recalling the

pattern of sedentary behaviours (in terms of the number of breaks or interruptions in a given period) is likely to be especially challenging and therefore a significant limitation of self-report measures. In addition, it is possible that as a consequence of increased public awareness of the potential consequences of inactivity, reporting of sedentary time may be influenced by social desirability bias leading to an underestimation of the true scale of the exposure.[60] All of these factors may lead to misclassification of sedentary time. Exposure misclassification can either be non-differential (the probability or degree of misclassification is the same across population subgroups) or differential (the probability or degree of misclassification differs between population subgroups).[92] Non-differential misclassification tends to have the effect of disrupting exposure-outcome trends and will attenuate estimates of true effect towards null.[92] Differential misclassification could be observed if the degree of misclassification was associated with either the exposure (for example sedentary time) or an outcome (for example disease risk), or membership to a particular population subgroup or groups, and could potentially move estimates of effect away from the null leading to incorrect conclusions. The risk of misclassification of the true level of behaviour has to be weighed against the low cost of self-reports when making decisions about measurement selection.

Issues of misclassification or error in the measurement of physical activity and sedentary time caused by imperfect recall or bias in reporting are well recognised.[93] Objective, device based measurement of sedentary time, can address these issues and is therefore an attractive alternative to self-report

measures. Recent technological advancements have allowed device-based measures to become an increasingly popular choice in the large scale measurement of physical activity and sedentary behaviour.

2.3. Device-based measures for assessing sedentary behaviour

Device based measures have been used in large scale observational studies to assess sedentary time, and their utility depends on a number of factors. Firstly it is important to consider what an individual device is actually measuring. To date, no large scale studies have employed devices which can specifically identify sitting; rather they assess physical or physiological markers associated with sitting (such as heart rate or movement). For this reason there is likely to be some exposure misclassification inherent in any measurement. The sources and potential extent of this misclassification must be considered when evaluating the strengths and weaknesses of device based measures. Similarly the participant burden involved must also be considered as this may determine participant drop-out which if differential may cause sampling bias and distort any observed associations. The practical and logistical aspects of various device based measures (cost, complexity of programming and administering to participants, and data reduction and processing) must also be considered. Two main device based measures (heart rate monitors and accelerometers) have been used to assess population level sedentary time to date and these are evaluated below using these criteria.

2.3.1. Heart rate monitoring

Berggren and Christensen[94] observed a linear relationship between heart rate and oxygen consumption over 60 years ago. This linear relationship has subsequently allowed researchers to estimate physical activity intensity from acquired heart rate data.[95] Modern heart rate monitors such as the Actiheart (Actigraph, Pensacola, Florida US) consist of a lightweight transmitter which is attached to the chest by adhesive electrodes. Real time heart rate data is then transmitted via short wave telemetry and to a receiver, usually hidden in a watch, where it is recorded. Physical activity can be classified by intensity using predetermined heart rate thresholds. Such systems have also been utilised to objectively measure sedentary time by applying an individually calibrated threshold value known as Flex Heart Rate (FHR) to recorded heart rate data, below which an individual is assumed to be engaged in sedentary behaviour. In order to obtain this individual threshold value, both resting heart rate and heart rate response to graded exercise need to be assessed. Flex Heart Rate is then determined as the mean of the highest resting heart rate and the lowest heart rate while exercising.[95-97] This has then been applied to free-living heart rate data with all time spent at a heart rate lower than or equal to FHR assumed to be sedentary time.[83 98 99] Ceesay et al[100] examined the criterion validity of this approach in assessing activities of different intensities. Energy expenditure predicted from heart rate yielded a small non-significant underestimation (1.2% [95% CI -11.4% to 10.6%]) of true energy expenditure measured simultaneously using indirect calorimetry.[100]

2.3.1.2. Strengths and limitations of heart rate monitors

Assessing sedentary time in this way eliminates the misclassification associated with self-report measures and has been shown to be effective in estimating physical activity and energy expenditure in adults.[100] [101] The relatively cheap unit cost and low participant burden (particularly for short measurement periods) makes them suitable for use in most populations. The application of individually calibrated Flex Heart Rate thresholds also make data analysis fairly simple. Acquired heart rate data can be used to determine frequency and duration of bouts of sedentary behaviour as well as total daily sedentary time, and periods where the monitor has been removed are easily identifiable.

However, a number of limitations must be acknowledged regarding the use of heart rate monitors to assess sedentary behavior including its inability to determine posture and the potential limitation of the association between heart rate and energy expenditure at low activity intensities.

The most important limitation of using this method to assess sedentary time is that heart rate monitoring systems do not measure the posture of sitting, rather they infer lack of movement based on low heart rate recordings.[102] In order for FHR to truly represent lack of movement the linear relationship between heart rate and energy expenditure would have to be unaffected by any factors other than movement. Further, for the FHR to represent sitting, rather than just lack of movement, it would need to differentiate between sitting and

standing. In reality, the changes in heart rate between sitting behaviours and standing/slow ambulation are small, making this distinction very difficult. In addition at low intensities factors such as climate, anxiety, feeding and caffeine intake may confound the association between heart rate and movement, potentially leading to misclassification of sedentary time as activity. There is also a slight lag effect between initiation of activity and heart rate response which would also contribute to misclassification.[103]

2.3.2. Accelerometers

Accelerometers are small lightweight devices, usually worn on the wrist or hip, which measure body movements in terms of their acceleration.[61] Acceleration refers to a change of speed over a given time and is measured in metres per second squared (m/s^2) or expressed in gravitational acceleration units (*g*: where 1 *g* is equal to 9.81 m/s^2).[104] Most accelerometers contain one or more piezoelectric acceleration sensors. When these sensors undergo acceleration the piezoelectric element within the sensor is subject to deformation. This deformation causes a displaced charge to build up on one side of the sensors which generates output voltage proportional to the applied acceleration.[104] Uniaxial accelerometers (such as the Actigraph 7164 and GT1M models [Actigraph, Pensacola, Florida, US]) measure acceleration in a single orthogonal plane (the vertical plane), while triaxial accelerometers (such as the newer Actigraph GT3X and GT3X+) are able to measures accelerations in three orthogonal planes (vertical, anteroposterior, and mediolateral planes).[105] While it would seem advantageous to quantify acceleration in more than one axis very high levels of agreement have been reported (Inter-class

correlation coefficient= 0.99) between uni and triaxial models (Actigraph GT1M and RT3 [Stayhealthy, Monrovia, California])[106] when measuring sedentary behaviour and physical activity of different intensities. Newer models of accelerometer provide an output in the form of raw acceleration data in the SI units described above. However in studies that have examined sedentary behaviour, which have employed older models of accelerometer (most commonly the Actigraph 7164 or GT1M), the raw voltage signal describing the magnitude and direction of acceleration is then converted from the SI units, to a dimensionless unit known as a 'count'.[61] Accelerometer counts are then summarised over a user defined period, or epoch, and are then used to make inferences about behaviour or activity intensity/energy expenditure. Generally counts registering under a pragmatic yet somewhat arbitrary threshold[107] (for example <100 counts per minute) have been used to identify sedentary behaviour.[32 54 108-110]

Various studies have validated the use of accelerometers for the assessment of free-living activity in adults by examining the agreement between a range of devices (and associated data cut points for sedentary time and physical activity) with energy expenditure measured in both controlled laboratory settings using direct calorimetry[111] and in field validation studies using indirect calorimetry.[112 113]

A number of studies have assessed the validity of accelerometer data cut-points for use in the assessment of free living physical activity and sedentary behaviour.[113-116] Kozey-Keadle et al[115] examined the criterion validity

of an Actigraph accelerometer in classifying sedentary time using the threshold value of 100 counts per minute. It was observed that compared to direct observation the Actigraph underestimated sedentary time by 4.9% (SE 3.4%). Nevertheless data from hip mounted Actigraph accelerometers from a number of large scale population studies including the National Health and Nutrition, Examination Study (NHANES),[54] The Australian Diabetes and Lifestyle Study (AusDiab)[34 110] and the ProActive UK study,[117] have been used to examine the associations between sedentary time and a range of health outcomes.

2.3.2.2. Strengths and limitations of the use of accelerometers

The size and weight of accelerometers makes them relatively unobtrusive. This allows them to provide information on movement patterns with minimal burden to the user, [118] that is free from the random and systematic errors associated with self-report measures.[119] The objective and continuous assessment of movement also allows the capturing of short sporadic bouts of sedentary behaviour which may be difficult to accurately recall and quantify using self-report measures.

There are also a number of limitations in the use of accelerometers to define sedentary time which must be acknowledged including the difficulty in comparing findings between studies, the inability of accelerometers to define posture and the potential for misclassification.

To date population based research examining the associations between accelerometer defined sedentary behaviour and health have employed accelerometers which provide the movement output in counts. Commercially available devices will differ in the way raw acceleration data is converted, filtered and summarised into ‘count‘ values which prevents the comparison of outputs from different devices. The choices of sampling frequency and data cut-points (≤100 counts per minute is the most common but cut points of up to 200 counts per minute have been used)[120] may also limit the comparability of results across studies even if they have used the same device.

Accelerometer based measures allow only the approximation of total sedentary time as it is not possible to distinguish between different sitting activities. As different sitting activities have different correlates and determinants and therefore may also have differential associations with health outcomes, the inability to differentiate between them is a key limitation.

It must also be recognised that like heart rate monitors, accelerometers do not measure sitting behaviour itself, rather they measure movement. The assumption is that a level of movement below that determined by an arbitrarily defined threshold is achieved through sitting. Indeed a key limitation of the use of accelerometers to define sedentary time is the inability to discern sitting from standing[107] and although widely used the 100 counts per minute cut-point was not empirically derived.[115] This of course may lead to a degree of misclassification as levels of movement similar to those recorded during sitting could be observed during standing.[121] It has been observed that the 100 counts

per minute threshold can also be exceeded during sitting.[42] Kozey et al observed that hip-worn Actigraph accelerometer outputs for activities including standing while folding laundry or washing dishes can be near or even below 100 counts per minute.[121] Conversely Kozey-Keadle et al[115] compared the utility of five different Actigraph cut-points for identifying sedentary time (50, 100, 150, 200 and 205 counts per minute) and found that the 100 counts per minute significantly underestimated sedentary time and that a cut point of 150 counts per minute was more accurate. In fact all of the cut-points examined over or underestimated observed sitting behaviour to a greater or lesser extent, which highlights the importance of the chosen threshold value to the extent of the potential exposure misclassification. A number of other recent laboratory based studies also suggest that only 50-60% of sedentary behaviour is accurately classified using established cut-points.[107 122-124] This imprecision may not only lead to incorrect estimates of the population prevalence of sitting time but may also mask true associations with health outcomes.

2.3.2.3. Methodological considerations for the use of accelerometers in determining sedentary time

There are a number of other important methodological considerations associated with the use of accelerometers to measure sedentary behaviour, including issues of compliance, variations in accelerometer wear time, and the determination and exclusion of periods of non-wear.

2.3.2.3.2 Non-compliance with wear time protocol

In existing population studies which have used accelerometers to define sedentary time [54 110 117] participants were instructed to wear accelerometers for seven days during all waking hours and to remove them only for water based activities (as the units used in these studies are not water proof). A number of wear time criteria are imposed to determine whether a person's data are included in analyses. Typically a person must have between one[32] and four[110] valid wear days each with at least 600 minutes of wear time. However compliance with accelerometer protocol has been poor in a number of these population studies. For example in the 2003-2006 NHANES cohort only 40-70% of participants (compliance varied by age group) wore a hip mounted accelerometer for the required 600 minutes per day for 6 days.[125] This in itself can introduce a selection bias within the data as compliance and therefore inclusion, may vary between population subgroups. Several approaches have been undertaken by researchers to promote compliance to accelerometer protocols including daily monitoring logs, education about the monitor and its proper wear, reminder phone calls, financial incentives and identification of individual barriers to compliance[126] with varying degrees of success.[127] However low levels of compliance and the subsequent possibility of selection bias remain significant issues in device based measurement of sedentary behaviour.

It is possible to increase compliance by reducing the number of valid days needed for inclusion in the analysis, which may reduce the effects of selection bias. However this has its own limitations. By including participants

with only one or two days of valid wear time, the number of weekdays and weekend days will vary between participants. For adults in employment it is logical that sedentary and physical activity behaviours will be more discretionary at weekends than on weekdays when they may be working. Therefore any estimate of average daily sedentary time will be affected by the number of weekdays and weekend days included in the measurement period. The only way to rule out this possibility is to ensure that all participants are measured on the same days (or the same number of working and non-working days) or to obtain seven valid days of accelerometer data from each participant.

2.3.2.3.3. Variations in wear time

Even within a sample of people whose data meets the criteria for inclusion, individual accelerometer wear time can be highly variable [61] In order to account for this studies have adjusted analyses for minutes of daily wear time,[128 129] or additionally reported sedentary time as a percentage of wear time. [61] However, there is potential for further bias in the estimation of sedentary time depending on the definition of a valid measurement day and the time of day that the monitor is worn.[130] The majority of adults are awake for more than 10 hours on any given day meaning that the inclusion of data based on only 10 hours (600 minutes) of wear time may exclude a significant amount of measureable activity. This is particularly important in the measurement of sedentary behaviours as it is logical that adults may engage in sedentary behaviours both during their working day and between the end of their working day and when they go to bed. If an individual had worn an accelerometer from the time they awoke, at for example 7.00am, for only the required 10hrs, their data would be

included in analyses despite excluding any activity (including presumably at least some sedentary time) after 5.00pm. The use of these wear time thresholds can also cause comparisons to be made between individuals for whom the measurement periods were markedly different. If two individuals had exactly the same daily activity profile but one was assessed between 7.00am and 5.00pm and the other was assessed between 12.00pm and 10.00pm, their measured sedentary behaviour and physical activity may be very different. In this way both low compliance and decision rules regarding wear time lead to selection bias and misclassification that affect the precision of estimates of sedentary behaviour.[130]

2.3.2.3.4. Measurement and exclusion of non-wear time

Any periods in which the accelerometer was not worn must be excluded from any analysis of activity, although the method by which non-wear time is identified may also cause misclassification. Criteria for identifying non-wear time within accelerometer data is established a priori. Periods of 'zero counts' (thought to reflect no movement) of a predetermined duration are considered non-wear time. Periods of 60 minutes or more of zero counts have been used to define non-wear time in population studies examining using accelerometer defined sedentary time.[34 54 117] However it is possible that periods of zero counts could reflect either non-wear time or sedentary behaviour,[131] indeed a recent study observed that of 8 accelerometer cut-points examined (0, 5, 10, 15, 20, 25, 50 and 100 counts per 15 second epoch), a cut-point of zero counts per epoch was actually the most sensitive for identifying sitting behaviour.[107] An inability to adequately make the distinction between periods of non-wear and

sitting could lead to an over estimation of sedentary time and exclusion of these periods could equally lead to an underestimation of total daily sedentary time.

2.3.5. Developments in device based measures

The emergence of newer devices and techniques may help address a number of these issues for future population based studies. The activPal Professional physical activity monitor (PAL technologies Ltd, Glasgow, UK) is an inclinometer based device that adheres to the midline of the anterior aspect of the thigh with custom adhesive pads. Due to its unique positioning the inbuilt inclinometer is able to distinguish between sitting (when the thigh would be more or less horizontal) and standing or walking (when the thigh would be vertical). In addition to this it is able, like other devices, to monitor ambulation. The activPal has allowed researchers to differentiate between sitting and standing[132] and has been validated for the measurement of sitting and walking in adults,[133] for examining posture during free living activities,[134] and for examining total sedentary time in both adults[115] and children.[135] It has also demonstrated better agreement with direct observation of sedentary time than an Actigraph accelerometer (model GT3X).[132] The ability to distinguish sitting from standing significantly reduces the possibility of misclassification usually associated with the use of arbitrary cut-points in accelerometer count data to determine sitting. However the activPal has a number of limitations regarding its use in population surveillance. Firstly the accurate positioning and attachment of the monitor may necessitate its attachment by an investigator rather than the participant, preventing the monitors being sent to study participants in the post. The monitors are not waterproof and therefore require removal or covering with

a custom waterproof sheath when bathing or swimming. Although there is no available data on compliance with activPal monitors within large samples these steps would add to participant burden and could potentially contribute to non-compliance or participant drop-out. Removal of the monitor for bathing would also increase non-wear time, particularly if it is not reattached immediately afterwards. In addition a number of studies have observed a degree of misclassification of sitting behaviour as standing. This may be due to irregular sitting postures such as sitting on the edge of the chair.[136]

Studies using accelerometers to examine sedentary time have, to date, used hip mounted accelerometers. The placement of accelerometers on the hip is most commonly used,[137] in order to capture movement near the wearer's centre of mass.[138] However wrist worn accelerometers such as the GENEActiv may improve compliance.[139] Indeed in the 2011-2012 NHANES wrist worn accelerometer study compliance has been reported as being between 70 and 80% for six valid days of data with a median daily wear time of 21-22 hrs per day (compared to 40-7-% using hip worn accelerometers in the 2003-2006 NHANES). A subsample of participants from the 11th Phase (2012-13) of data collection in the Whitehall II cohort study were also asked to wear a wrist mounted GENEActiv accelerometer and over 94% of participants met the wear time inclusion criteria (≥ two weekdays and two weekend days).[140]

In addition, several newer monitors including the Actigraph GT3X+ and the GENEActiv (ActivInsights Ltd, Kimbolton, Cambridge UK) can not only be worn on the wrist but can be worn in water which eliminates the need to remove

the monitor at any point during a given measurement period. The possibility of 24 hour monitoring would provide a far clearer more inclusive measure of a person's activity and would reduce the potential misclassification associated with minimum wear time thresholds and the identification of non-wear time. Twenty-four hour monitoring would be of particular benefit when assessing sedentary behaviour as it is logical to assume that people are likely to engage in sedentary behaviours first thing in the morning (for example when they are sitting eating breakfast) or at the end of the day before they go to sleep and that these periods are the most likely to be affected by missing data due to non-wear.

Developments in the treatment of accelerometer output data also have the potential to improve the precision with which sedentary behaviour can be measured. The Actigraph GT3X+ and the GENEActiv monitors provide output in the form of raw unfiltered acceleration data which not only allows direct comparison between monitors and between studies but also allows the use of pattern recognition approaches to identify sitting.

Pattern recognition is a branch of artificial intelligence concerned with classifying or describing observations from numeric data using a set of pre-determined patterns or algorithms. When applied to accelerometer data the identification of behaviours using the characteristics of their specific data pattern would seem to address many of the problems inherent in the use of movement cut-points to denote specific activities.[42] These patterns are determined using a 'training' study featuring the behaviours or activities of interest and can then be

used to identify these same behaviours in real time surveillance data. In this case statistical or structural patterns in raw acceleration data associated with specific activities such as sitting or standing can be recognised and quantified providing precise real time data on the patterns frequencies and durations of sedentary activities. Studies have shown reasonable success in classifying a small range of controlled physical activities in adults.[136 141]

The utility of pattern recognition is highly dependent on the activities used in the training study although there is evidence that it can be used to identify sitting behaviour with a reasonable degree of accuracy.[142] One example of this approach is the 'Sedentary Sphere', a tool developed by GENEActiv for the analysis of data from a wrist worn GENEActiv monitor. When triaxial wrist acceleration data are plotted in three dimensional space, periods of consecutive points form distinct clusters which can be differentiated by their position and distribution. When a person is sedentary, gravity provides the primary signal to the monitor and the clusters are distributed on the surface of a sphere of radius 1 *g*.[143] Any additional acceleration caused by movement will cause the clusters to depart from the surface of the sphere to a greater or lesser extent depending on the magnitude of the acceleration. The positioning of the clusters during various activities can, once observed, be used to identify the same activity in the future. The identification of sitting from data plotted on the sedentary sphere is based on the proximity of the clusters to the surface of the sphere indicating little or no acceleration, and the most likely posture based on the orientation of the arm. Higher than 15 degrees below the horizontal indicates a sitting or reclining position and lower than 15 degrees below the horizontal indicates a

standing position. A recent validation of this method showed that classification of sitting during free-living conditions was significantly correlated with sitting measured using the activPal monitor (r=0.93, p<0.001).[144] Although the degree of misclassification will most likely depend on the population under observation, the classification of the postural aspects of sitting using data from an accelerometer which can be worn on the wrist for extended periods without removal shows significant promise for the determination of sitting behaviour in future population studies.

As discussed a major limitation of current device base measurement is the absence of contextual information about the type of sitting activity which is being undertaken. Direct observation is the criterion standard for behavioural assessment although this is impractical in free-living settings. Direct observation is also often required in pattern recognition approaches to initially define data patterns for the identification of free-living activity.[42] The utility of pattern recognition approaches is dependent on the ability of defined patterns to accurately identify specific behaviours. Behaviour misclassification at the algorithm training stage will lead to inaccuracy in the measurement of free living behaviour. As such studies have employed laboratory based protocols with a small range of behaviours, which are directly observed, to train the algorithm simply because of this need for precision.

However, wearable cameras may provide a suitable proxy for direct observation, which is feasible to deploy in free-living environments. Cameras such as the Microsoft SenseCam[42] are worn around the neck and capture and

store thousands of daily images through a wide-angle (fish-eye) lens that maximises the field of view. This means that nearly everything that is seen by the wearer is captured by the camera.[145] Photographs are taken automatically every 30 seconds although a number of electronic sensors built into cameras such as the SenseCam prompt additional image capture in response to changes in light level or the detection of a person in front of the camera.[145] Images are downloaded, coded and postures and behaviours classified based on existing taxonomies. Wearable cameras have the potential to provide an important measurement advantage over other devices as they enable simultaneous domain and contextual information about sedentary behaviour to be collected.[42 146]

Image capture data may also allow greater understanding of the correlates of sedentary behaviours and the measurement properties of certain types of sitting. For example hip-stationary activities may be classified as sedentary by movement sensors when they are not (some resistance and conditioning exercises). Some activities occur concurrently such as sitting, watching television and eating and this is often not adequately captured by self-report.[42] Although sitting or TV viewing may be the behaviours of interest, associations between these behaviours and health may be confounded by dietary factors which may not be recorded and identified using self-report measures. Information from wearable cameras can be used alongside time-stamped accelerometer data to provide 24 hr information on both movement and activity type which would allowing the precise quantification of sedentary behaviours in the domains in which they occur. Coded images could also

support pattern recognition models by allowing the training of algorithms using free-living participant data featuring a wide range of activities. These algorithms could then be applied to large scale epidemiologic cohorts.[42] This approach has already been used in a study examining the behavioural characteristics of women at risk of breast cancer.[147]

2.4. Summary

The definition of sedentary behaviour proposed by Pate[2] and described in the previous chapter is ontologically complex as it combines two distinct concepts: behavioural topography (*'seated or reclining postures'*) and metabolic rate (*'do not require an energy expenditure substantially above resting levels'*). To date, researchers have often conflated the different features of sedentary behaviour (i.e. postural topography, type, and energy expenditure) by measuring one and inferring or ignoring the others.[20] Self-report measures identify time spent in certain sitting behaviours and it is assumed that energy expenditure is below 1.5 METs and movement is minimal (<100 accelerometer counts per minute), while accelerometers and heart rate monitors can measure movement or physiological consequences of movement and it is assumed that all activity below a predetermined threshold represents sitting.

Technological advancement in the field of physical activity and sedentary behaviour measurement has led to an increasing focus on device based measures.[93] However there are advantages and limitations of both self-report and device based approaches to measuring sedentary behaviour. Self-report measures are able to provide rich information on specific behaviours in context and allow the separate examination of these behaviours and their potentially

differential associations with health outcomes. However they rely on the accurate recall of often sporadic behaviours and are subject to misclassification, positive representation and bias.[42] Device based methods are able to provide accurate reliable data on movement over extended periods but as discussed they cannot discern posture and can introduce misclassification and bias due to decisions made regarding data processing.

Decisions on the use of various measures currently available would be greatly improved by a more comprehensive understanding of how sitting can negatively affect health. By establishing the underlying biological mechanisms it will be possible to identify which features of sitting behaviour are important from a health perspective and inform decisions regarding measurement.

Given the limitations of the current available methods for assessing sedentary behaviour in population studies, the ideal measurement tool would:

- Be accurate and reliable across different population groups
- Distinguish between sitting and standing/walking
- Provide contextual information about the various sitting activities which are being undertaken
- Be low cost, have low participant burden and be able to be worn continuously for extended periods of time
- Produce data that are easily analysed and interpreted [61]

Currently no such individual measure exists. The use of a combination of self-report and device based measurement would seem logical in order to achieve both reliable continuous assessment with qualitative information of

types of sedentary activities. However advances in objective monitoring (including newer devices such as wearable cameras) and in data treatment and analysis may in future allow the accurate identification of sitting behaviour in population studies during free-living conditions without the misclassification associated with self-report measures. These methods hold promise for the future of the surveillance of sedentary behaviour at a population level and will enhance our understanding of the associations between sitting and health.

Chapter 3

Review of current literature

3.1. Introduction and overview

Since sedentary behaviour was first identified as a potential independent risk factor for chronic disease a large body of evidence has developed regarding the associations between sitting and various health outcomes. In order to identify the outstanding research questions in this field it is first necessary to review the existing literature. The following chapter therefore contains a systematic review of existing research relating to sitting behaviour and four health outcomes: mortality (all-cause and cause specific), cardiovascular disease (CVD), metabolic disease and obesity. Following a discussion of the evidence regarding sedentary time and these four outcomes three subsequent sections will examine: evidence for associations between sedentary time and metabolic risk markers, the effects of sitting pattern as well as duration on the associations between sitting and health, and the potential biological mechanisms which might underpin the associations between sitting and health.

The case for a causal relationship between sitting time and health will also be evaluated. In 1965 Sir Austin Bradford-Hill proposed a set of criteria with which to evaluate the likelihood that an observed association between an exposure and an outcome is causal.[39] None of the nine criteria alone can infer causality: they were not intended as prescriptive rules which must all be obeyed before causality can be accepted. Rather they are nine perspectives from which

to examine the relationship between exposure and outcome. Bradford-Hill's nine criteria for causality are as follows;

1. Coherence

'How well does the idea of a detrimental effect of sedentary behaviour fit with current health trends? The cause-and-effect interpretation of the exposure outcome relationship should not seriously conflict with accepted facts about the outcome.'

2. Analogy

'Have associations between similar exposures and diseases been shown?'

3. Consistency

'Have the findings been replicated in different settings, using different methodologies/populations?'

4. Biological gradient

'Does there appear to be a dose response relationship between exposure and outcome?'

5. Strength

'The stronger the association between exposure and outcome the less likely it is to merely reflect the influence of some other aetiological factors'

6. Temporality

'Does the exposure precede the outcome or is reverse causality possible?'

7. Specificity

'Are the exposure and outcome measures specifically defined? Is there an inherent relationship between specificity and strength in that the more accurately defined the outcome and exposure the stronger the observed relationship should be?

8. Plausibility

'Is it plausible that sedentary behaviour affects health?'

9. Experiment

'The demonstration that under controlled conditions, manipulating the exposure causes change in the outcome.'

The extent to which the current evidence meets these criteria will be examined and the case for a causal association between sitting time and health evaluated.

As discussed there are a number of similar definitions of sedentary behaviour and a range of measurement tools have been used to try and quantify time spent in these behaviours in different ways. Despite this, a number of terms (sedentary time or behaviours/sitting/inactivity) have been used interchangeably and do not always accurately reflect what is being measured. It is therefore important, for consistency, to operationally define the relevant terms for the purposes of this review. As the term ‘sedentary behaviour’ refers to sitting activities (and the postural topography associated with sitting is an important part of the definition) the terms ‘sitting/sitting time’ will be used to refer to time spent sitting where some authors have used ‘sedentary time.’ Total sitting time will refer to sitting time from all spheres of life (occupational, transport and leisure time). Specifically measured sitting behaviours such as television viewing time or screen time refer to time spent sitting engaged primarily in that particular activity. Combined sitting measures such as ‘leisure time sitting behaviour’ comprised of a number of sitting activities will be detailed individually as they arise. As discussed in the previous chapter, objective measurement tools cannot determine changes in posture, (rather they measure movement or a physiological consequence of movement) so where an objective measure has been used to infer sitting based on accelerometry or heart rate monitoring the exposure will be referred to as objectively defined sedentary time (and the specific methodology detailed as necessary).

3.2. Methods

In order to assess the current evidence base regarding the association between sitting behaviour and health outcomes a systematic review was conducted using the Medline research database, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The focus of this review was studies examining associations between self-reported sitting or objectively defined sedentary time with mortality, cardiovascular disease, metabolic disease (including type II diabetes mellitus) and obesity published since 1st October 1991 (to give a period of 20 years from the first iteration of the literature search). As 'sedentary lifestyle' was only recognised as a medical subject heading (MeSH) term in 2010, the search protocol featured a broad range of search terms to incorporate exposures including specific common sitting activities and combined measures of sitting from a number of domains. Major topic headings were included for health outcomes (mortality, CVD, obesity, metabolic disease, metabolic syndrome X, and diabetes mellitus) as well as general search terms for these outcomes and associated risk factors.

3.2.2. Systematic review search strategies

The search strategy for the systematic reviews is detailed below.

Example Search Strategy

1 AND (2 OR 3 OR 4 OR 5 OR 6) AND 7.

1. sedentary[Title] OR sitting[Title] OR TV [Title] OR television[Title] OR sedentary lifestyle [MeSH Terms OR sedentary/epidemiology [MeSH Terms OR "sedentary"[Title/Abstract] OR "sitting"[Title/Abstract])

2. AND ("mortality"[MeSH Major Topic] OR "mortality/epidemiology"[MeSH Major Topic] OR "death"[MeSH Major Topic] OR all-cause mortality[Title] OR mortality[Title] OR death[Title])

3. AND ("cardiovascular disease"[Title] OR "cardiovascular risk"[Title] OR "cardiovascular diseases"[MeSH Terms])

4. AND ("type ii diabetes"[Title] OR "diabetes"[Title] OR "type ii diabetes mellitus"[Title] OR "insulin resistance"[Title] OR "insulin sensitivity"[Title] OR "metabolic syndrome x"[Title] OR "metabolic syndrome"[Title] OR "diabetes and complications"[MeSH Major Topic] OR insulin resistance[MeSH Major Topic] OR "metabolic diseases"[MeSH Major Topic] OR "metabolic syndrome x"[MeSH Major Topic])

5. AND ("obesity"[Title] OR "obesity/adiposity"[Title] OR "adiposity"[Title] OR "waist circumference"[Title] OR "body mass index"[Title] OR "body fat percentage"[Title] OR "obesity"[MeSH Major Topic] OR "overweight"[MeSH Major Topic] OR body mass index"[MeSH Major Topic])

6. Limits; English, Journal articles, Adults subjects, published between 01.10.1991 and present

Selection for the review was dependant on meeting a number of prespecified criteria. For inclusion, studies must:

1. Be cross-sectional or prospective in design

2. Report data on adults(≥18 years of age)
3. Employ a specific measure of sitting or sedentary behaviour/s. These measures could be self-report or objective, categorical or continuous, and could focus on sitting during leisure time and/or occupation sitting. Studies featuring measures such as sedentary lifestyle (as defined by an absence of moderate to vigorous physical activity) were also excluded.
4. Include one of the following as an outcome: Mortality, cardiovascular disease, metabolic disease, diabetes, or obesity.

The search was limited to articles published in English and searches for each health outcome were carried out separately. Articles related to mortality could feature analyses of sitting time with mortality from either all-causes or from specific diseases such as cardiovascular disease or cancer. Cardiovascular disease outcomes could include non-fatal myocardial infarction, heart failure, stroke or transient ischaemic attack (TIA), or a cardiometabolic risk score such as the Framingham score. Metabolic disease outcomes include type II diabetes mellitus, metabolic syndrome or insulin resistance. Obesity outcomes included BMI, waist circumference, weight gain or adiposity. The reference lists from papers meeting the inclusion criteria, and previous review articles were additionally searched by hand for relevant articles. Following literature searches and the removal of duplicate articles, titles and abstracts were reviewed to exclude articles outside the scope of the review. Full text versions of any potentially eligible articles were then obtained to ensure they met the inclusion criteria described above. The associations reported in the review are from the final fully adjusted models (where both adjusted and unadjusted models are reported) in each analysis presented in the individual

manuscripts. Fully adjusted models are compared to allow discussion of the treatment of well documented potential confounders such as BMI and physical activity. Figures 3.1-3.4 describe the evidence synthesis process and information flow through each phase of each review. Figure 3.5 illustrates the results of the evidence synthesis in terms of the number of positive, inverse and null associations reported between sitting time or objectively defined sedentary time and the four health outcomes in the existing literature.

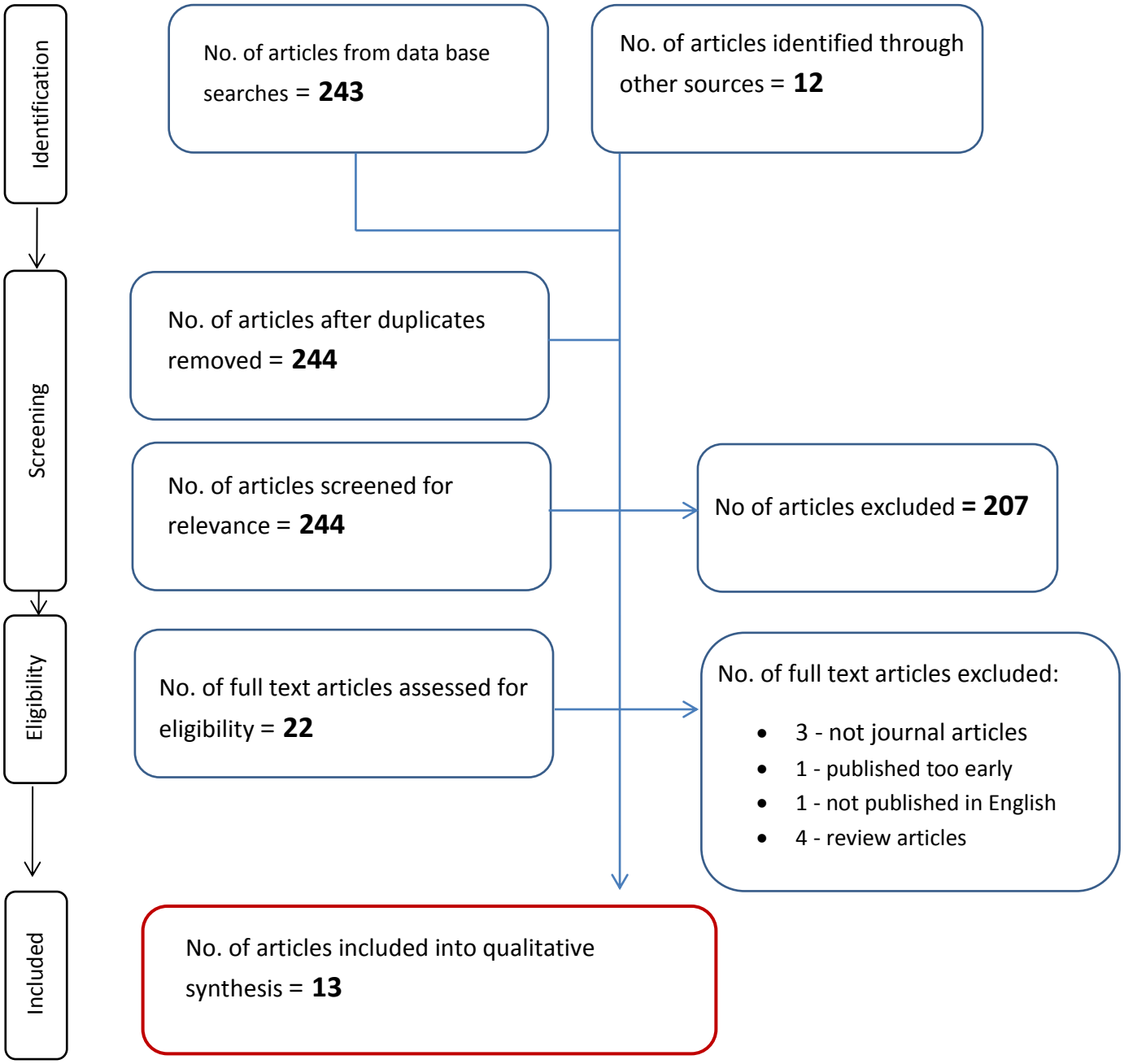

Figure 3.1. Evidence synthesis and information flow through different stages of the systematic review of studies examining sedentary behaviour and mortality risk

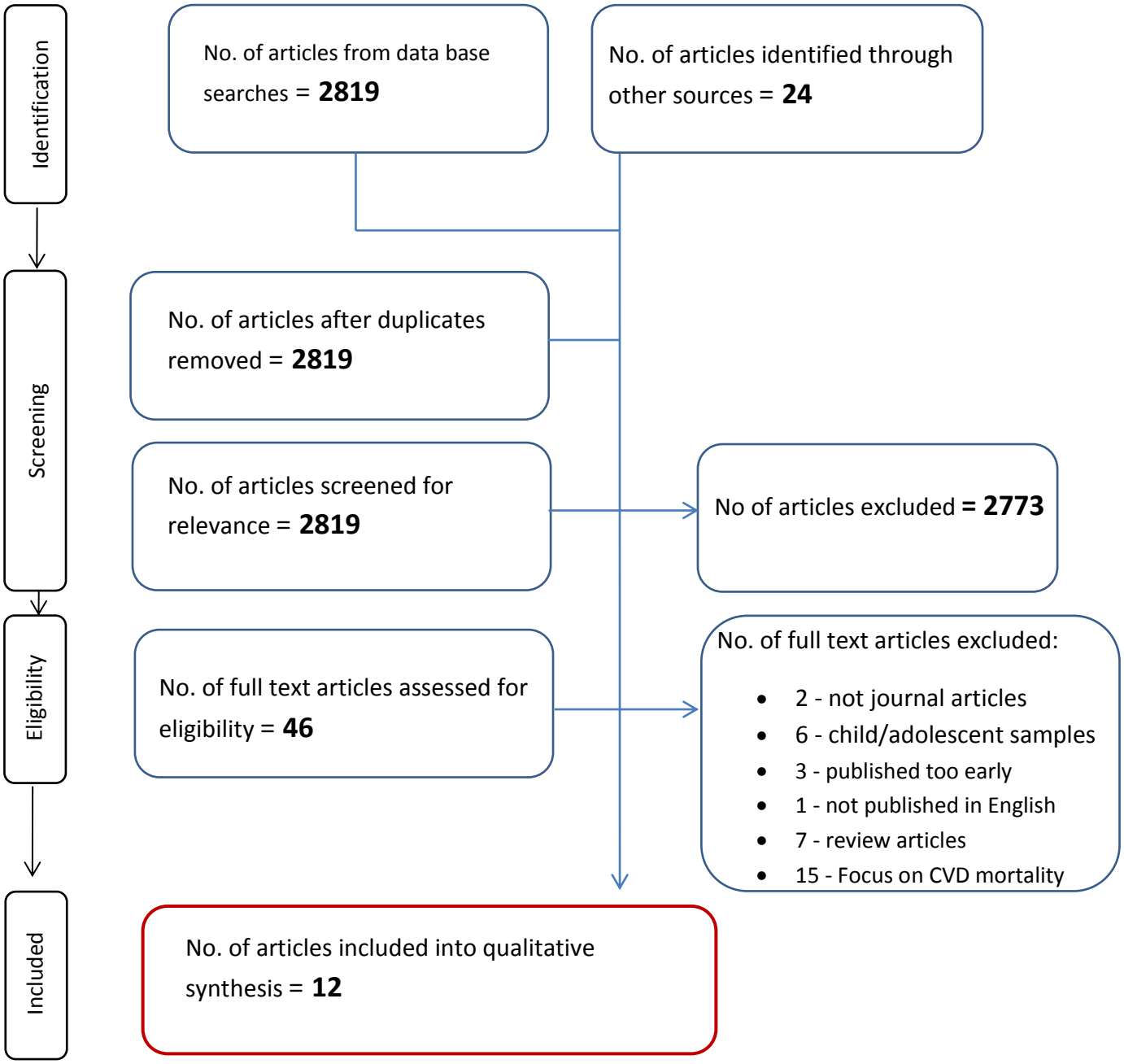

Figure 3.2. Evidence synthesis and information flow through different stages of the systematic review of studies examining sedentary behaviour and cardiovascular disease risk

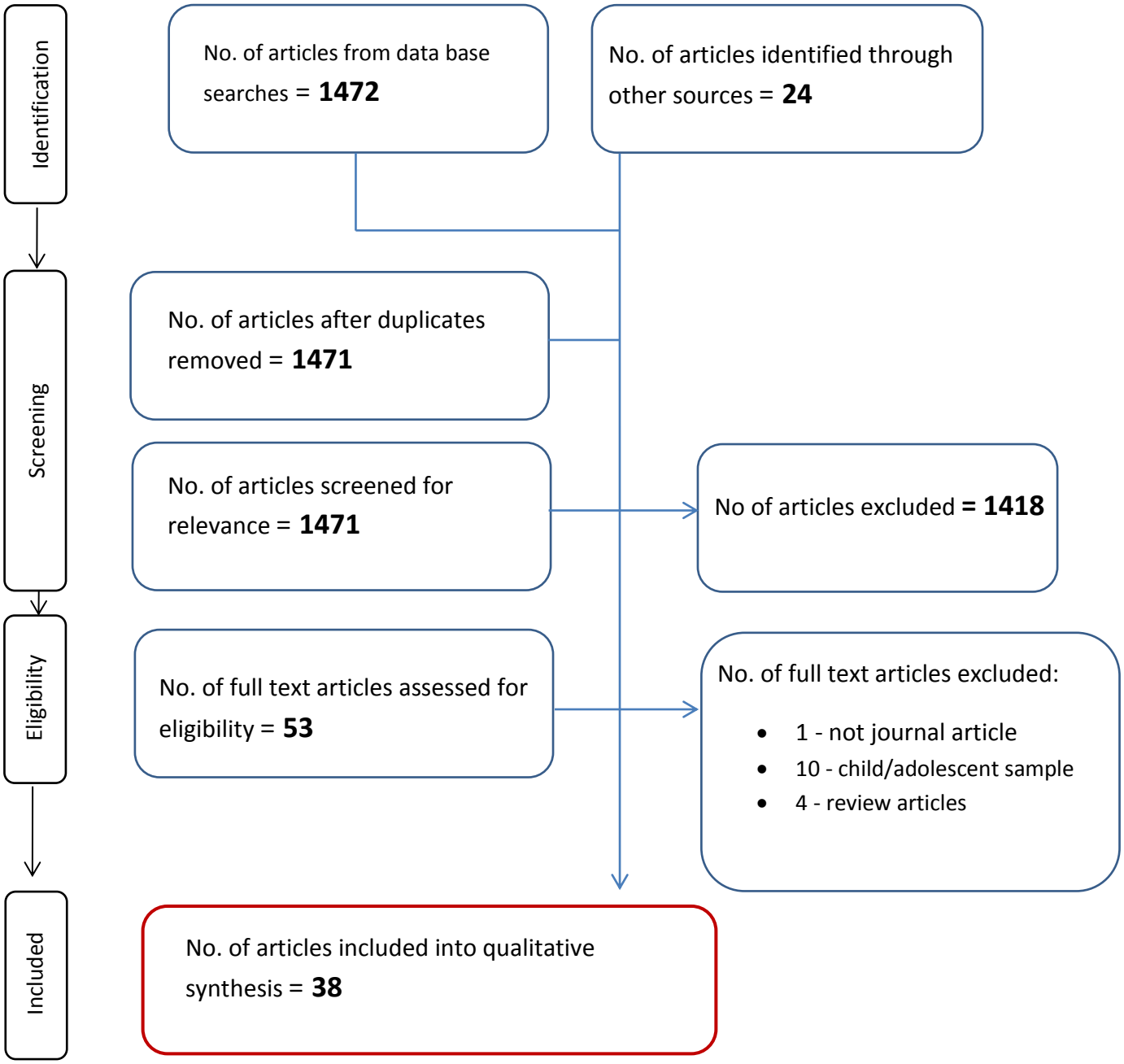

Figure 3.3. Evidence synthesis and information flow through different stages of the systematic review of studies examining sedentary behaviour and risk of metabolic disease including diabetes and insulin resistance

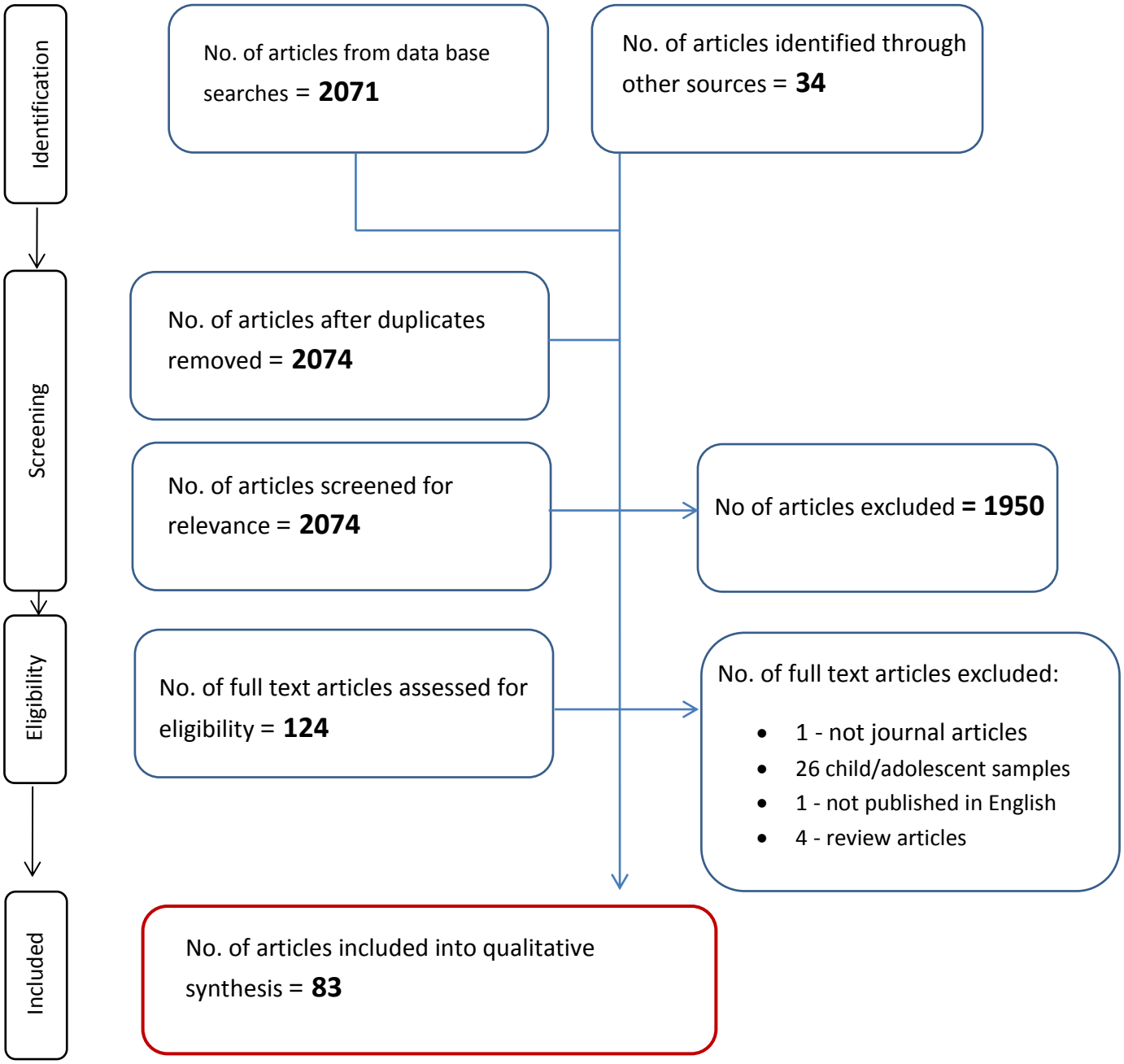

Figure 3.4. Evidence synthesis and information flow through different stages of the systematic review of studies examining sedentary behaviour and obesity, adiposity or weight gain.

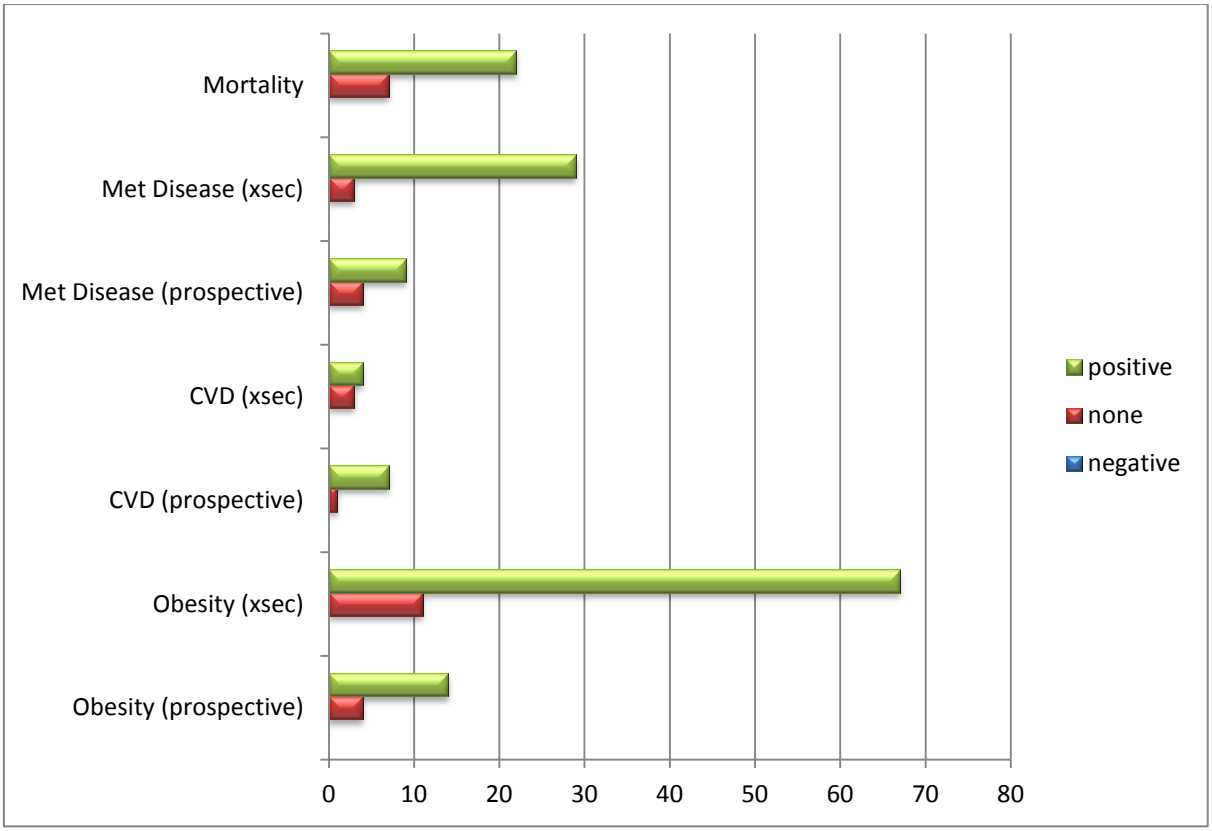

Figure 3.5. A summary of the number of individual cross-sectional and prospective analyses (including subgroup analyses) from studies (n=146) reporting positive, negative and null associations between sitting behaviour or objectively defined sedentary time and health outcomes including mortality, CVD, metabolic disease (including diabetes) and obesity. The green bars represent a positive association between sitting time and health, the red bars represent null associations and the blue bars represent negative associations.

3.3. Sedentary behaviour and mortality

There are currently thirteen published prospective studies examining the associations between sedentary behaviour and mortality.[53 55 62 67 70 148-155] A number of these studies have examined multiple mortality outcomes (29 sets of analyses are included in the review in total) and all have reported at least one significant positive association. These studies are summarised in appendix 1.1.

Twelve [53 55 62 67 70 148 149 151-155] of these studies employed self-report measures of sitting and of these, five focussed exclusively on TV viewing or screen time as their exposure,[53 65 67 70 154] while only two examined multiple sitting exposures.[70 148] One study examined associations between mortality risk and accelerometer defined sedentary time.[150]

3.3.2. Total sitting and mortality risk

The earliest analysis of the association between self-reported total sitting time was part of a study by Weller and Corey[155] who observed that sitting 'more than half the time' during the day was associated with an increased risk of all-cause and cardiovascular mortality. However, sitting was not the main exposure of interest in this study and the associations reported were unadjusted. There are a large number of health related behaviours, biological variables and demographic factors which may confound associations between sitting and health outcomes, and these must be accounted for in any analyses. Importantly, by not adjusting for physical activity it is not possible to examine whether sitting and physical activity are independent influences on health, which is a central hypothesis in this field of research. More recently Katzmarzyk et al [62] examined mortality rates in a representative sample of 17000 Canadians over a 12 year follow up period. Significant differences in mortality risk were observed across five categories of self-reported total daily sitting time. Overall a dose-response relationship was observed between categories of daily sitting time (*1. almost none of the time, 2. approximately one fourth of the time, 3. approximately half of the time, 4. approximately three fourths of the time, or 5 almost all of the time*) and mortality rate which remained significant when stratified by physical activity level, BMI and smoking status categories. As well as all-cause mortality

(Hazard Ratios [HR] 1.00, 1.00 (95% CI 0.86, 1.18), 1.11 (95% CI 0.94, 1.30), 1.36 (1.14, 1.63), 1.54 (1.25, 1.91); P_{trend} <0.0001) (P_{trend}<0.0001, significant positive relationships were observed with CVD (1.00, 1.01 [95% CI 0.77, 1.31], 1.22 [95% CI 0.94, 1.60], 1.47 [95% CI 1.09, 1.96], 1.54 [1.25-1.91] ; P_{trend} <0.0001) and other-cause (all causes except CVD) mortality (1.00, 1.06 [95% CI 0.78, 1.44], 1.15 [95% CI 0.84, 1.57], 1.65 [95% CI 1.18, 2.31], 2.15 [95% CI 1.47, 3.14]; P_{trend} <0.0001) but not cancer mortality. In largest prospective study of mortality and self-reported total sitting time, van der Ploeg et al[153] analysed data from 222497 participants from the Australian '45 and up' cohort study over a four year follow-up period. Increasing daily sitting time was positively associated with all-cause mortality risk (HR 1; 1.02, [95% CI 0.95-1.09]; 1.15 [95% CI 1.06, 1.25]; and 1.27 [95% CI 1.27, 1.55] for 0≥ and <4hrs/day, 4≥ and <8 hrs/day, 8≥ and <11 hrs/day, and ≥11 hrs/day respectively. Leon-Munoz et al[151] also observed that in 2635 older adults, changes in daily sitting time influenced mortality risk. Those who, over a nine year period, consistently reported a daily sitting time above the sample median had a 25% greater mortality risk than those who consistently reported sitting less than the sample median, and 19% greater mortality risk than those whose daily sitting time increased from below to above the sample median during follow-up. While previous studies have assumed that sitting time, measured once at baseline, is relatively stable, this is the first study to demonstrate how trends in sitting time are associated with mortality risk during the follow-up period.

Only one study has examined mortality rates across categories of accelerometer defined sedentary time. Koster et al[150] compared all-cause mortality rates across quartiles of daily sedentary time (defined as time spent at

≤100 accelerometer counts per minute) and compared to the reference category (lowest quartile), mortality rates were significantly higher in the third (HR 2.74, 95% CI 1.35, 5.52) and fourth (HR 3.26, 95% CI 1.59, 6.69) quartiles.

3.3.3. TV viewing and mortality risk

Dunstan and co-workers[53] examined television viewing and its association with mortality from all-causes, CVD and cancer in a sample of 8800 (3846 men and 4954 women) from the Australian Diabetes and Lifestyle (AusDiab) study over a six year follow up period. It was observed that an incremental increase of 1hr/day of television viewing was associated with an 11% (95% CI 1.03- 1.20) and an 18% (95% CI 1.03-1.55) increase in all-cause and CVD mortality risk respectively. Compared with a television viewing time of ≤2 hrs/day the fully adjusted hazard ratios for all-cause mortality were 1.13 (95% CI 0.87-1.36) for >2 to ≤4 hrs/day and 1.46 (95%CI 1.04 - 2.05) for >4 hrs/day. For CVD mortality, corresponding hazard ratios were 1.19 (95% CI 0.72 to 1.99) and 1.80 (95%CI 1.00 to 3.25). These figures are adjusted for age, sex, waist circumference, smoking status, alcohol intake, education, diet quality, blood lipid profile, glucose tolerance and leisure time exercise behaviour. No such association was evident between TV viewing and cancer mortality. In a study of over 13000 British men and women, Warren et al[154] observed that over 10 years of follow up each 1 hr/day increase in TV viewing time was associated with a 4% increase in risk of mortality from all-causes (HR 1.04, 95%CI 1.01, 1.09) and a 7% increase in risk of mortality cardiovascular disease mortality (HR=1.07, 95% CI 1.01, 1.15) following adjustment for age, family history, diabetes, blood lipids, smoking status, alcohol intake and adherence to physical

activity guidelines. Again, in this analysis no association was observed with cancer mortality.

In another British study of over 4500 participants from the Scottish Health Survey, Stamatakis et al [67] observed a significant positive association between hours of daily leisure screen based entertainment (including TV/video viewing, computer use and video gaming) with mortality risk over a 4 year follow-up period. They observed fully adjusted (covariates included age, sex, longstanding illness, occupational activity level, smoking status, alcohol intake, marital status, BMI and minutes of daily MVPA) hazard ratio for all-cause mortality of 1.52 (95%CI 1.06, 2.16) for those engaging in at least 4hrs/day of screen time compared to those who engaged in less than 2hrs/day.

3.3.4. Multiple discrete sitting behaviours and mortality risk

Only two studies have examined the associations between mortality risk and multiple sitting behaviours in the same cohort. Matthews et al[70] demonstrated that both TV viewing and total daily sitting time were associated with all-cause and cardiovascular mortality (P_{trends} <0.0001 for both) but not cancer mortality in over 240000 US adults following adjustment for age, sex, education, smoking, diet, race and MVPA. However Chau et al[148] observed that while self-reported total daily sitting time was significantly associated with all-cause and cardiometabolic disease related mortality (P_{trends} <0.0001 for both) following adjustment for covariates including MVPA, self-reported daily TV viewing and occupational sitting time were not.

All of the thirteen prospective studies examining the associations between an indicator of sitting or accelerometer defined sedentary time have observed positive associations with all-cause mortality. Those who examined mortality from cardiovascular disease also consistently observed increased risk with higher daily sitting time, although no associations have been observed between sitting and cancer mortality. These studies also all took steps to eliminate the potentially confounding effects of occult disease by repeating their analyses and excluding deaths which occurred in the first few years of follow up (range of 1[153] to 4[70] years). With the exception of the analyses by Weller and Corey all of the studies featured in this section of the review have adjusted their analyses for a wide range of relevant confounding factors including demographic (age, gender, socioeconomic position) and health related (BMI/waist circumference) covariates. These studies have also adjusted for health related behaviours including smoking status, alcohol consumption and time spent in MVPA. This is important as it suggests that the deleterious effects of high levels of sedentary behaviour on mortality risk are independent of MVPA.

3.4. Sedentary behaviour and cardiovascular disease

The following section of this review will examine evidence regarding the associations between sitting time and cardiovascular disease. As evidence for the relationship between sitting and cardiovascular disease mortality has been addressed above, the following section will focus on non-fatal cardiovascular disease/events or diagnosed associated conditions such as hypertension and atherosclerosis. There is a wealth of cross-sectional literature examining the association between sitting time and various biological risk markers for CVD.

Although these risk factors may contribute to CVD risk, these will be addressed in the subsequent section.

A summary of all studies examining sedentary behaviour and cardiovascular disease outcomes included in this review can be found in appendix 1.2.

3.4.2. Cross-sectional evidence

Six cross-sectional studies have examined associations between sedentary time and range of diagnosed conditions associated with cardiovascular disease.[29 156-160] Of these, five have employed self-report measures of either sitting time or TV viewing[29 156 157 160 161] and two have used accelerometers to define sedentary time as time spent below 100 accelerometer counts per minute.[158 159] Findings have been mixed. George et al[29] examined self-reported sitting time in a sample of over 63000 Australian men and observed no association with self-reported heart disease. Allinson et al[156] examined chronic adiposity associated inflammation in a diverse sample of 1543 participants in the Multi-Ethnic Study of Atherosclerosis. Time spent in a range of sitting activities such as reading, sitting, watching television and both recreational and non-recreational computer use was reported for a typical week. The authors observed a significant increase in adiposity related inflammation across tertiles of increasing total sitting behaviour which persisted following adjustment for age, gender, ethnicity, alcohol consumption, hypertension, diabetes, dyslipidaemia and waist circumference (P_{trend} <0.05). Studies have also observed positive cross-sectional associations between self-reported sitting time with acute coronary syndrome[161] (including Q-wave and non Q-wave myocardial infarction and unstable angina pectoris) and both self-reported[157]

and clinically diagnosed (as having a systolic blood pressure of at least 140 mm/Hg and a diastolic blood pressure of at least 90 mm/Hg) hypertension.

Two studies have also observed null associations between sedentary time and cardiovascular disease outcomes. Hamer et al[159] examined the association between accelerometer defined sedentary time (time spent at <100 counts per minute) and pericardial fat volume in 446 healthy participants from the Whitehall II study (mean age 66 ± 6 years). Pericardial fat was positively associated with sedentary time after initial adjustment for covariates but importantly was attenuated following further adjustment for MVPA suggesting the association is not independent of physical activity. In a separate study using a similar sample (443 Whitehall II participants), Hamer et al [158] observed no association between accelerometer defined sedentary time and coronary artery calcification. It is possible that these differential findings may be due to the choice of exposure measure (self-reported sitting versus accelerometer defined sedentary time). Two studies have directly compared associations of self-reported sitting and accelerometer defined sedentary time with cardiovascular disease risk markers and found associations to be markedly different.[162 163] Nevertheless it is also important to acknowledge that these studies examined different cardiovascular disease outcomes and it is entirely plausible that they may simply have differential relationships with sedentary behaviour.

It is necessary to acknowledge the possibility that diagnosed CVD may be a cause of increased sedentary behaviour rather than a consequence.

Cross-sectional studies by design cannot establish causal direction so examination of prospective evidence is required.

3.4.3. Prospective evidence

As described above, there are to date six published prospective studies which have examined the associations between indicators of sitting time and incident cardiovascular disease.[65 67 164-167]

3.4.3.2. Total sitting and cardiovascular disease risk

Three previous studies have examined associations between incident cardiovascular disease and total self-reported sitting time and findings have been equivocal. Manson et al[166] examined data from approximately74000 women enrolled in the US Women's Health Initiative Observational Study (WHI -OS) and observed an odds ratio for cardiovascular events (including myocardial infarction, heart failure, or stroke), of 1.38 (95%CI 1.07, 2.64) for women who reported sitting for longer than 16 hrs per day than those who sat for less than four hrs per day over a mean follow up time 3.2 yrs. No other durations of sitting were associated with a change in cardiovascular disease risk. Moreover these associations were adjusted for age and leisure time energy expenditure only. By not accounting for other factors associated with both sitting and cardiovascular risk, the possibility remains that the observed association may simply be due to confounding. A decade on from the study by Manson et al, Chomistek et al[167] extended these findings by examining associations between self-reported total daily sitting time using updated data from the WHI-

OS. They observed that over a median follow-up of 12.2 yrs the hazard ratio for any cardiovascular event was 1.18 (95%CI 1.09, 1.29) for women who reported sitting for more than 10 hrs per day compared to those who sat less than 5hrs per day. Similarly, compared to the reference group, the hazard ratios were 1.18 (95%CI 1.05, 1.32) for incident coronary heart disease and 1.21 (95%CI 1.07, 1.37) for stroke for those who reported sitting for more than 10 hrs per day. Sitting for between 5.1 and 9.9 hrs per day was not associated with an increase in cardiovascular disease risk. These analyses were adjusted for a broad range of covariates including age, race, education, income, marital status, smoking, family history of MI, depression, alcohol intake, hypertension, high cholesterol, a range of dietary factors, and leisure time physical activity.

These findings are inconsistent with those of Herber-Gast et al[165] who examined sitting and incident CVD in nearly 7000 women in the Australian Longitudinal Study on Women's Health. They observed no association between self-reported daily sitting time with incident cardiovascular disease over 10 years of follow up following adjustment for covariates (age, education, smoking status, alcohol consumption, leisure time physical activity and BMI). It is possible that these differential findings are due to differences in exposure to sitting, as the mean sitting time was far lower in the study by Herber-Gast et al compared to that in both Manson et al and Chomistek et al. However Wijndaele et al[65] observed dose-response associations between sitting time and incident CVD at one hour intervals starting at very low volumes of sitting time so a low sample mean sitting time should not necessarily prevent the detection of an association. The sample sizes in Manson et al and Chomistek et al were also

far bigger and therefore the number of reported cardiovascular events was far higher. However, with the available sample Herber-Gast et al still had enough statistical power to detect an effect size of 1.17 which is smaller than those observed in the WHI-OS studies.[166 167]

3.4.3.3. TV viewing and cardiovascular disease risk.

Three of six prospective studies examining associations between sitting and CVD have focussed on TV viewing or screen-based entertainment only and have all demonstrated positive associations with risk for cardiovascular events which are independent of MVPA.[65 67 164] Wijndaele and co-workers[65] examined the association between self-reported television viewing time and incident cardiovascular disease in 12600 participants (aged 49-75 at baseline) in the EPIC-Norfolk study between 1998 and 2007 (mean follow up 6.9 ±1.9 yrs). Television viewing time was positively associated with incident total CVD, non-fatal CVD and coronary heart disease independent of age, gender, education, smoking, alcohol, hypertension, dyslipidaemia, antidepressant medication, baseline diabetes status, family history of CVD, sleep duration, and total physical activity energy expenditure. There was an increase in risk associated with each hour increase in TV viewing time for total CVD (HR1.06 95%CI 1.03-1.08; 2620 cases), non-fatal CVD (1.06 95%CI 1.03-1.09; 2134 cases) and coronary heart disease (HR 1.08 95CI 1.03-1.13; 940 cases). The relative risk did not appreciably change when individuals who experienced a CVD event in the first year of follow up (n=237) were excluded. Additional analysis also demonstrated similar positive associations between TV viewing and incident cardiac failure (results not reported).

Stamatakis et al [67] also observed a hazard ratio for CVD events (defined as CVD related hospital episode including myocardial infarction, coronary artery bypass, angioplasty, stroke, heart failure) of 2.30 (95%CI: 1.33 to 3.96) for people engaging in greater than 4hrs of screen time per day (including television, computer and video game use) compared to those who engaged in less than 2hrs following adjustment for covariates (age, sex, ethnicity, social class, longstanding illness, marital status, diabetes, hypertension, and leisure time physical activity).

3.5. Sedentary behaviour and metabolic disease

The following section of this review will examine evidence regarding the associations between sitting time and metabolic disease, focussing primarily on type II diabetes and metabolic syndrome. These conditions are closely linked in terms of their pathology and have separately received a significant amount of research attention in the sitting literature in recent years. Since its recognition by the World Health Organisation (WHO) and later in the United States National Cholesterol Education Program (NCEP) as an operational clinical entity associated with cardiovascular risk[168 169] research into the metabolic syndrome has increased markedly. The term refers to the co-occurance of metabolic abnormalities which are associated with increased risk for type II diabetes and cardiovascular disease.[170]

The Metabolic syndrome has been defined in terms of the presence of a number of clinical parameters with some groups placing different importance on different facets of the pathology. Its diagnosis and therefore its overall

prevalence will vary depending on which definition or criteria are used. The 1999 WHO definition requires the presence of insulin resistance (impaired fasting glucose, impaired glucose tolerance or type 2 diabetes) along with another two of five criteria relating to obesity (BMI>30, or waist/hip ratio of >90cm for men or >85cm for women), dyslipidemia (triglycerides >150mg/dl or HDL-C <35mg/dl for men or <39mg/dl in women), hypertension (>140/90mmHg) and microalbuminuria. The National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) definition has no compulsory criteria and relies on the presence of three from five criteria concerning waist circumference, fasting glucose, dyslipidemia (triglycerides as in WHO, or HDL-C <40mg/dl in men or <50mg/dl in women) and hypertension (>130mHg systolic or >85mmHg diastolic). The International Diabetes Federation (IDF) definition requires the presence of central obesity (waist circumference >94cm for men or >80cm for women) plus two of four criteria regarding fasting glucose (>100mg/dl) dyslipidemia, and hypertension (both as described in NCEP ATP III definition). Abnormal glucose tolerance, insulin resistance and compensatory hyperinsulinaemia appear to be the common threads that predispose the development of these clinical conditions clustered in the same individual. For this reason, studies examining associations between sitting time and insulin resistance (as defined by Matsuda Insulin Sensitivity Index,[171] Homeostatic Model Assessment of Beta-cell function [HOMA-%B] and insulin sensitivity [HOMA-%S] have also been included in this section of the review.

A summary of all studies included in this section of the review can be found in appendix 1.3.

3.5.2. Cross-sectional evidence

A total of 27 cross-sectional studies met the criteria for this review. Four of these studies examined associations between a measure of sedentary time and diagnosed diabetes prevalence,[29 128 157 172] nine examined associations with abnormal glucose tolerance or insulin resistance[35 54 98 109 110 173-176] and 14[129 177-189] focussed on metabolic syndrome. In a sample of over 63000 Australian males aged 45-64, George et al[29] observed that after adjusting for, age, household income, educational attainment, smoking status, BMI, functional limitation, and MVPA, self-reported total sitting time was positively associated with diabetes risk. Compared to a reference group who sat for less than 4 hrs per day odds ratios for diabetes were 1.03 (95%CI 0.92, 1.14) for 4 to <6hrs, 1.15 (95%CI 1.03, 1.28) for 6 to <8hrs and 1.21 95%CI 1.09, 1.33) for >8hrs per day. Similarly, Tonstad et al[172] reported that compared to a reference group who watched <1 hr of television per day fully adjusted odds ratios for type II diabetes for 1-2hrs and >3 hrs per day were 1.31 (95%CI 1.16, 1.47) and 1.62 (95%CI 1.44, 1.83) respectively. These findings are consistent with those from Stamatakis et al[128] who, in an analysis of data from 2765 respondents from the Health Survey for England (aged ≥60yrs), examined associations between multiple self-reported indicators of sedentary time (TV viewing time, non-TV leisure time sitting, and total leisure time sitting) and accelerometer defined sedentary time (defined as time below 100 accelerometer counts per minute) with prevalent diabetes. Significant positive associations were observed with all self-report indicators of sedentary time following adjustment for covariates including MVPA, although no association was observed with accelerometer defined sedentary time.

De Heer et al[157] observed significant associations between self-reported total sitting time and prevalent diabetes which persisted following adjustment for demographics, employment status, family disease history and light, moderate and vigorous intensity physical activity but which were attenuated to null following adjustment for BMI. In the study by Tonstad et al associations between TV viewing and diabetes were significantly attenuated following adjustment for BMI, although they remained significant. The studies by George et al and Stamatakis et al also observed that associations were substantially attenuated following additional adjustment for BMI These findings suggest that adiposity might be an important factor in the association between sitting and health.

Eight studies examined cross-sectional associations between sedentary time and abnormal glucose tolerance or insulin resistance which is an important clinical precursor for diabetes and a central criterion for diagnosis of the metabolic sydrome. Dunstan and co-workers[173] examined impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and undiagnosed type 2 diabetes in relation to self-reported TV viewing time in a sample of over 8000 adult (25 yrs and older) participants in the Australian Diabetes and Lifestyle (AusDiab) study. Following adjustment for age, education, family history, smoking, dietary covariates, and leisure time physical activity, greater daily TV viewing was positively associated with increased risk of abnormal glucose metabolism in women, but not men. Separate regression models demonstrated that each 1hour increment of TV viewing was associated with an 18% (95% CI 9-29%; p=0.001) increase in risk of abnormal glucose metabolism in women

while the effect in men was not statistically significant. Men and women who watched less than 14hrs of TV per week were also significantly less likely to have undiagnosed type 2 diabetes than those who watched more than 14hrs per week (OR 2.4 [95%CI 1.41-4.12] in men and 2.2 [95%CI 1.32-3.61] in women). The findings by Dunstan et al are consistent with 7 other studies [35 54 109 110 174-176] who have observed associations between sitting behaviour or sedentary time and abnormal glucose metabolism.

These same authors also observed similar cross-sectional associations between TV viewing time and metabolic syndrome (according to the 1999 World Health Organisation definition) in just over 6000 participants in the AusDiab study. [181] After adjusting for lifestyle factors including dietary intake and physical activity level, each one hr increase in TV viewing time was associated with a 26% (95%CI 14-46% *P*=0.0001) increase in metabolic syndrome prevalence in women. A positive but non-significant association was observed in men (12% 95%CI -0.01-27% *P*=0.07). As discussed above there are a number of different definitions of the metabolic syndrome which vary in the clinical parameters employed. Interestingly in this instance Dunstan and colleagues repeated their analysis using the NCEP ATP III and the IDF definitions and although not explicitly reported, the associations between TV viewing time and metabolic syndrome incidence were similar. The fact that metabolic syndrome was significantly associated with TV viewing time regardless of which criteria were used for diagnosis suggests that prolonged TV viewing may be detrimentally associated with on a broad range of metabolic risk factors. In a community based cross-sectional study of 2353 Taiwanese participants, Chang et al[179]

also observed that compared to those who watched less than 14 hrs of TV per week, men who watched more than 20hrs per week had a 1.5 fold (95% CI 1.10, 2.03) increase in risk, and women a 1.93 fold increase in risk of metabolic syndrome according to the NCEP ATP III definition. Overall, of the 14 studies examining metabolic syndrome identified by the systematic review,[129 177-189] only two[186 187] report a positive association with a measure of sitting or sedentary time. Metabolic disease is consistently associated with sedentary time in cross-sectional studies although examination of prospective evidence is necessary to determine the direction of the association

3.5.3. Prospective evidence

Of the eleven prospective studies identified by the systematic review three examined associations between objectively defined sedentary time and abnormal glucose tolerance[98 99 175] while eight examined associations between self-reported TV viewing and diabetes risk[56 65 67 70 164 190-192] including one study which examined multiple discrete self-reported sitting behaviours including TV viewing.[191]

3.5.3.2 Total sedentary time and metabolic risk

Of the eleven prospective studies identified by the systematic review three have examined prospective associations between sedentary behaviour and abnormal glucose tolerance or insulin resistance and findings are mixed. Helmerhorst et al[99] used data from the Isle of Ely study to examine the prospective association between objectively assessed sedentary time and

insulin resistance. The Isle of Ely study followed 393 healthy middle aged people for just over five and a half years. Using the method described previously (chapter 2) resting heart rate and heart rate response to graded exercise were assessed for each individual and then flex heart rate (heart rate threshold, calculated as the mean of the highest heart rate recorded during rest and the lowest recoded during exercise), was determined. For a four day period after both baseline and follow-up measurements participants wore heart rate monitors during all waking hours. When a participant's heart rate was below their flex heart rate threshold they were deemed to be engaged in sedentary behaviour and total sedentary time was expressed as a percentage of total daily monitoring time. After adjustment for age, sex, fat mass, fasting insulin, smoking status, and follow-up time, percentage sedentary time at baseline was significantly and positively associated with log fasting insulin at follow-up (β= 0.003, 95%CI 0.0006–0.006, *P*=0.015) . Following adjustment for time spent in moderate to vigorous physical activity this association was strengthened (β= 0.004, 95%CI 0.0009–0.006, *P* =0.009). Cooper et al[175] also observed as small positive association between accelerometer defined sedentary time and insulin resistance in 528 adults (aged 30-80 yrs) over a six month follow-up period. However a study by Ekelund et al[117] observed no associations between objectively assessed sedentary time and insulin resistance. Ekelund et al followed 191 participants for one year as part of the ProActive UK trial. Physical activity and sedentary time data was recorded using seven days of accelerometer measurement at baseline. Sedentary time was defined as time spent below 100 accelerometer counts per minute. Moderate to vigorous physical activity but not sedentary time was associated with insulin sensitivity at follow-up.

3.5.3.3. TV viewing and diabetes risk

There are eight prospective studies which have examined the associations between sitting behaviours and risk of type II diabetes,[56 65 67 70 164 190-192] and nearly all have focussed exclusively on TV viewing or screen based entertainment.[56 65 67 164 190 192] Two of the largest of these studies originated in the US. Krishnan et al[192] used ten years of data on 45688 participants of the Black Women's Health Study (BWHS) to examine associations between self-reported TV viewing and risk of developing type II diabetes. Nearly 3000 new cases of diabetes were recorded during follow up and relative risk was positively associated with TV viewing. Compared to the reference group (<1hr of TV per day), hazard ratios for type II diabetes were 1.43 (95%CI 1.19, 1.71) for 1-2 hrs per day, 1.53 (95%CI 1.28, 1.83) for 3-4 hrs per day, and 1.86 (95% CI 1.54, 2.24) for more than 5hrs per day.

In a study of nearly 38000 male participants in the Health Professionals Follow Up study, Hu et al[190] examined the effects of both physical activity and TV viewing time on risk for incident type II diabetes. Over ten years of follow up between 1986 and 1996, 1158 new cases of type II diabetes were recorded. Relative risk for type II diabetes across five TV viewing categories (1.00, 1.49 95%CI 1.03-2.15, 1.39 95%CI 0.95-2.05, 1.77 95%CI 1.18-2.64, and 2.23 95%CI 1.13-4.39 demonstrated a significant positive trend (P_{trend}=0.02) following adjustment for individual covariates including family history of diabetes, and behavioural factors such as physical activity level, smoking, dietary habits, alcohol intake and BMI the relationship persisted.

Using data from the German base of the European Prospective Investigation into Cancer and Nutrition (EPIC-Potsdam, Germany), Ford et al [56] examined associations between TV viewing and incident diabetes in 23855 men and women over 7.8 years of follow-up. Following adjustment for a range of relevant confounding factors (age, sex, educational status, occupational activity, smoking, alcohol use, dietary variables and systolic blood pressure, and leisure time physical activity) hazard ratios for type II diabetes were 1.13 (95%CI 0.84, 1.52) for 1 to <2 hrs of TV per day, 1.23 (95%CI 0.92, 1.64) for 2 to <3hrs per day, 1.65 (95%CI 1.22, 2.23) hrs of TV per day, and 1.63 (95%CI 1.17, 2.27) for more than four hours per day (P_{trend} <0.001) compared to the reference group (<1hr TV per day).

3.4.3.4. Multiple discrete sitting behaviours and diabetes risk

As discussed above, sitting in different domains may have different patterns which may influence their associations with health outcomes. However, only one study has examined the association between, multiple sitting behaviours and diabetes risk in the same cohort. As part of the Nurse's Health study nearly 70000 women were followed over six years and the effect on type 2 diabetes risk of a range of sitting behaviours including TV viewing, sitting at work or while away from home or while driving, and other domestic sitting were examined. [191] The exposure variables were arranged into five categories; 0-1 hrs/wk, 2-10 hrs/wk, 11-20 hrs/wk 21-40 hrs/wk and >40hrs.wk. Over the six year follow up period just over 1500 participants were newly diagnosed with type II diabetes and all sitting time variables were significantly associated with an increased risk. The fully adjusted relative risk across five sedentary behaviour categories were; 1.00, 1.09 (95%CI 0.85-1.39), 1.30 (95%CI 1.03-

1.63), 1.44 (95%CI 1.12-1.85), and 1.70 (95% CI 1.20-2.43 P_{trend} <0.001) for TV viewing; 1.00, 0.99 (95%CI 0.81-1.20), 1.10 (95%CI 0.91-1.33), 1.12 (95%CI 0.89-1.41), and 1.48 (95% CI 1.10-2.01 P_{trend} =0.005) for sitting at work; and 1.00, 0.87 (95%CI 0.67-1.13), 0.98 (95%CI 0.76-1.26), 0.94 (95%CI 0.70-1.24), and 1.54 (95% CI 1.10-2.18 P_{trend} =0.004 for other sitting at home).

The current evidence base demonstrates consistent associations between sitting time and risk for type II diabetes and metabolic disease. These studies have been conducted on large samples and over significant follow-up periods and have been well controlled for a range of relevant confounding factors. However, only three prospective studies adjusted their analysis for a measure of obesity or adiposity.[56 190 192] In these studies the associations between sitting and diabetes risk were attenuated and following additional adjustment for BMI and one was attenuated to null.[56] This may suggest that the development of diabetes in those who sit a lot may be due at least in part to the development of obesity.

3.6. Sedentary behaviour and obesity

The following section of this review will examine evidence regarding the associations between sitting time and obesity. Within the current sitting literature studies have examined associations between sedentary time and adiposity using a range of different outcomes. The following systematic review contains studies examining the relationship between sitting or sedentary time and obesity (defined as having a BMI of ≥30), body composition, waist circumference, body weight and weight gain. A summary of all studies included in this section of the review can be found in appendix 1.4.

3.6.2. Cross-sectional evidence

The review identified 83 studies examining associations between sitting or sedentary time and markers of obesity or adiposity, 65 of which are cross-sectional. Of these 65 studies, 33 examined associations with TV viewing, [35 160 178 179 181 183 193-218] five used objective measures determine sedentary time including accelerometers[54 109 219 220] and heart rate monitors[83] and the remaining 27 used self-report measures for total sitting or sitting behaviours other than TV viewing.[64 69 81 128 157 176 200 221-240]

Heinonen et al[241] observed that in a study of just over 2000 men and women, TV viewing was consistently related to both BMI and waist circumference. Each additional hour of TV was associated with a 1.81 ± 0.44cm increase in waist circumference in women and a 2.00 ± 0.44cm increase in men. These associations remained highly significant following adjustments for a range of relevant covariates. Within this sample intake of several potentially obesogenic food items including sausage, beer and soft drinks was directly associated with TV viewing. Importantly when intake of these food items was added as a covariate to the multivariate models for TV viewing and obesity markers the observed associations persisted.

In a cross-sectional analysis of 466605 healthy Chinese adults (aged 30-79 yrs), Du et al[223] examined associations between self-reported hrs per day of leisure time sitting and both BMI and waist circumference. Each1.5 hr/day interval of leisure time sitting was associated with a 0.19 kg/m^2 (95%CI 0.18,

0.20) increase in BMI, a 0.57cm (95%CI 0.54, 0.59) increase in waist circumference and 0.44 (95%CI 0.42, 0.46) percentage points more body fat. These associations remained significant when analyses were stratified by volume of daily physical activity. In another large cross-sectional study, Banks et al[193] used data from nearly 75000 Thai students (aged 20-50 yrs) attending Sukhothai Thammathirat Open University in 2005-06 to examine the associations between both daily screen-time (leisure time computer use and TV viewing) and total daily sitting with obesity risk (using the Asian criteria of a BMI ≥25kg/m^2). Following adjustment for age, sex, income and educational attainment, daily housework and gardening and daily exercise-related physical activity there were significant increases in obesity risk across categories of daily screen time in both men and women. Compared to those with <1hr per day of screen time odds ratios (95% CI) for obesity were: 1.22 (1.14, 1.30), 1.38 (1.27, 1.50), 1.58 (1.36, 1.83) and 1.80 (1.53, 2.13) for men and: 1.15 (1.05, 1.27), 1.50 (1.35, 1.67), 1.62 (1.36, 1.92) and 2.13 (1.78, 2.55) for women for 2-3, 4-5, 6-7, and ≥8hrs per day respectively. Additional adjustment for consumption of fried foods, soft drinks and junk food, smoking, and alcohol consumption did not significantly affect these odds ratios. Following adjustment for covariates total daily sitting time was associated with obesity in women (P_{trend} <0.001) but not in men.

3.6.3. Prospective evidence

There are currently 18 studies which have included analyses of the prospective associations between sitting and obesity/adiposity and findings have been mixed. Six of these studies focus exclusively on associations with

TV viewing,[66 197 217 242-245] one used heart rate monitoring to define sedentary time[83] and the remaining 11 used self-report measures for individual or multiple measures of sitting.[191 213 227 231 236 246-251] Two studies also examined he possibility of reverse causality in the association between sedentary time and obesity.[83 250]

3.6.3.2. TV viewing and Obesity risk

Using data from the 1958 birth cohort study Parsons et al [66] examined whether frequency of TV viewing during early adulthood influenced waist circumference and BMI in mid adult life (aged 45). At age 23 TV viewing frequency was reported in the following categories: ≥5, 3-4, 1-2 times per week, 2-3 times in the last 4 weeks, once in the last 4 weeks or not at all in the last 4 weeks. TV viewing was significantly associated with waist-hip ratio at 45 years. After adjustment for potential confounders both male (n=3911) and female (n=4076) participants watching ≥5times per week had an estimated mean waist-hip ratio 0.01 and 0.09 higher than those watching less often (P<0.0001). This association persisted, although was attenuated, after further adjustment for BMI and TV viewing at age 45. A subsequent study of data from this cohort,[227] examined associations of TV viewing time and work sitting time(in hrs per day) with BMI in a sample of 6562 over a five year follow-up period from age 45 to 50 yrs. There was a significant increase in BMI at age 50 across categories (0, 0-1, 1-2, 2-3, 3-4, >4 hrs per day) of TV viewing at age 45. For each category increase in TV viewing, five year gain in BMI was greater by 0.11 (0.06, 0.17) kg/m^2. There was no evident prospective association between work sitting at 45 yrs and either BMI at 50 yrs of change in BMI between 45 and 50.

3.6.3.3. Multiple discrete sitting behaviours and obesity risk

Hu and co-workers [191] examined sitting behaviours and incident obesity in over 50000 30-55yr old women with an average of six years of follow up as part of the US Nurses Health Study. The study examined television viewing, sitting time while at work or commuting, and sitting at home while not watching television (including working at a desk, reading and sitting during meal times). In multivariate analysis television viewing was significantly and positively associated with obesity risk across five categories of viewing time. Relative risk (RR) of obesity for each TV viewing category were; 1 for 0-1hrs.wk; 1.22 95%CI 1.06-1.42 for 2-5hrs.wk; 1.42 95%CI 1.24-1.63 for 6-20hrs.wk; 1.65 95%CI 1.41-1.93 for 21-40hrs.wk; and 1.94 95%CI 1.51-2.49hrs.wk ($P_{trend} < 0.001$). There was also a significant increase in obesity risk across categories of occupational sitting (RR=1 for 0-1hrs.wk; 1.02 95%CI 0.89-1.18 for 2-5hrs.wk; 1.13 95%CI 0.98-1.29 for 6-20hrs.wk; 1.13 95%CI 0.96-1.31 for 21-40hrs.wk; and 1.25 95% CI 1.02-1.54hrs.wk; $P_{trend} = 0.02$). These associations are adjusted for age, smoking, hormone use, alcohol consumption, leisure time physical activity and a range of dietary factors including, total fat and total calorie intake. Leisure time sitting excluding TV viewing showed no significant association with incident obesity.

3.6.3.4. Examination of reverse causality in the association between sitting and obesity

Ekelund et al [83] examined the relationship between objectively assessed sedentary time and obesity using data from The Isle of Ely study which followed 393 healthy middle aged people for just over five and a half years. Participants

visited a laboratory at baseline and at follow up where BMI, waist circumference and fat mass were established. Flex heart rate was used to determine sedentary time (method described previously [chapter 2]). Although cross-sectional analyses at baseline and follow-up showed sedentary time to be significantly correlated with markers of obesity, baseline sedentary time was not predictive of any of these measures at follow up. When BMI, fat mass, and waist circumference were modeled as predictor variables for percentage sedentary time at follow up, significant and independent associations were observed, suggesting that high BMI, body fat and central adiposity may lead to increased sedentary time. Beta coefficients were 0.33 (95%CI 0.15, 0.50) for body weight (Kg), 1.10 (95%CI 0.58, 1.63) for BMI (Kg/m^2), 0.59 (95%CI 0.11, 0.40) for fat mass (kg) and 0.44 (95%CI 0.23, 0.66) for WC (cm). Changes in body weight, BMI and fat mass were also significantly and independently associated with changes in sedentary time between baseline and follow up. Further evidence for reverse causality was found by Mortensen et al.[250] They reported BMI to significantly predict sitting but found no association in the other direction. It is plausible that while high volumes of sitting may contribute to adiposity, being overweight or obese may influence choice of leisure time activity or even occupation. The idea of reverse or bidirectional causality between sedentary behaviour and obesity has seldom been investigated in prospective cohort studies and certainly requires further attention as this may be an important contributory factor in the observed relationships between sedentary behaviour and other health outcomes. The idea that BMI may contribute to both increased sitting time and disease risk is supported by evidence demonstrating the attenuation of associations between sedentary time and metabolic disease [56 190 192] following adjustment for body mass index.

3.7. Sedentary time and biomarkers of cardiometabolic risk

There are a number of studies which have examined the relationship between sedentary behaviour and a range of biological risk factors associated with cardiovascular and metabolic disease. Because changes in these biological parameters do not in themselves necessarily represent clinical endpoints or specific diagnosed conditions, and because of the heterogeneity of the ranges of risk markers measured in these studies, they have not been included in the main systematic review. Instead they will be discussed in the following section.

Healy et al[54] used accelerometer data from 4757 adult participants from the 2003/04 and 2005/06 US National Health and Nutrition Examination Survey (NHANES) to examine associations between daily sedentary time (defined as time spent below 100 accelerometer counts per minute) with cardiometabolic risk markers. Independent of covariates (including MVPA) there were detrimental associations between daily sedentary time and waist circumference, HDL-cholesterol, C-reactive protein, plasma triglycerides, fasting insulin, beta cell function and insulin sensitivity. These findings are consistent with those of Thorp et al[200] who used data from the AusDiab study to examine cross-sectional associations between self-reported daily sitting time and TV viewing with a range of metabolic risk markers including waist circumference, BMI, resting blood pressure, fasting serum triglycerides, fasting HDL cholesterol, fasting serum insulin and 2-hr post load plasma glucose (plasma glucose measured over two hours following a standardised oral glucose tolerance test). Following adjustment for covariates (age, educational attainment, family history

of diabetes, employment status, cigarette smoking, daily energy intake, alcohol intake, diet quality and total leisure time physical activity), all metabolic markers were detrimentally associated with daily sitting time (*P* <0.05 for all) with the exception of diastolic blood pressure in men and fasting plasma glucose in women. TV viewing was detrimentally associated with all markers except HDL cholesterol in women and blood pressure in men (*P* <0.05 for all). These associations were attenuated following additional adjustment for waist although most remained significant.

Similar findings were observed in a subsequent prospective study by Stamatakis et al[197] which used data from 1958 British Birth Cohort Study. Frequency of TV viewing (≥5, 3-4, and ≤2 times per week) at age 23 was positively associated with C-reactive protein, fibrinogen, waist circumference, systolic and diastolic blood pressure and clustered cardiometabolic risk (*P* <0.05 for all) at age 44 following adjustment for covariates (including MVPA and television viewing at age 44). However following additional adjustment for baseline BMI these associations were attenuated to null. Similar to findings from previous studies examining clinical health outcomes these findings suggest that the detrimental associations between sitting time and metabolic risk may be attributable in part to differences in adiposity. Stamatakis and Hamer[252] directly tested the extent to which adiposity markers explain the association between sitting behavior and cardiometabolic risk factors in a subsequent cross-sectional analysis. Subjects were 5067 Health Survey for England (2008) respondents aged between 16 and 65. Following adjustment for covariates (age, sex, social class, employment status, alcohol consumption, fruit and vegetable

consumption, frequency of unhealthy food consumption, psychological stress, antihypertensive medication and MVPA), self-reported daily sitting time was associated with systolic blood pressure (mean difference per 10 min per day greater: 0.025 mm Hg, 95% CI: 0.002 to 0.047), diastolic blood pressure (0.023 mm Hg, 0.007 to 0.040), total cholesterol (0.004 mmol/l, 0.002 to 0.005) and HDL-C (-0.0006 mmol/l, - 0.00119 to −0.0001). TV time was associated with SBP (0.075 mm Hg, 0.036, 0.113), DBP (0.052 mm Hg, 0.024, 0.081), total cholesterol (0.005 mmol/l, 0.002 to 0.008), and HDL-C (-0.0013mmol/l, -0.0023 to -0.0002). It was observed that body mass index explained 95.9% of the association between total sitting and systolic blood pressure, 91.4% with HDL-cholesterol, 64.7% with diastolic blood pressure and 33% with total cholesterol. Waist circumference explained a slightly lower, proportion of the association between total sitting time and risk markers (90% for systolic blood pressure, 85% for HDL-cholesterol, 60% for diastolic blood pressure and 38% for total cholesterol). A smaller but still considerable proportion of the associations between TV viewing and these risk markers was explained by BMI (range 28.6-60.3%) and waist circumference (27.3-60.7%).

The evidence regarding the associations of sitting or sedentary time with individual metabolic markers is important as it provides insight into the possible mechanisms underpinning the observed associations with clinical outcomes such as cardiovascular and metabolic disease. The observation that adiposity appears to be an important factor in these associations is also important as it again highlights the complex nature of the association with sedentary time, adiposity and disease.

3.8. 'Sedentary Breaks': Interrupting sedentary time

Another important feature of the reported associations between sedentary time and metabolic markers is the idea that interrupting extended periods of sedentary time might attenuate a proportion of the associated negative metabolic effects. Healy and co-workers[109] collected accelerometer data (Actigraph WAM 7164) from 168 participants from the AusDiab cohort and examined cross-sectional associations between sedentary time (defined as time spent below 100 accelerometer counts per minute) and a range of metabolic outcomes including waist circumference, BMI, plasma triglycerides, HDL-cholesterol, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, and 2 hr post challenge plasma glucose (2hrs post glucose tolerance test). The authors hypothesised that breaking up or interrupting sustained periods of sedentary time would have a beneficial effect on these risk markers. A 'break' or interruption in sedentary time was defined as one minute or more at above 100 accelerometer counts per minute. It was observed that following adjustment for covariates a greater the number of breaks in a given period of sedentary time was associated with significantly lower waist circumference, BMI, triglycerides and 2 hr post challenge plasma glucose (P <0.03 for all). These effects were independent of a broad range of demographic and health related covariates (age, gender, employment status, alcohol intake, income, education, smoking status, family history of diabetes, diet quality and MVPA) but also independent of the total amount of sedentary time, and the average activity intensity during the breaks. The average accelerometer count value during a sedentary break was 514 counts per minute which the authors classified as being light intensity activity using previously validated accelerometer count cut-points for Actigraph accelerometers[111] (moderate to

vigorous physical activity was classified as being above 1952 counts per minute, meaning light intensity physical activity was defined as 100-1952 counts per minute). The average duration of these sedentary breaks was less than five minutes.

In a separate study using accelerometer data from nearly 5000 participants from the NHANES study Healy et al[54] observed that independent of confounders (including demographic and health related factors, MVPA and sedentary time) that the number of sedentary breaks (again defined as 1 minute or more at more than 100 accelerometer counts per minute) was beneficially associated with both waist circumference and C-reactive protein. The findings from these two studies suggest that irrespective of how long you are sedentary over the course of a day, regularly interrupting sedentary time can benefit a range of metabolic markers even if the interruptions are short and only consist of very light activity such as walking. These findings have practical applications for interventions to reduce or prevent the proposed negative health consequences of sedentary time as they suggest that small behavioural modifications could potentially have a significant protective effect.

Nevertheless these findings must be interpreted with a degree of caution. In the earlier study by Healy et al[109], although associations were observed between sedentary breaks with waist circumference, BMI, triglycerides and 2 hr plasma glucose, following adjustment for waist circumference these associations, with the exception of BMI, were attenuated (we can assume attenuated is attenuated to null although this is not explicit). The sample for this

study was also relatively small. In the later study by Healy et al[54] which had a far larger sample, although associations are observed between sedentary breaks and both waist circumference and C-reactive protein, these were only two of ten biological markers measured (waist circumference, systolic blood pressure, diastolic blood pressure, HDL-cholesterol, C-reactive protein, fasting triglycerides, fasting plasma glucose, plasma insulin, beta cell function [HOMA-%B] and insulin sensitivity [HOMA-%S]).

In addition, a recent study by Cooper et al[175] examined the cross-sectional and prospective associations between sedentary time and sedentary breaks with a range of biological risk factors and evidence for the benefit of interrupting sedentary time was limited. In cross-sectional analyses each hour of sedentary time was associated with a larger waist circumference, higher fasting insulin, and reduced insulin sensitivity, and lower HDL-cholesterol (P <0.005 for all). Volume of sedentary time also predicted HDL-cholesterol, fasting insulin and insulin sensitivity over six months of follow-up. However sedentary breaks were associated with a lower waist circumference only in the cross-sectional analyses and were not associated with any metabolic outcomes in the prospective analyses.

The potential beneficial effects of interrupting sustained sitting on metabolic markers are best examined using controlled laboratory based intervention studies. In such studies sitting and interruptions in sitting can be directly observed and the acute or cumulative effects of sitting on metabolic parameters can be monitored. The following sections will examine mechanistic

and laboratory based evidence for both the associations between sitting and metabolic health, and the metabolic benefits of interrupting prolonged sitting.

3.9. Potential mechanisms for the associations between sitting and health outcomes.

3.9.1. Sitting and lipid metabolism

As described previously, a number of cross-sectional studies have reported positive associations between sitting or sedentary behaviours and markers of lipid metabolism including plasma triglyceride[35 54 175 200] and both HDL-cholesterol[54 175 200] and total cholesterol concentration.[175] However there are no laboratory based studies which have examined the changes in lipid metabolism during a prolonged period of sitting. An early study by Bey and Hamilton[23] used rodents to demonstrate a potential mechanism by which sedentary behaviour might affect lipid metabolism but as yet there have been no studies to examine the same processes in humans.

Bey and Hamilton[23] examined the regulation of lipoprotein lipase (LPL) activity in the skeletal muscle of rodents during physical inactivity in comparison with low-intensity contractile activity of ambulatory controls. As well as its presence in adipose tissue LPL is found on the endothelial wall of muscle capillaries and plays a central role in several aspects of lipid metabolism.[253] A number of studies designed to manipulate LPL concentration and action[254 255] have concluded that it is critical for the tissue-specific uptake of triglyceride rich lipoproteins by non-hepatic tissues. There is also compelling evidence that

physiological modulation of LPL activity may contribute the aetiology or prevention of a number of metabolic disorders.[23] Low LPL function has been associated with blunted plasma triglyceride uptake, reduced plasma HDL cholesterol[256] and may also effect hypertension[257] and diabetes induced dyslipidaemia.[258] Wittrup et al[259] also reported that a partial reduction in LPL function due to a specific polymorphism was associated with a five-fold increase in risk of death and coronary heart disease.

Prior to this study the majority of evidence relating to the relationship between physical activity and LPL function focuses on the effects of high intensity exercise and less was known about the contrast of sedentary behaviour with low level muscular contractions. If the underlying mechanisms regulating LPL happen to be dependent on intensity then much could be gained by examining sedentary versus light intensity activity as this comprises the majority of human behaviour in waking hours. Specifically Bey and Hamilton tested the hypothesis that the normally high LPL activity in skeletal muscle (particularly in oxidative muscle fibres) used for ambulation and to maintain posture during standing would be significantly decreased by physical inactivity compared with ambulatory controls, and that restoring ambulation in previously inactive rodents would raise muscle LPL activity.[23]

Hind-limb unloading (HU) was performed on a group of Sprague-Dawley rats to prevent weight baring and contractile activity of the hind limbs. This was achieved by attaching the tail to a length of fishing wire suspended from an overhanging metal rod and elevating it just high enough to prevent the rear feet

from touching the floor. In a chronic study, eight rats were inactive with HU for 10 hrs per day for 11 days and compared to a control group without HU. In an acute study 20 rats were inactive for 12 hrs before normal ambulatory activity was allowed to resume. LPL activity, LPL protein mass, LPL mRNA concentration, plasma triglycerides and HDL-cholesterol concentration and triglyceride uptake were measured in the soleus and quadriceps of the hind leg.

Hind limb muscle LPL activity was profoundly reduced (to less than 25% of control groups in both soleus and quadriceps) by inactivity in both acute and chronic trials. There was no significant difference in the magnitude of the reduction between acute and chronic trials, suggesting that this is an acute effect of a single bout of inactivity rather than a cumulative one. There was no evident change in LPL activity in the cardiac or diaphragm muscle suggesting that this is a localised effect attributable to muscle inactivity rather than a systemic effect of reduced movement or energy expenditure. This was confirmed when tetonomy of the Achilles tendon was used to demonstrate that unilateral unloading of one hind limb would only decrease LPL activity in the unloaded limb compared to the loaded limb. Triglyceride uptake and HDL-cholesterol were also dramatically reduced following HU. All of these negative effects were rapidly reversed following short periods of low intensity ambulation.

In addition this study suggests that the mechanisms involved in reducing LPL function during inactivity may be qualitatively different to those involved in increasing LPL function during physical activity. During high intensity exercise LPL activity has been demonstrated to increase two and half fold in the least

oxidative regions of the leg muscle (the fast twitch white fibres) while the most oxidative postural leg muscles which already had high levels of LPL activity did not demonstrate any such increase. The changes shown in fast twitch fibres during exercise were mirrored by increases in LPL mRNA expression. In contrast, during inactivity LPL activity decreased in the most oxidative muscle fibres only (and then increased following low-intensity ambulation) despite there being no significant change in LPL mRNA expression. This suggests that unlike during higher intensity activity changes in LPL transcription is not central to changes in LPL activity during lower intensity activity or inactivity.

Lipoprotein lipase is the first protein to be identified in the cellular pathway from muscular inactivity to adverse metabolic sequellae.[27] As discussed a number of cross-sectional and prospective studies[35 200] have demonstrated sitting time to be adversely associated with fasting plasma triglycerides, and HDL-cholesterol levels. The study by Bey and Hamilton suggests that LPL regulation is one of the most sensitive metabolic responses to physical inactivity and low-intensity contractile activity and it therefore offers an explanation for how sedentary time is related to lipid markers and chronic disease.[24] As it is well established that tissue specific triglyceride uptake is limited by local LPL activity the findings from this study suggest that it is plausible that prolonged sedentary behaviour, or unloading of postural muscles (for example while sitting) could cause metabolic disturbance in humans. In addition the reported qualitative differences between the effects of exercise and inactivity support the idea of sedentary behaviours being an independent class of behaviour with specific determinants and effects.

While the findings of Bey et al are compelling, a degree of caution must be taken when inferring these findings to human subjects. The measurement of skeletal muscle LPL action is very difficult and invasive so these findings have never been replicated in humans. Miyashita et al[260] used three two-day trials to examine the effect of a full day of sitting compared to a day of standing (45 minutes of every hour) and a day with a 30 minute brisk walk, on a subsequent days postprandial lipid metabolism. On the second day of each trial participants rested and were provided with two standardised test meals. Repeated blood samples were taken to examine between trial differences in triglyceride concentrations, circulating LPL mass, apolipoprotein C-II (an activator of LPL) and apolipoprotein C-III (an inhibitor of LPL). They observed that while there were no significant differences between sitting and walking trials, triglyceride levels over the six hour observation period were 18% lower. While no between trial effects were observed in the LPL markers it is important to note that LPL protein mass in free circulation, is in the form of inactive monomeric LPL protein[261] and only represents a small fraction of total LPL. It is therefore unlikely that the LPL protein mass measured in this study is directly involved in the hydrolysis of circulating triglyceride rich lipoproteins. However the reduction in postprandial lipaemia following the walking trial along with absence of a difference in LPL activator or inhibitor factors between trials suggests that increased LPL mediated triglyceride clearance may not be the dominant triglyceride lowering mechanism. It has been previously observed that low levels of energy expenditure achieved through walking can be effective in reducing postprandial lipaemia.[262-266] It is therefore possible that small differences in energy expenditure caused by ambulation during a day where

people are predominantly seated could provide a potential mechanism for the observed associations between sitting and health.

In order to gain a clearer understanding of the effects of sitting on lipids, additional intervention studies are required which examine associations between different patterns of sitting in humans (sustained versus interrupted) and the acute effects on lipid measures such as triglyceride clearance and plasma cholesterol.

3.9.2. Sitting and glucose and insulin metabolism

In skeletal muscle and adipose tissue, insulin stimulates the uptake of glucose by translocation of the GLUT4 glucose transporter to the cell surface. In the skeletal muscle and liver tissue, insulin stimulates the synthesis of glycogen from glucose and inhibits glycogenolysis. In the liver insulin also decreases hepatic gluconeogenesis, preventing an influx of more glucose into the bloodstream. In adipose tissue, insulin inhibits lypoloysis and stimulates glucose uptake. The net effect of all these functions is to increase glucose uptake and reduce circulating glucose levels.[267] In insulin resistance, the insensitivity of muscle, adipose and liver cells to insulin causes circulating glucose levels to remain high which leads to pathology.

As discussed previously insulin resistance and compensatory hyperinsulinaemia appear to be the common threads that predispose the

development of a range of clinical conditions and there is cross-sectional[54 200] and prospective[268] evidence linking high volumes of sitting or sedentary time with reduced insulin sensitivity. In addition there is some supportive experimental evidence for these associations.

Early laboratory studies examining the metabolic effects of inactivity in human subjects have focused on bed rest and spinal injury models where complete inactivity is prescribed for a number of days.[269-272] Hamburg et al [272] measured insulin sensitivity, total cholesterol, plasma triglyceride concentration and vascular function in 20 healthy subjects before and after 5 days of prescribed bed rest. During this period subjects were permitted up to 30 minutes out of bed over the course of each 24 hr period for reasons of personal hygiene. Insulin sensitivity was measured using a standardised glucose tolerance test. Briefly, following a baseline blood sample subjects consumed a drink containing 75g glucose. Further blood samples were then taken at 30, 60, 90 and 120 minutes. Net glucose and insulin responses to glucose loading were calculated as area under the concentration versus time curve over 2 hours. Following five days of bed rest net glucose response was 6% higher (P =0.003) and net insulin response was 67% higher (P <0.001) indicating a significant reduction in insulin sensitivity. Smorawinski et al[270] used a similar protocol to examine the effect of three days of bed rest on insulin sensitivity in both trained and sedentary (defined as undertaking no regular exercise) participants. Following bed rest, they observed a 100% increase in the area under the insulin versus time curve in trained subjects and a 40% increase in sedentary subjects (P<0.001 for both). Such studies employ an unusual pattern of inactivity which

is substantially different in terms of both volume and posture from the day to day sedentary patterns of healthy free living individuals. However their findings should not be discounted as they may provide some insight into the possible mechanisms underpinning the observed associations between sitting and chronic disease. As insulin sensitivity was only measured pre and post bed rest, the timescale for the observed metabolic changes cannot be established. However if such changes were apparent following one day of bed rest then it would be reasonable to hypothesize that similar changes might be induced during a day of uninterrupted sitting.

To date only three randomised control trials have looked to investigate the acute effects of sustained versus interrupted sitting on metabolic outcomes including insulin sensitivity. Dunstan et al[273] compared the effects of three 7 hr sitting trials on glucose and insulin profiles following the ingestion of a mixed test drink in overweight and obese adults (aged 45-65yrs). One trial involved sustained sitting, while during the other two, sitting was interrupted by repeated two minute bouts of either light (3.2km/h) or moderate (5.8/6.4km.h) intensity walking. Compared to the sustained sitting trial, interrupted sitting lowered the area under the plasma glucose and insulin versus time curves by 30% and 23% respectively. No difference was seen between the light and moderate intensity walking trials. These results seem to indicate that regardless of the exercise intensity of the interruptions, breaking up prolonged periods of sitting has a beneficial effect on glucose and insulin metabolism. However, what is not clear from this study is whether the reductions in glucose and insulin concentrations were due to the act of disrupting sitting, or whether they were due to the

accumulation of a higher total daily energy expenditure due to the repeated walking bouts.

Stephens et al[274] used a similar three trial design to examine insulin action in a younger (aged 19-32yrs) population. The first two trials involved a day of uninterrupted sitting and a day of activities which were designed to replicate the normal day to day movements of a healthy adults (sitting was restricted). Energy intake was controlled and was the same in the first two trials. The third trial involved a day of uninterrupted sitting in which energy intake was reduced in order to balance the reduced energy demands of a completely sedentary day. Compared with the active trial, one day of sitting reduced insulin action by 39%. Reducing energy intake to match the lower energy demands of sitting significantly attenuated but did not completely prevent the decline in insulin action. Unlike in the study by Dunstan et al, by removing the effect of energy balance in one of the trial arms it is possible to see whether there are physiological changes which relate to sitting itself which may contribute to observed associations with disease. The findings suggests that a positive energy balance (due to low energy expenditure) may account for a large proportion of the difference between uninterrupted and interrupted sitting patterns, but that other factors specific to sitting behaviour such as haemodynamic changes caused by low muscle activity or differences in posture during sitting may be also involved.[274]

In a similar study Peddie et al [275] examined differences in plasma glucose, insulin and triglyceride concentrations across three nine hour trials in

70 adults (aged 25.9 ± 5.3 yrs). The first trial involved sustained sitting, while during the second a single 30 minute bout of walking was undertaken at the start of the day (physical activity trial). During the third trial sitting was interrupted every 30 minutes with a walking bout lasting 1 minute 40 seconds (activity breaks trial). Three meal replacement drinks were consumed at 60, 240 and 420 minutes. Incremental area under the curve for glucose was significantly reduced in the activity breaks compared to the physical activity (37% $P<0.001$) and sustained sitting (39% $P<0.001$) trials. Incremental area under the curve for insulin was also significantly reduced in the activity breaks compared to the physical activity (18% $P<0.001$) and sustained sitting (26% $P<0.001$). No differences were observed between the physical activity and sustained sitting conditions. The total duration of activity and average heart rate during both the activity breaks and physical activity conditions were the same, suggesting that differences in total daily energy expenditure do not explain the reduction in glucose and insulin concentrations in the activity breaks trial relative to sustained sitting. Rather there are factors related to the regular interruption of sitting which may be beneficial. The authors postulate that the frequent nature of the short bouts of activity may maintain increased permeability of muscle cells to glucose and that perhaps frequent activity also maintains GLUT-4 transporter proteins in a position in the cell from which they can be readily recruited.[276]

While these studies suggest that changes in glucose and insulin regulation may contribute to the observed negative health consequences of uninterrupted sitting it is still not possible to say with any certainty whether the

observed beneficial effects are related to posture (sitting versus standing) or movement.

3.9.3. Shear stress and haemostatic changes during sitting

Another potential mechanism by which sitting might affect metabolic health and ultimately contribute to disease relates to the postural aspect of the behaviour: i.e. the haemostatic changes related to the sitting position. The endothelium is the single layer of cells lining the vascular system which performs anti-atherogenic functions such as preventing coagulation, inflammation and adhesion and regulating permeability and vasomotor control.[277] It follows that when the endothelium is compromised it's protective anti-atherogenic activities are diminished, thus promoting atherosclerosis. Nitric oxide is an antioxidant molecule that is involved in all of the anti-atherogenic properties of the endothelium.[278] One of the primary features of endothelial dysfunction is oxidative stress, which is caused by an imbalance between pro-oxidative and anti-oxidative molecules, and is the primary etiology of cardiovascular disease.[279] Shear stress is the tangential force due to blood exerted across the endothelium and is essential for the release of vasoactive substances, gene expression and cell metabolism. The synthesis of nitric oxide is catalysed by the phosphorylation of endothelial nitric oxide synthase (eNOS) which is facilitated by shear stress. The magnitude of shear stress therefore directly influences the function of endothelial cells. Areas of high shear stress where endothelial function is good are relatively protected from atherosclerosis, whereas areas of low shear stress are at greater risk.[280] Thus, low shear stress has been identified as one of the etiologies of atherosclerosis and CVD.

During sitting, muscular activity in the lower extremities is greatly reduced. The absence of the muscular contractions usually associated with postural support and ambulation decreases blood flow, increases blood pooling in the calf, augments mean arterial pressure and deforms the natural shape of arterial segments relative to upright or supine positions. The net result of these changes is a reduction in shear stress and the reduced availability of nitric oxide which compromises endothelial function. Padilla et al[281] observed that 30 minutes of sitting was enough to significantly reduce shear stress, and other studies have observed venous pooling and reduced blood flow in the legs after only an hour.[282] In light of this it has been suggested that prolonged sitting exposes the endothelium to a pro-atherogenic milieu which will increase the risk of cardiovascular disease. Conversely, bouts of activity which interrupt sitting, could interrupt the harmful hemodynamic environment associated with the sitting posture.[278] This hypothesis provides a biologically plausible mechanism for the observed associations between sitting time and chronic disease. It also fits well with epidemiological evidence for the beneficial effect of interrupting extended periods of sitting. Importantly, as this potential mechanism centres around haemodynamic changes associated with the postural or topographical aspect of sitting, it adds to the argument that sitting itself is a risk factor for disease, rather than sitting being a proxy for reduced energy expenditure or positive energy balance.

However, insulin sensitivity also plays a key role in the synthesis of nitric oxide. As discussed previously, sitting time has been observed to reduce insulin sensitivity and therefore the effect of haemostatic changes associated with

sitting down may be less important. If the reduced availability of nitric oxide relates to reduced insulin sensitivity rather than changes in blood flow, then the associations between sitting and health may yet be attributable to increased adiposity or a positive energy balance (and subsequent insulin insensitivity) resulting from reduced energy expenditure rather than a direct effect of sitting itself. As insulin and shear stress act to facilitate the synthesis of nitric oxide through the same chemical pathway[278] it may be difficult to separate the effect of one from the other. There are currently no studies which have concurrently examined both the metabolic and haemostatic effects of prolonged sitting. However, in the study by Hamburg et al[272] (described previously [3.9.2]), while the authors postulated that insulin resistance caused by five days of bed rest was the primary mechanism for the reduction in endothelial function, they also suggested that low vascular shear stress may have had a significant contribution.

3.10. Evaluation of evidence base

As described earlier in this chapter, Sir Austin Bradford-Hill proposed a set of criteria with which to evaluate whether an association between an exposure and an outcome could be considered causal. These criteria will provide a framework with which to evaluate the evidence presented in this review for an association between sitting and health.

3.10.2 Coherence with current health trends and analogous evidence

Bradford-Hill's criteria for causality refer to the coherence of an observed association with what is already known about the prevalence of the exposure and the outcome i.e. does the idea of a detrimental effect of high levels of sitting fit with current health trends? As discussed previously over the last 30 years sitting has become ubiquitous with technological development in all domains of day to day life allowing previously manual or active tasks to be automated and more sedentary. Alongside these changes the prevalence of chronic conditions such as cardiovascular disease, type II diabetes and obesity has risen and these increases are predicted to continue over the next 20 years.[283-285]

In a similar way, analogous evidence of associations between similar exposures and health outcomes can strengthen a case for a causal association. The hypothesis that high levels of sitting can have a deleterious effect on health is certainly consistent with what has been previously observed in studies examining the health consequences of a 'sedentary lifestyle'.[286] In such studies a sedentary lifestyle is characterised in part by high levels of sitting, although no direct measurement of sitting is made. Patel et al[287] examined the metabolic deterioration in the sedentary control groups of physical activity training studies. These control groups remained 'inactive' (remained largely sedentary and undertook no physical activity) for six months while participants in other experimental conditions received a range of exercise training regimes. It was observed that over the follow-up period participants in these sedentary control groups experienced deterioration in several metabolic parameters including increased adiposity, worsening lipoprotein profiles and a range of indicators of

glycaemic regulation. Similar effects were also observed over shorter four month, follow-up periods. As discussed previously, a number of studies have also observed deterioration in insulin sensitivity following periods of enforced bed rest.[269-272] These studies employ exposures which are not reflective of the sitting patterns observed in day to day living which are the focus of this thesis, but they do provide the type analogous evidence referred to in Bradford-Hill's criteria to offer support for the idea of a causal association between sitting and health outcomes.

3.10.3. The specificity of the exposure and outcome measures

Bradford-Hill also refers to the specificity of the exposure and outcome measures i.e. how well defined they are and how accurately are they measured? The more accurately defined the exposure and outcome the stronger an association should be. Within this review the outcome measures examined have been well defined as studies have predominantly focused on associations between sitting time or objectively defined sedentary time and either disease outcomes which are diagnosed by medical practitioners according to accepted diagnostic criteria or on biological risk markers which are objectively measured under controlled conditions. However the definition of the exposure in these associations is less clear and this is one of the fundamental questions in the field of sedentary behaviour research.

As discussed previously (chapter 2), a range of self-report and objective methods have been used in studies examining associations between sedentary

behaviour and health. These methodological differences have led conjecture as to the true nature of the exposure captured in observational studies. Nevertheless, studies using different measurement tools, which measure exposures including total sitting, individual sitting behaviours or objectively assessed sedentary time (defined by low levels of movement or physiological indicators of low movement), often compare their findings as if they are measuring the same thing.

3.10.3.2. The use of self-report measures to assess sitting

Self-report measures are the most prevalent in the literature. Although there is inconsistency in the measures used and which specific sitting behaviours are included they are similar in the fact that they focus on sitting itself as defined initially by its postural topography and then by type of sitting or sitting in different contexts. A major benefit of self-report measures is that they can provide information on specific sitting behaviours and the specific contexts in which they occur. The majority of the observational studies in this review have focussed either on highly prevalent leisure time sitting behaviours such as TV viewing or screen time, or have examined sitting from all domains combined. Only a few have separately examined multiple discrete sitting behaviours such as occupational sitting time, non-TV leisure time sitting or time spent in motorised transportation. Two studies examined associations of multiple sitting behaviours with mortality,[70 148] only one study has examined associations with diabetes and obesity[191] and there is no published evidence of associations between multiple sitting behaviours and CVD risk. Chau et al[148] observed that mortality risk was associated with total daily sitting but not with TV viewing or

occupational sitting. Hu et al[191] observed that while all indicators of sitting (TV viewing, sitting at home and sitting at work) were associated with diabetes risk the strength of the associations varied considerably (stronger for TV viewing than for occupational sitting or other sitting at home). Moreover while TV viewing and occupational sitting were associated with obesity risk, other sitting at home was not.

It seems that the existing evidence for an association with disease risk is stronger for TV viewing than for total daily sitting time or other sitting behaviours. All three studies examining associations between TV viewing and cardiovascular disease risk observed positive associations[65 67] while evidence of the association with total sitting time is equivocal.[165-167] As discussed previously, regular TV programming and TV schedules may also make TV viewing easier to accurately recall than other types of sitting or total sitting from all domains. Misclassification due to inaccuracies in reporting would attenuate any true association towards the null. If TV viewing is reported with less error than total daily sitting then perhaps an association is more likely to be observed. It might be that TV viewing is more strongly associated with CVD risk as people are more likely to sit and watch TV for prolonged uninterrupted periods than they are while engaged in other sitting behaviours. It is also possible that the strength of the association observed with TV viewing may be due to the confounding effects of snacking behavior (during TV viewing itself) which is not present during other types of sitting. If different types of sitting occur in different patterns (in terms of frequency and duration), are subject to different confounding and are differentially associated with health outcomes, then this

highlights the need to separately examine associations with range of sitting behaviours (including occupational and leisure time activities and combined measures of total sitting) within the same cohort.

3.10.3.3. The use of objective measures to assess sedentary time

Objective measures of sedentary time address a number of limitations of self-report measures and studies employing such objective measures such as accelerometers and heart rate monitors have also observed significant positive associations between their exposures (time spent engaged in activities producing accelerations of <100 accelerometer counts per minute, and time spent below flex heart rate respectively) with health outcomes including mortality,[150] abnormal glucose regulation[99] and metabolic risk factors.[110] In these studies the exposure is described as 'sedentary time', and it is assumed that participants are engaged in one of a number of sitting based activities. But the measurement devices used cannot measure sitting directly. As discussed the measurement of one aspect of sitting (low movement) and inferring or ignoring the others (the posture specific to sitting)[20] can lead to considerable measurement error. While self-report measures would exclude standing or slow ambulation, movement based measures such as accelerometers are likely to include it as it may not produce acceleration values or increase heart rate over the predetermined sedentary threshold. This misclassification is particularly important when attempting to distinguish between sitting and very short bouts of very light intensity activity.

3.10.3.4. Implications for our understanding of the exposure

The use of both self-report measures of sitting and various objective measures of sedentary time limits the comparability between studies. Differential associations have been observed between self-reported sitting and objectively assessed sedentary time in the same cohort [120] suggesting that they are measuring different things. Importantly the lack of specificity in the measures employed in studies examining associations between sedentary behaviour and health also highlights the uncertainty over the true nature of the exposure in this association. Although accelerometry and heart rate monitoring cannot accurately define sitting behaviour (from standing or low movement), studies have shown that prolonged periods involving low levels of movement or reduced heart rate (including during sitting behaviour) are associated with increased health risk. It could therefore be argued that it is not specifically sitting time which is important but low levels of movement (defined by time spent below a movement or metabolic threshold regardless of the specific activity or posture) which is associated with increased health risk. Time spent sitting may be characterised by relatively little movement and a relatively low metabolic rate. It could follow that in the observed association between self-reported sitting time and health, sitting time is simply a proxy marker for low levels of movement or a low energy expenditure. Conversely it is possible that the time spent engaged in low levels of movement captured by objective measures is characterised predominantly, if not exclusively by sitting and that sitting is the true exposure.

Controlled laboratory based studies of the metabolic effects of sustained sitting are needed, in order to isolate the biological mechanisms involved in the reported associations between sitting and health risk and to establish whether these changes are attributable specifically to sitting itself or to low levels of movement or low energy expenditure. Understanding these mechanisms will clarify the true nature of the exposure and allow more precise estimates of the scale of the exposure and the risk associated with it.

3.10.3. Strength, consistency and the temporal nature of the association between sitting and health

3.10.3.1 Strength and consistency and the possible effects of misclassification

The results of the systematic reviews (figure 3.5) suggest that the weight of both the cross-sectional and prospective evidence supports a detrimental effect of high levels of sitting time and health. The large number of studies reporting significant positive associations demonstrates the consistency required by the Bradford-Hill criteria for an association to be considered causal. This criterion questions whether an association has been observed in a variety of settings, using a variety of methodologies and in different populations. As described throughout this review associations between sitting or sedentary behavior and health outcomes have been observed using a range of exposures (including TV viewing, [35] [173] [181] [200] [206] [288] leisure time sitting behaviour, [188] occupational sitting, [69] and total sitting time) [54] [64] using a number of

measurement tools (self-report, [35 53 67 190 191] accelerometer, [54 109 110] heart rate monitoring) [83 99 117] in adults from various countries (UK, [55 65-67 99 117 206 289] US, [54 188 190 191] Australia, [35 53 109 110 173 181 200 207 230 288] Belgium, [189] Germany, [56] and Portugal).[64]

While the consistency of these findings was far greater in the literature relating to mortality and metabolic disease than in the literature regarding cardiovascular disease morbidity it is possible that this is due in part to the variation in cardiovascular disease outcomes examined in these studies. The inconsistency of findings related to sitting time and obesity suggests a complex relationship which may influence associations with other health outcomes and which require further examinations.

Bradford-Hill highlights the importance of consideration of the strength of an observed association when considering the case for it being causal. The stronger a relationship appears, the less it could merely reflect the influence of some other aetiological factors. A one hour increase in daily TV viewing has been associated with an 11% (95%CI 3-20%) increase in all-cause mortality risk; [53] an 18% (95%CI 3-35%) increase in CVD mortality risk; [53] a 6% increase in risk of both total (95%CI 3-8%) and non-fatal (95%CI 3-9%) CVD incidents; [65] and a 12% (95%CI 0.001-27%) and 26% (95%CI 14-46%) increase risk of metabolic syndrome in men and women respectively. [181] A two hour increase in TV viewing has also been associated with a 14% (95%CI 5-23%) increase in diabetes risk and a 23% (95%CI 17-30) increase in obesity risk.

The case for an association to be considered causal is also strengthened by the presence of a biological gradient or a dose-response relationship between exposure and outcome. There are examples of dose response relationships between sitting and risk of mortality,[53 55 62] incident CVD, [65 166 167] metabolic disease,[181 190-192] obesity [191 227 231] and a range of risk markers[54 197 200] indicating that risk to health may be greater with increasing amounts of sedentary time . These relationships have most often been reported as an increase in risk across discrete categories of increasing sedentary time although a number of studies have quantified a change in risk per unit of sedentary time. This type of associations has been observed in samples with different distributions of sitting time indicating that the dose response relationship may apply even at low levels of sitting.

However a number of studies have only reported associations when comparing extreme categories of sitting. An increase in risk for incident CVD was only observed by Manson et al[166] when comparing those who sit for >16hrs per day and those who sit for <4hrs per day. Similarly Chomistek et al[167] reported a greater risk in those who sit for >10hrs per day compared to those who sit for <5hrs per day suggesting that the association between sitting and risk for CVD is not linear.

In addition effect sizes observed in associations between sedentary time and disease risk suggest a consistent but relatively weak association. The wide confidence intervals often observed with these effects also indicates a lack of precision in the measurement of the exposure. As discussed previously the

measures employed in studies examining the associations between sitting or objectively defined sedentary time and health are likely to be affected by measurement error. Sitting behaviours are difficult to accurately recall and objective measures can't determine sitting from standing and therefore there is likely to be a degree of misclassification inherent in both measures. This measurement error, if non-differential will attenuate observed associations. However it is also likely that sitting behaviours may be differentially under-reported by different groups within the population due to social desirability. If healthier people under-report sitting more than less healthy people then this will artificially inflate the observed association between sitting and health. Improvements in the measurement of sedentary behaviour will allow a clearer indication of the strength of the association with health outcomes, although as discussed such improvements are dependent on a clear definition of the exposure of interest.

3.10.3.2. Adjustment of analyses for the confounding effects of physical activity

Generally, prospective studies have adjusted analyses for important covariates including age, gender, socioeconomic position, health status and physical activity. As discussed previously, a central hypothesis in sedentary behaviour research is that the effect of sitting time on health is independent of, and in addition to the effect of physical activity. The persistence of observed associations following adjustment for physical activity is cited in evidence of this. Most commonly studies have adjusted their analyses for time spent in moderate to vigorous PA,[53 67] although a number of studies have measured

leisure time physical activity,[165 167] leisure time exercise,[193] and adherence to public health guidelines (based on MVPA).[154] Light intensity physical activity has rarely been included as a covariate in previous prospective analyses of sedentary behaviour and health outcomes. Measuring light intensity activities using self-report is problematic as such activities occur throughout the day in many different contexts and often for very short amounts of time. While time spent engaged in light intensity activity can be measured using accelerometers, it cannot be included as a covariate in analysis of sedentary time along with MVPA as time spent in these four activity intensities would comprise 100% of accelerometer wear time. This would cause collinearity in the analytical models. Nevertheless without adjusting for all physical activity it is not possible to say for certain that the observed associations are not a result of residual confounding due to differences in light intensity physical activity.

3.10.3.3. The temporal nature of the association between sedentary time and health, and the complex relationship with adiposity

In order for an association to be causal Bradford-Hill states that the exposure (in this case sitting) must precede the outcome. A number of studies examining associations between sedentary behaviour and mortality risk repeated their analysis after excluding all deaths within the first year,[62 150 153] two years,[55 63 67] three years[70 149] or four years[53] after baseline. One study also stratified the analyses by 3 categories of follow-up time in order to examine differences in the observed association (it was reported that the associations were similar for each category of follow-up time).[154] Some of these studies also excluded participants with a history of conditions such as cardiovascular

disease, myocardial infarction, stroke, cancer, and emphysema.[53 55 62 67 70 149 150 154] As discussed previously it is possible that deteriorating health may cause people to engage in more sedentary activities, increasing their baseline sedentary time as well as their mortality risk. These steps reduce the possibility that prior health conditions and subclinical or undiagnosed illness will affect the exposure prior to its baseline measurement and doing so reduces the risk of reverse causality. Those prospective studies which observed associations between sedentary time and incident CVD used similar methods to reduce the possible effects of reverse causality, with most repeating analyses following exclusion of all cardiovascular events from the first year of follow-up.[65 67 164 166] In studies by Chomistek et al[167] and Manson et al,[166] as well as excluding participants with previous history of cardiovascular and cerebrovascular disease the authors excluded participants with any medical condition which would normally be associated with a predicted survival of less than 3 years including liver and kidney disease, alcoholism and some mental illnesses.

It is more difficult to rule out the possibility of reverse causality in the prospective studies examining associations between sedentary time and both metabolic disease and obesity. None of the studies examining associations with incident type II diabetes report repeating the analysis following exclusion of those diagnosed early in follow-up. While some studies excluded participants with a history of conditions including CVD, cancer, stroke, myocardial infarction and gestational diabetes,[190-192] none have accounted with the presence of abnormal glucose metabolism or subclinical diabetes at baseline (either by excluding participants or adjusting for baseline measures of insulin sensitivity in

their analyses). Also, only three of these studies adjusted their analyses for baseline BMI[56 191 192]. Krishnan et al[192] explain that this decision was taken as obesity can be viewed as being on the causal pathway between sitting and obesity and therefore should not be included as a covariate. However as described above the nature of the association between sitting and obesity is unclear. By not adjusting for either BMI or insulin sensitivity the possibility that subclinical illness or undiagnosed diabetes may influence baseline sedentary time remains.

It is very plausible that high levels of sedentary time might be both a cause and consequence of obesity and as described previously two authors[117 250] have suggested that obesity or adiposity may predict sedentary time rather than sedentary time predicting obesity. Clarifying the apparent bi-directional relationship between sitting and obesity is important, not just for obesity research but also for studies examining the associations between sitting and other health outcomes for which obesity or adiposity is a precursor. Within this review a number of prospective studies have observed that following adjustment for BMI, significant associations with disease outcomes have been substantially attenuated[190 192] or attenuated to null.[56] This effect was also apparent in the cross-sectional analyses by George et al,[29] Stamatakis et al,[128] Tonstad et al[172] and de Heer et al.[157] In addition it has been observed that variance in BMI explained a significant proportion of the associations between accelerometer defined sedentary time and metabolic risk markers.[128 252] It is therefore possible that obesity or adiposity may play a mediating role in the associations between sitting and disease outcomes. In order to better

understand these relationships, further research is needed to clarify the nature and direction of the association between sedentary time and obesity.

3.10.4. Biological plausibility and experimental evidence

The last of Bradford-Hill's criteria refer to whether an association between an exposure and an outcome is biologically plausible and whether there is experimental evidence for an association. As discussed previously (3.7) a number of studies have observed significant detrimental associations between both self-reported sitting and objectively assessed sedentary time with a range of individual risk markers which are important precursors to chronic conditions such as cardiovascular and metabolic disease.[34 35 54 128 200 252] These studies suggest that deleterious effects on insulin sensitivity, lipid metabolism and inflammatory markers may provide the biological pathway by which sitting might increase disease risk. It has also been demonstrated that interruptions in sedentary time may attenuate these detrimental effects.[109]

The argument for causality can be further strengthened if it is demonstrated under controlled laboratory conditions that a manipulation of the exposure (i.e. different patterns of sitting/interruptions) causes a change in these outcome measures. There is currently a dearth of experimental studies which have examined the acute metabolic effects of sustained sitting behaviour. The findings of three of these studies, those by Dunstan et al[273] Stephens et al,[274] and Peddie et al[275] suggest that interrupting prolonged periods of sitting with light intensity activity may have beneficial effects on glucose and insulin

regulation. However what is not clear is the underlying mechanism of this effect and whether it is caused by sitting or by an increase in movement or energy expenditure. Dunstan et al observed that there was no difference in the magnitude of this effect between trials, where sitting was interrupted between two different walking speeds and concluded that any interruption of sitting (regardless of the energy expenditure) would provide a benefit.[273] Stephens et al observed that a reduction in energy intake, to match a lower energy expenditure during a day of sustained sitting, eliminated a large proportion of the between trial differences and concluded that the detrimental effects of sitting may be largely due to a positive energy balance.[274] This suggests that energy expenditure and energy balance may be important factors in the association between sitting and metabolic health. This is also supported by Miyashita et al[260] who suggested that small differences in energy expenditure between a day of sitting and a day of sitting with a single walking interval may account for the observed differences in postprandial lipaemia. However Stephens et al also suggest that as not all of the observed effects could be explained by differences in energy balance there may be additional factors, specific to sitting behaviour, which may contribute. These factors may relate to changes in blood flow and resultant low or turbulent shear stress caused by the sitting posture.

Further controlled experimental studies are needed to clarify the biological changes which may occur with sustained sitting behaviour and the timeframe over which they occur. Changes in these metabolic markers with different patterns of sitting, i.e. different numbers and distributions of sedentary breaks (interruptions in sitting) also require further examination. As described

above, by isolating and manipulating these mechanisms in a controlled setting it will also be possible to clarify the true nature of the exposure i.e. whether the observed detrimental effects of high levels of sedentary time are due to sitting itself, or because sitting is simply a proxy for lower energy expenditure.

3.11. Summary and directions for research

The idea that sitting can have detrimental effect on health is coherent with current health trends and analogous evidence of associations between inactivity or sedentary lifestyle and disease. From the literature described above it is clear that there is evidence for an association between sitting or sedentary time and health outcomes. Large, cohort studies from a range of different populations have demonstrated significant positive associations between self-reported sitting time and both all-cause and cardiovascular disease mortality risk and there is also evidence for an association between sitting or sedentary time and metabolic disease. However the evidence for an association between sitting and both incident cardiovascular disease and obesity is less consistent.

There are examples of dose-response associations between sitting and health risk, observed in a wide range of populations using a number of different methodologies. Associations with individual biological risk markers from both epidemiological and early experimental studies also suggest that a mechanistic link between sitting and health risk is biologically plausible. However a number of fundamental research questions remain.

The temporal relationship between sitting and obesity is unclear and this may confound associations between sitting and other health outcomes. As it is plausible that high volumes of sitting are both a cause and a consequence of obesity further research is needed to clarify the direction of this association in order to clarify the role of obesity in the relationship between sitting and other health outcomes.

An examination of the potentially differential associations of a range of separate sitting behaviours with health outcomes is also necessary. Both epidemiological and experimental evidence has suggested that different patterns of sitting might determine the magnitude of any negative health effects. However, only a few studies have separately examined multiple sitting behaviours, which may differ in in their determinants, frequency and duration, in the same cohort.

The true nature of the exposure also needs to be clarified. It is possible that the observed associations between sitting or sedentary time with health outcomes are attributable to low levels of movement resulting in a low energy expenditure or from metabolic changes associated with sitting itself. If low movement/energy expenditure is the crucial factor and the postural aspect of sitting has no bearing on the association between sitting and health then it is possible that non-sitting activities such as standing or slow walking (with similar low energy expenditures) may be equally detrimental to health. However if there are features of the postural aspect of sitting which contribute to deleterious effect on health then sitting itself can be regarded as the true exposure. The relatively wide confidence intervals for the reported effects of increasing sitting

often reported in the literature speak to a possible lack of precision in the measurement. By clarifying the exposure decisions can also be made on how best to accurately measure it and subsequently improve the precision of the estimates of the association between sitting and health outcomes.

Further experimental evidence is needed to identify the biological parameters which are affected by acute exposure to sustained sitting, the time frame over which these changes occur and the potential benefits of interrupting sustained periods of sitting. This will not only provide better insight into the mechanisms underpinning the observed associations with disease risk but will also clarify whether sitting itself or low levels of movement is the true exposure. This insight could in time provide a basis for future behavioural intervention to improve population health.

As discussed previously, the criteria proposed by Bradford-Hill are not intended as nine strict rules which must be adhered to in order for a causal association to be established. Others have proposed differing criteria and it has also been argued that the myriad reservations and exceptions to such criteria undermine their use altogether.[290] However these criteria do provide a framework of perspectives from which to analyse a given body of evidence and to highlight gaps or weaknesses that can guide future research. Based on this review of the current evidence regarding sitting and health the following research questions have been identified and these will form the basis of my thesis. These questions fall under three main themes:

What is the risk associated with high volumes of daily sitting?

1. Is sitting time associated with risk for major health outcomes?
2. Are associations between all types of sitting and major health outcomes the same?
3. What is the direction of the association between sitting and obesity?

Who is at risk?

4. What is the prevalence of sitting in England and does sitting vary across population subgroups?

What causes the reported risk of sitting?

5. What are the biological mechanisms that underpin the observed associations between sitting and health outcomes?
6. Can interrupting sustained sitting beneficially affect these mechanisms?

These questions will be address in the subsequent chapters.

Chapter 4

The Whitehall II study

In order to examine the health risks associated with sitting time I have drawn upon data from the Whitehall II study, a longitudinal cohort study of London based employees working within 20 departments of the Whitehall offices of the British Civil Service.

4.1. The Whitehall and Whitehall II studies: History

The original Whitehall study was set up by Donald Reid and Geoffrey Rose in the 1960's as a longitudinal study of cardiorespiratory disease and diabetes.[291] Personal letters were sent to male Civil Servants aged between 40 and 64, working in selected departments within approximately 2 miles of Whitehall in London, explaining the study's objectives and inviting them to participate. The response rate was 77%, ranging from 57% among messenger grade employees to 87% amongst senior grades.[292] The baseline cohort consisted of 18403 participants. The study was based at the London School of Hygiene and Tropical Medicine and Guy's Hospital Medical School and initially included a standardised questionnaire and a simple baseline screening examination between 1967 and 1969 (consisting of measurements including height, weight, blood pressure, plasma cholesterol concentration, a glucose tolerance test and a 6-lead electrocardiogram).[293] Follow-up was limited to deaths identified from the National Health Service registry. Although the Whitehall studies have become closely associated with socioeconomic differences in health, investigation of social stratification was not the original

focus of the study.[291] Although it had been observed that mortality risk was markedly higher in men and women from the working classes than those of higher status,[294] the general view was that social differences in health were due to people in the lowest social strata suffering with diseases associated with material deprivation while the more affluent were more likely to be afflicted with conditions of excess such as heart disease.[291 295]

Nevertheless evidence from the Whitehall study demonstrated that over ten years of follow up there was a steep inverse social gradient in mortality from all-causes, from coronary heart disease (CHD) and from non-coronary causes. Compared to senior administrative staff the relative risk of death from CHD was 2.2 for clerical employees and 1.6 for those in the intermediate professional and executive grade.[296] Men in the lower employment grades tended to be shorter and heavier for their height, had higher blood pressure and fasting plasma glucose, smoked more and reported less time in physical activity than those in higher grades.[294] However, after adjustment for these conventional risk factors two thirds of the risk differential between clerical and administrative grades remained unexplained.[294 296 297] These findings suggested that health inequalities were not, as had been previously assumed, limited to the consequences of poverty.

It was therefore hypothesised that other psychosocial and nutritional factors may contribute to the social gradient in mortality. The Whitehall II study was set up by Professor Sir Michael Marmot in 1985 to continue the central themes of the original study, but also with the long term aim of determining the

specific biological mechanisms which account for the previously observed social inequalities in health outcomes including cardiovascular disease, diabetes and mortality. With such mechanistic questions the study sought to build evidence for disease occurrence and for explanations of social inequalities in incidence.[291]

4.2. The Whitehall II study: The participants

All civil servants (men and women) between the ages of 35 and 55 working in the London offices of 20 Whitehall departments were invited to participate by letter and 73% agreed.[298] The achieved baseline sample of 10308 (3416 women and 6895 men) were from clerical and office support grades, middle ranking executive grades and senior administrative grades. Each participant gave written informed consent and the University College London ethics committee approved the study. The baseline examination (Phase 1, 1985-88) involved a self-administered questionnaire and a clinical examination. Subsequent phases of data collection alternated between postal questionnaire alone and a combination of questionnaire and a clinical exam. In order to minimise attrition between measurement phases careful attention was paid to the quality of all contacts with participants and considerable diligence taken in tracing those lost to postal contact.[291] Measurement phases, number of participants and response rates are detailed in table 4.1.

Table 4.1. Summary of Whitehall II study measurement phases

Phase	Dates	Type	Participants	Response rate
1	1985-1988	Screening and questionnaire	10308	73% of responders
2	1989-1990	Questionnaire	8132	79% of P1 responders
3	1991-1993	Screening and questionnaire	8815	86% of P1 responders
4	1995-1996	Questionnaire	8628	84% of P1 responders
5	1997-1999	Screening and questionnaire	7870	76% of P1 responders
6	2001	Questionnaire	7355	71% of P1 responders
7	2003-2004	Screening and questionnaire	6967	68% of P1 responders
8	2006	Questionnaire	7173	70% of P1 responders
9	2008-2009	Screening and questionnaire	6761	66% of P1 responders
10	2011	Screening and questionnaire*	277	84% of those invited
11	2012-2013	Screening and questionnaire	6318	61% of Phase 1 responders
12	2015-2016	Screening and questionnaire	Currently in planning stage	

P1= Measurement Phase 1. *Pilot. A small group of Stress and Health participants were selected randomly and invited to attend Phase 10 clinic. This enabled the successfully pilot of new measures for mental well-being introduced at Phase 11.

4.3. The Whitehall II study: Funding

The recruitment process and baseline measurements were funded through a series of small grants from the Medical Research Council in the UK, the National Heart Lung and Blood Institute in the USA and the UK Health and Safety Executive. The Whitehall II study is currently supported by grants from the Medical Research Council (G0902037), British Heart Foundation (RG/07/008/23674), Stroke Association, National Heart Lung and Blood Institute (5RO1 HL036310) and National Institute on Aging (5RO1AG13196 and 5RO1AG034454).

4.4. The Whitehall II study: The measurements

The study was designed to provide regular contacts with the cohort in order to track changes in social and economic circumstances, psychological states, health behaviours and biological pathways to clinical and subclinical diseases.[291] The non-biological and biological factors measured are described in tables 4.2 and 4.3.

Table 4.2. Summary of non-biological data collected in the Whitehall II study

Subheading	Description
Demographic data	Age, gender, ethnicity
Socioeconomic data	Education, household composition, income, financial assets, work and work change (retirement).
Area-level indicators	Deprivation, classification of area.
Psychosocial/work exposure	Effort-reward, demand-control, social support, social networks.
Health behaviours	Smoking, alcohol, diet-food frequency, physical activity.
CVD	WHO chest pain, details of CVD symptoms investigations and treatment.
General health (subjective)	Self-rated health, well-being, longstanding illness, hospital admissions, medications, musculoskeletal conditions, quality of life (SF-36).
Mental Health (subjective)	General Health Questionnaire (GHQ) (anxiety, depression), Centre for Epidemiological Studies Depression Scale (CESD), SF-36 Activities of daily living (ADL), Instrumental ADL.
Health outcomes (objective)	Sickness absence, myocardial infarction and coronary surgery, stroke, clinical depression, CVD/CHD mortality, mortality.

Adapted from Marmot et al. 2005[291]

Table 4.3. Summary of physiological assessments by measurement phase of the Whitehall II study

	Phase 1 (1985-1988)	Phase 3 (1991-1993)	Phase 5 (1997-1999)	Phase 7 (2003-2004)	Phase 9 (2008-2009)	Phase 11 (2012-2013)
Examination	weight, height, BP	weight, height, w/h ratio, BP	weight, height, w/h ratio, BP	weight, height, w/h ratio, BP, walking speed, spirometry	weight, height, w/h ratio, body composition, BP, walking speed, spirometry	weight, height, w/h ratio, body composition, BP, walking speed, spirometry
Neuroendocrine	BP reactivity		HR variability, hypothalamic-pituitary – adrenal axis measurements	HR variability, salivary cortisol diurnal rhythm	HR variability, salivary cortisol diurnal rhythm	HR variability, diurnal rhythm
Subclinical CVD	ECG: Minnesota codes, ECG LVM	ECG: Minnesota codes, ECG LVM	ECG: Minnesota codes, ECG LVM, US measures of endothelial dysfunction, carotid artery wall thickness/ distensibility, MRI	ECG: Minnesota codes, ECG LVM, US measures of endothelial dysfunction, carotid artery wall thickness/ distensibility	ECG: Minnesota codes, ECG LVM, US measures of endothelial dysfunction, carotid artery wall thickness/ distensibility	ECG: Minnesota codes, ECG LVM, US measures of endothelial dysfunction,
Lipids	Total cholesterol, apoA1, and apoB	Total, LDL & HDL cholesterol apoA1 & B I.p(a), triglycerides, cholesterol ester fatty acids	Total, LDL & HDL cholesterol, triglycerides	Total, LDL & HDL cholesterol, triglycerides	Total, LDL & HDL cholesterol, triglycerides	Total, LDL & HDL cholesterol, triglycerides
Carbohydrate metabolism		Fasting and post-load glucose and insulin, HOMA %β, HOMA %IS	Fasting and post-load glucose and insulin, HOMA %β, HOMA %IS	Fasting and post-load glucose and insulin, HOMA %β, HOMA %IS, HbA1c	Fasting and post-load glucose and insulin, HbA1c	Fasting and post-load glucose and insulin, HbA1c
Haemostatic and other	Fibrinogen, Factor VIIc	Fibrinogen, IL-6, CRP, factor VIIc, von Willebrand factor PAI-1, Plasma β-carotene	Fibrinogen, IL-6, CRP, SAA, viscosity D-dimer	Fibrinogen, IL-6, CRP,	Balance, chair rise, grip strength	Chair rise, grip strength, liver function

Adapted from Marmot et al. 2005[291] BP = blood pressure, w/h = waist-hip, HR = heart rate, ECG = electrocardiogram, LVM = left ventricular mass, US = ultrasound, MRI = magnetic resonance imaging, HDL = high density lipoprotein

4.5. Strengths and limitations of the Whitehall II study

The interdisciplinary nature of the Whitehall II study is a significant strength. Differences in health behaviours, risk factors and disease incidence across social strata are examined from social, psychological and biomedical perspectives. Repeated measurements of such a breadth of potential health determinants in a large sample, and the relatively low levels of attrition between measurement phases allows the tracking of changes in disease risk and the identification of biological plausible links between exposures and disease outcomes.

However the study is not without limitation. Occupational cohort participants are by definition sufficiently healthy to be in active employment, which may reduce the extent to which conclusions may be generalised to a wider population. Although the relatively rigid occupational hierarchy within the Civil Service allows the examination of the health effects of working at different levels of stratified organisation, this structure may not reflect those observed in other large employers.

The baseline sample reflected the composition of the Civil Service at the time of the study's inception. Women comprise only a third of the baseline group and around half of these were in the clerical and office support grade which may limit the ability to examine social differences in women's health. There is also an absence of manual workers (in common with other white-collar organisations) and a relative lack of ethnic minority participants in the higher

employment grades. Attrition may also be higher amongst those from the lower employment grades and from ethnic minority groups.

4.6. Assessment of physical activity in the Whitehall II study

At the inception of the study the questionnaire items relating to physical activity focussed on frequency and duration of leisure time sporting activities and day to day household tasks. Participants were asked '*How often do you take part in sports or activities that are: a) mildly energetic (including walking, woodwork, weeding, hoeing, bicycle repair, playing darts, general housework), b) moderately energetic (including scrubbing, polishing car, chopping, dancing, golf, cycling, decorating, lawn mowing, leisurely swimming), or c) vigorously energetic (including running, hard swimming, tennis, squash, digging, cycle racing)*. Response categories were*: 3 or more times per week, 1 or 2 times per week, 1 to 3 times per month, never or hardly ever*. Participants then reported the total volume of time, in hours per week that they spent in activities that were mildly, moderately or vigorously energetic using three open text response fields.

These items were used again in phases 2 and 3 to assess physical activity. In phase 3, two additional items were included. Participants were asked how their normal walking pace compared to someone of the same age and sex (slower, faster, same pace) and how many times per week the engaged in physical activity long enough to work up a sweat. These items were repeated in the phase 4 questionnaire. Complete versions of the Whitehall II questionnaires are available from the following address (http://www.ucl.ac.uk/whitehallII/data-sharing).

A more detailed assessment of physical activity behaviour was included in the phase 5 questionnaire. Participants were asked to report on average how many minutes they walked and cycled and how many flights of stairs they climbed during weekdays and weekend days over the past week. The questionnaire then assessed physical activities using a modified version of the Minnesota leisure-time physical activity questionnaire[299] which assesses both occupational, domestic and leisure-time physical activities, and which has been validated previously.[299] Twenty items assessed time spent engaged in the following activities: walking, sports (cycling, football, golf, swimming and two open-text responses for any other sports), gardening (lawn mowing, weeding and one open-text response for other gardening activities), and housework (cooking, handing washing, carrying shopping, and two open text responses for other housework activities). As a measure of typical activity, participants were required to report the amount of time, in hours per week, spent engaged in each of these activities over the previous four weeks. Each activity was then assigned an energy expenditure value using reference values from a compendium of physical activity energy costs. The reference energy expenditure values used in the early stages of Whitehall II were originally published by Passmore and coworkers in 1955 [300] and were used to compute total energy expenditure in participants of the Harvard Alumni Study.[6 17] Some of these reference values were updated following the publication of an updated compendium of physical activity costs in 1993.[301] Physical activities were classified by metabolic equivalents (MET) where 1 MET was equal to energy expenditure at rest (approximately 3.5 ml O_2 per kg body mass/per minute.[302] Moderate intensity activities (e.g. heavy gardening, heavy household maintenance activities, some sports,) ranged from 3-5.9 METS and vigorous

intensity activities (e.g. sports) 6 METS or greater. As physical activity guidelines[13] make their recommendations based on the required volume of activity of moderate level or above to promote and maintain good health, time spent in moderate and vigorous activity was combined as a measure of moderate to vigorous physical activity (MVPA).

4.7. Sedentary behaviour in the Whitehall study; common methods for subsequent analyses

The subsequent four chapters examine the associations between sitting time and four of the most common health outcomes in the sitting literature; mortality, cardiovascular disease, diabetes and obesity. The following section details the development of sitting exposures which are common to each of these four analyses.

4.7.2. Determination of sitting time indicators

Measures of occupational and leisure time sitting were first included in the Whitehall II screening questionnaire at Phase 5 (1997-99) and it is this phase which forms the baseline for the analyses in the subsequent four chapters. Participants were asked '*On average how many hours per week do you spend: sitting at work, driving or commuting?' and 'sitting at home e.g. watching TV, sewing, at a desk?'*, and responded by selecting one of eight time categories (none, 1hr, 2-5, 6-10, 11-20, 21-30, 31-40, >40hrs). For sitting at home participants were given an open text response option to specify two types of sitting (each of which was subsequently given an activity code) and then selected a time category for each.

Leisure time activities were recoded from original activity codes (in tsitho1 and tsitho2) as follows; None = 0; TV=1(originally 231); Reading = 2 (originally 224); Deskwork/Various sitting things = 3 (originally 256); Eating =4 (originally 227); Other = 5 (all other activity codes and including cases with a missing activity code but with a time value). Total hours spent in activities 1-5 were summed from the two time categories. Using the midpoint of each time category, 5 indicators of sitting expressed as hours per week were then computed: 1) work related sitting time, 2) TV viewing time, 3) Non-TV leisure sitting time, 4) Total leisure time sitting (sum of 2 and 3 above), and 5) Total sitting time (sum of 1-3 above). These items have been used previously[191] and their validity is described elsewhere.[303]

The next four chapters will examine the associations between these sitting indicators with: mortality, from all causes and from cardiovascular and coronary heart disease (Chapter 5); cardiovascular disease morbidity including myocardial infarctions and angina (Chapter 6); type II diabetes (Chapter 7); and obesity (Chapter 8).

Chapter 5

Sedentary Behaviour and Mortality Risk

5.1. Introduction

The protective effect of physical activity of a moderate or vigorous intensity is well established.[304] Previously it had been assumed that the negative health consequences associated with a 'sedentary lifestyle' were attributable to an absence of moderate to vigorous intensity physical activity (MVPA). However, in the last decade sedentary behaviours, i.e. those which elicit an energy expenditure of less than 1.5 metabolic equivalents (METs) and in which sitting predominates,[21] have been viewed as a distinct class of behaviours with their own correlates. There is now growing evidence that prolonged periods of sitting during activities such as watching television and working at a computer are associated with a number of non-communicable diseases including cardiovascular[65 67] and metabolic conditions[56 190-192] independent of MVPA. A recent prospective study by van der Ploeg et al[153] examined death from all causes in over 222000 Australian adults and observed a positive association across four categories of self-reported daily sitting time. Several other prospective studies have also shown increases in the risk of all-cause[62 63 148 150 153 305 306] and cause specific[62 70 148 152 154] mortality with increased sitting time, and changes in daily sitting time over a two year period have been shown to reflect changes in risk of death from all causes.[151]

Although sitting in all contexts can be broadly described as having the same behavioural or postural topography, it can serve many different functions

(e.g. sitting while watching TV or sitting at work) and can therefore be further classified by type.[20] Different types of sitting have been demonstrated to have different correlates.[30] Both epidemiological[109] and experimental[273] evidence suggests that interrupting prolonged periods of sitting may attenuate any potential harmful effects, highlighting the importance of pattern as well as duration of sitting. As discussed previously (3.8) Healy et al[109] reported that independent of the total duration of sitting time, the number of interruptions or breaks in sitting time (1 minute or more at >100 accelerometer counts per minute) was beneficially associated with a number of cardiometabolic risk factors. Given that different sitting types occur in a variety of contexts and differ in duration and pattern,[109] it is logical that they may also demonstrate differential associations with health outcomes, as evidenced by a number of epidemiological studies.[68 190 191 128 163]

As discussed in chapter 1, a reduction in the environmental demands for physical activities due to technological advancement affecting transportation, the workplace and leisure time entertainment has led to an increasing prevalence of daily sitting in a range of contexts.[26] For this reason a comprehensive understanding of the associations between health and both total sitting time and different sitting types is essential. However, no previous studies have sought to separately examine the associations between mortality risk and both total sitting and different sitting types in the same cohort. Such studies have either focussed on single common sitting behaviours such as TV viewing,[53 55 70 154] screen time,[55 67] or travelling in a car,[153] or have only examined all types of sitting combined.[149 152 153 305 306]

This study aims to enhance the evidence base by drawing on 15 years of data from the Whitehall II cohort study to examine the type-specific associations of five different sitting indicators and risk for all-cause mortality, and mortality from both coronary heart disease and cardiovascular disease.

5.1.2. Hypotheses

Based on the current available evidence it is reasonable to hypothesise that:

i. Time spent in indicators of sitting will each be positively associated with risk of mortality from all causes, from coronary heart disease, and from cardiovascular disease
ii. These associations will be independent of time spent in moderate to vigorous intensity physical activity

5.2. Methods

5.2.1. Determination of Sedentary Behaviours and Mortality

The five sedentary behaviour exposures were determined from Phase 5 data as described previously (4.7.2).

In the present analysis mortality was established through the national mortality register kept by the National Health Service (NHS) Central Registry, using the unique NHS identification number assigned to each British citizen. It is a requirement that this registry, subsequently part of the Office National

Statistics and as of 2013 part of the HM Passport Office (an agency of the Home Office), records all deaths before burial or cremation can take place. International classification of Disease (ICD) codes were used to identify CHD and CVD deaths (ICD-9, 390.0-458.9; ICD-10, 100-199).

5.2.2. Covariates

The sociodemographic covariates included in the current analysis were age, gender, ethnicity and employment grade. Ethnicity was classified as one of the following; Black-Caribbean, Black-African, Black-Other (open text option to specify), Indian, Pakistani, Bangladeshi, Chinese, White, or other (open text option to specify). Employment grade (3 levels: clerical and support, professional and executive, senior administrative) in the Whitehall II Study is a comprehensive marker of socioeconomic circumstance relating to social status, salary and level of responsibility[307] For retired participants, their last reported employment grade was considered. Health related covariates included self-rated health (reported as; excellent, very good, good, fair, or poor), smoking status (current, previous, or never a smoker), alcohol consumption, diet quality, body mass index (BMI) and physical functioning. Participants reported the number of 'measures' of spirits, 'glasses' of wine, and 'pints' of beer consumed in the previous seven days, and this was then converted to units (1 unit=8g) of alcohol. Diet quality was represented by frequency of fruit and vegetable consumption and was assessed using an eight point scale ranging from: 1) *"seldom or never",* to 8) *"two or more portions per day*". Height (m) and weight (kg) were recorded during clinical examination and BMI calculated using a standard formula. To assess perceptions of physical functioning the SF-36

questionnaire was used and scored with the Medical Outcomes Study scoring system.[308] The SF-36 assesses the extent to which participant's health limits their ability to perform physical activities, ranging in intensity from vigorous (sporting and volitional exercise activities) to light (day-to-day tasks) using the responses *"a lot", "a little",* and *"not at all"*. Responses were scored, summed and transformed to scale from 0 (limited a lot in performing all types of physical activities) to 100 (able to perform all types of physical activity without limitation). This scale has been demonstrated to have high internal consistency. [309]

Physical activity covariates included daily walking time (minutes/day), and time spent in moderate to vigorous physical activity (hrs/wk). Physical activity was assessed at Phase 5 using a modified version of the Minnesota leisure-time physical activity questionnaire which assesses both occupational and leisure-time physical activities, and which has been validated previously.[299] Twenty items (including five open-text responses) assessed time spent engaged in walking, sports and games, gardening activities, housework and do-it-yourself building/maintenance projects, in hours over the previous four week period. Each activity was subsequently assigned an energy expenditure value in metabolic equivalents (METs: where 1 MET is equal to energy expenditure at rest) using a compendium of activity energy expenditures.[302] Moderate intensity activities were classified as those eliciting an energy expenditure of 3-5.9 METs and vigorous intensity activities from 6 METs and upwards. The energy expenditure of walking activity is dependent on walking pace and could therefore not be determined from the Phase 5 questionnaire. As a result, while in some instances walking may have met the required energy expenditure, for

the purposes of the present analysis walking did not contribute to the measure of MVPA but daily walking time (minutes per day) was included as a separate covariate.

5.2.3. Statistical analyses

Due to low numbers in the original eight response categories for sitting time, these were collapsed into four categories of as near equal numbers as the data would allow. Exact quartiles were not possible due to the non-normal distribution of the data.

To examine mortality risk, firstly from all causes and then separately from coronary heart disease and cardiovascular disease, across categories of the five sitting indicators Cox proportional hazards models were fitted.[310] Survival time was measured from the date of measurement at Phase 5 to death or the censor point (the earliest of the date of withdrawal from the study or 31st August 2012). Hazard ratios and 95% confidence intervals were estimated for each sitting category with the lowest group (least time spent sitting) serving as the reference category. The proportional hazards assumptions were checked using Schoenfeld residuals and Nelson-Aelen cumulative hazards plots for analyses of associations between five sitting indicators and the three mortality outcomes. The Schoenfeld residuals did not suggest evidence for any deviations from proportionality in any of the Cox models and this was consistent with observations from the Nelson-Aelen plots.

Cox models were initially adjusted for age, gender, employment grade and ethnicity (model 1) and subsequently for smoking status, alcohol consumption, fruit and vegetable consumption, BMI, walking time and MVPA (model 2). Wald chi-square tests were used to test for linear relationships in individual parameters and likelihood-ratio chi-square tests for non-linear relationships. Analyses were limited to those free from cardiovascular disease at Phase 5.

To examine whether the associations between sitting indicators and mortality outcomes differed between a priori defined subgroups, interaction terms were fitted for each sitting indicator with gender, age (in ten year age groups), BMI (in categories according to WHO classifications of underweight, normal weight, overweight and obese),[311] and physical activity (according to adherence to the Department of Health guidelines for MVPA).[13] Likelihood-ratio tests were used to determine whether each interaction term improved the fit of the models.

To minimise the potential confounding effect of occult disease at baseline, analyses were repeated after additionally excluding those who died prior to Phase 6 (2001: 15278 person years of follow up excluded, and then Phase 7 (2003-04: 27808 person years of follow up excluded). In order to examine the possibility of bias due to differential loss from the original 1985 cohort, baseline age, gender, employment grade, alcohol consumption and the likelihood of being obese and of being a current smoker were compared between those who did and those who did not respond to questionnaire items

relating to occupational and leisure time sitting behaviour. Pearson's product-moment correlations were used to examine the relationship between the five sitting indicators and weekly MVPA. Analyses were conducted in 2013 using STATA version 11.2.

5.3. Results

The final sample consisted of 5132 participants who had complete data for sitting time and all covariates, and were free from any cardiovascular or coronary heart disease at Phase 5. Sample characteristics are described in table 5.1. Compared to those in the current sample, those lost to follow-up between the study's inception in 1985 and the Phase 5 were slightly older at date of screening (0.42 yrs; 95%CI 0.17, 0.67: *P*=0.001) consumed slightly less alcohol 1.19 units/wk; 95%CI 0.64, 1.73: *P* <0.001) and had a greater likelihood of being male (OR 0.11; 95%CI 0.09, 0.13), obese (OR 0.04 95%CI 0.03, 0.05), and in a higher employment grade (OR 0.05 95%CI 0.03, 0.07) in 1985. Inclusion in the current analysis was not associated with smoking behaviour in 1985. A total of 385 deaths from all causes, 40 CHD deaths and 79 CVD deaths were recorded over 72338 person-years of follow-up (mean follow up time 14.1 ± 1.8yrs).

There was very little evidence of a correlation between weekly MVPA with Work sitting (r=-0.15), TV viewing (r=0.02), Non-TV leisure time sitting (r=-0.04), Leisure time sitting (r=0.38), and Total sitting (r=-0.09).

Hazard ratios and 95% confidence intervals for mortality risk are described in tables 5.2 (for all-cause mortality), 5.3 (for coronary heart disease mortality), and 5.4 (for cardiovascular disease mortality). Unadjusted mortality rates are also presented (per 1000 person years) for each mortality outcome in the corresponding tables. There were no associations between any of the five sitting indicators at Phase 5 and all-cause mortality risk over the follow up period in either model 1 or 2. There were also no associations with risk of coronary heart disease or cardiovascular disease mortality. In addition, no significant interaction effects were observed between the five sitting indicators and gender, age, adherence to public health guidelines for MVPA, or BMI classification.

5.4. Discussion

The present study tested the hypothesis that sitting time would predict mortality risk independently of moderate to vigorous intensity physical activity. This is the first study to separately examine the associations between mortality risk and five separate sitting indicators including total sitting time, work and leisure time sitting, and both TV viewing time and other sitting based leisure time activities. Across 15 years of follow up there were no prospective associations observed between these five separate indicators of sitting time and mortality from all causes, CHD mortality or CVD mortality.

The primary strength of this study is that it is the first to examine the associations between all-cause and cause specific mortality with five separate

indicators of sitting time in the same cohort. This is important as evidence suggests that the pattern of sitting as well as the duration is an important factor in determining the magnitude of any health consequences,[109 274] and that sitting in different contexts may be subject to different patterns and determinants.[109]

The results of the current analysis are inconsistent with previous studies which have shown positive associations between all-cause mortality risk and TV viewing,[53 55 67 70 154] sitting at work[312] and total sitting time.[62 149 150 153 305 306] As discussed previously (2.2.4) inaccuracies in reporting and subsequent misclassification of sitting, if non-differential, may attenuate any true associations towards the null so it is possible that this contributed to the null findings in the current analyses. Objective measures of sedentary behaviour that are currently used to quantify sitting time (by assuming that movement or heart rate values below a predetermined threshold represent sitting)are unable to differentiate between different types, and therefore self-report measures are required to provide contextual information. Previous studies examining the associations between sitting time and mortality have also employed self-report measures, and the questionnaire items used to construct the five sitting exposures in the present study have been validated previously[303] and have also been used in a number of previous studies where significant associations between sitting time and health outcomes have been observed.[190 191]

The absence of any evident association between sitting and risk of CVD and CHD mortality is also inconsistent with a number of previous prospective studies.[55 70 149 152] In the current analyses 40 CHD deaths and 79 CVD deaths

were recorded. Previous studies examining associations between sitting time and cause specific mortality have recorded a far greater number of cardiovascular disease deaths (373,[55] 4684,[70] 6369,[152] and 148).[149] It is possible that due to the relatively low number of CVD and CHD deaths in the current analyses the study did not have enough power to detect any associations between sitting time and CVD outcomes. However, statistical power does not explain the absence of an association with all-cause mortality as previous studies[55 150] have detected associations with a similar number of events.

The volume of sitting time reported in the current sample is also lower than in a number of studies who have observed associations between sitting time and mortality.[53 55 62 150] Seventy-three percent of the current sample would fall into the bottom tertile for TV viewing described by Wijndaele et al[55] (<2.5 hrs per day) and only 7% in the top tertile (>3.6 hrs.day). Koster et al[150] also reported mean (SE) total daily sedentary time values for 4 sitting groups that are far higher than in the current study: 6.3 (1.0) for group 1 then, 8.2 (0.5), 9.6 (0.5), and 12.2 (2.0), compared to 2.24 (0.92) for group 1 then, 4.79 (0.68), 6.72 (0.51), 9.06 (1.25) in the current study. It is therefore possible that the volume of reported sitting time in the current study is insufficient to detect an association with mortality. However significant differences in mortality risk have been reported for as little as 1 hour differences in daily sitting,[53 55] even at low sitting volumes such as those reported in the current study so an effect should still be evident even if the sample mean sitting time is relatively low. It must also be noted that Koster et al measured total sedentary time using accelerometers and

as discussed in chapter 2 (2.3.2) accelerometers measure movement rather than sitting specifically, with cut-points in movement data used to classify activity intensities. As behaviours such as standing involve very little movement this approach may lead to an inflated estimate of total sitting and therefore the true difference in total sitting time may not be quite so pronounced.

While these findings are inconsistent with a number of previous studies the possibility of a degree of publication bias within the current literature must also be considered. A recent meta-analysis of studies examining associations between adult sedentary time and health outcomes reported evidence of significant publication bias in studies examining associations with diabetes[27] (Eggers test t=6.12, P≤0.001) and while no such analysis was possible for mortality outcomes due to the relatively low number of published studies it is possible that other unpublished null findings exist.

The absence of any associations between sitting and mortality in the present analysis may also be attributed to a protective effect of the high volumes of daily walking reported in the Whitehall II cohort. The public transport infrastructure in London is such that London based employees are far likelier to stand (on buses and trains) or walk during their commute to work than in those residing in other areas of the country.[313] This is reflected in the mean reported daily walking time for the current analysis group (42.68 ± 22.60 mins) which is over double the reported UK national average.[314] In a study of over 40 thousand Japanese men and women, Fujita et al observed a significant inverse association between daily walking time and mortality risk over an 11 year follow-

up period.[315] A number of other large prospective cohort studies, with participants of similar ages to those in the current analyses, have also demonstrated that both habitual active transport ,[316] and daily walking are [317 318] inversely associated with risk for mortality from all causes and from cardiovascular disease.

In comparison with previous prospective studies the amount of MVPA reported in the present sample is also high. This is consistent with previous evidence that London based Civil Servants on average are more active than the age matched wider population.[319] Recent experimental evidence has suggested that energy balance may be a significant factor in the association between sitting and metabolic health.[274] It is therefore possible that the higher than average energy expenditure in the current study may offer a degree of protection from the deleterious effects of high volumes of sitting. However it must also be considered that the high volumes of MVPA reported in this sample may be due to either over-reporting for reasons of social desirability, or to the way responses were classified and coded within the study. For example participants were asked to quantify time spent in a number of activities which would be intermittent in nature (football/golf/other sporting activities). Although all time spent in engaged in these activities would be classified as moderate intensity or above (according to standard reference values for these particular activities), intensity will vary significantly throughout a given period. Therefore the amount of time spent at an intensity of moderate or above may be overestimated.

5.4.2. Strengths and limitations

A strength of the current study is the examination of mortality in a large sample who were regularly assessed over a significant follow-up period. Due to the comprehensive assessment of health behaviours it was possible to adjust for a broad range of potential confounding factors, notably alcohol consumption, smoking status, and frequency of fruit and vegetable consumption. Detailed information on habitual physical activity was essential in examining the central hypothesis that sitting time represents a risk factor which acts independently of MVPA. In the current study physical activity was assessed using 20 questionnaire items which included open-text response options allowing the quantification of a broad range of individual activities. These activities were classified by intensity using reference MET values rather than self-reported exertion. In addition only one previous study has attempted to adjust for the potentially confounding effect of limitations in physical functioning.[153] Such limitations due to chronic pain, injury or ill-health may alter an individual's choice of leisure time activity or even job role which may therefore inflate their reported sitting time in a variety of contexts.

A number of limitations must also be acknowledged. The Whitehall II study is an occupational cohort of white collar workers. While this has a number of practical and methodological benefits such as ease of follow-up and the broad socioeconomic range of the British Civil Service,[307] it must be acknowledged that at baseline all participants were healthy enough to be in active employment which to some degree limits the ability to generalise the findings to the wider population. The use of a single industry sector may also

detract from the generalisability of these findings, although they remain relevant given the increasing proportion of workers in affluent societies employed in white-collar occupations.[320] In the present sample, the clerical and office support grade (lowest socioeconomic group) was underrepresented, comprising only 11% of total participants with the senior administrative (highest) grade and the professional and executive grade contributing 46% and 43% respectively. Women are underrepresented in the British Civil Service compared to the general population and this is reflected in the current analyses where women comprised 28% of the sample.

A degree of residual confounding must also be acknowledged. The associations between mortality and different sitting behaviours, with their own correlates and determinants, will be influenced by a number of different confounding factors. The work sitting-mortality relationship may be affected not only by duration of sitting but also by commuting habits and the working environment,[73] while the association with TV viewing may be influenced by the increased snacking behaviour often associated with high volumes of TV.[242 321] This potential source of confounding will be discussed in greater detail in chapter 7. Recent experimental evidence also suggests that a proportion of the unfavourable metabolic effects of prolonged sitting might be attributable to differences in energy balance.[274] Such factors could not be accounted for in the present analysis.

It is also possible that due to differential loss between 1985 and the phase five measurements in 1997 that a degree of bias may have influenced

the current findings. Those in the current sample were slightly younger, consumed less alcohol, were less likely to be obese and were more likely to be in a higher employment grade all of which may have reduced the overall mortality risk of the sample relative to those who were lost to follow-up. However the differences in these potential risk factors although statistically significant were, in absolute terms, relatively small (for example differences of less than 6 months in age, just over 1 unit per week of alcohol, and a 4% difference in obesity risk). In addition, inclusion in the current analysis was not associated with smoking, and was associated with a greater likelihood of being male which conversely would increase mortality risk.

Although the examination of total sitting time remains important, as it is possible that people might compensate for frequent sitting in one domain by sitting less frequently in another,[153] future research should continue to separately consider the individual effects, determinants, and confounding factors associated with sitting in different contexts. The use of self-report measures allows this kind of specific examination while current objective measures (accelerometry and heart rate monitoring) do not. However, issues arising from misclassification of self-reported sitting remain. As discussed previously in (2.3.5) improvement in the technology of sedentary behaviour measurement will greatly aid the advancement of this field with machine-learning and pattern recognition approaches allowing objective determination of postural, type and intensity components of sitting from raw acceleration data.[141] [322] Frameworks such as the Sedentary Sphere (described previously)[143] could potentially be applied to freeliving accelerometer data in order to provide

accurate estimates of sitting time which are free from problems associated with the both self-report of day to day health behaviours and the use of arbitrary data thresholds currently used to differentiate sitting from standing/walking. Further experimental evidence is also required to isolate the specific biological underpinnings of the previously observed negative effects of sitting, and to clarify which features of sitting (postural topography, type, energy balance), are important. Better definition and measurement of sitting as an exposure will allow a greater understanding of the associations with mortality risk and other health outcomes.

5.4.3. Conclusions

The current study is the first to examine the associations between mortality from all-causes, from CHD and from CVD, with five separate sitting time indicators. The results suggest that mortality risk is not associated with sitting time in this cohort. The findings may be due to in part to a protective effect of a higher than average energy expenditure due to the habitual active transport and associated with London based employees. Further research is needed to examine the effects of time spent engaged in different types of sitting on mortality risk.

Table 5.1. Subject characteristics at baseline (Phase 5 1997-99). Data are mean (SD)

			Sitting Group (Total from work and leisure time)			
		Whole sample	1 (n=1273)	2 (n=1384)	3 (n=1239)	4 (n=1236)
Age (yrs)		55.49 (5.97)	58.00 (5.80)	57.00 (6.00)	54.00 (5.30)	53.00 (5.00)
Male (%)		72.32	21.96	27.10	25.40	25.54
Ethnicity	White (%)	94.26	23.56	27.14	24.64	24.66
	Non-White (%)	5.74	45.52	24.14	15.86	14.48
BMI		25.72 (3.81)	25.63 (3.70)	25.64 (3.69)	25.56 (3.82)	26.02 (4.00)
Waist Circumference (cm)		89.16 (11.44)	89 (12)	90 (11)	90 (11)	92 (12)
Weight (Kg)		77.41 (13.20)	75 (13)	77 (13)	78 (13)	79 (14)
Walking (mins/d)		42.73 (22.59)	44.45 (24.77)	44.17 (22.53)	41.21 (21.23)	40.65 (21.31)
MVPA (hrs/wk)		14.02 (11.82)	15.09 (12.73)	15.70 (13.00)	12.97 (10.36)	12.61 (10.59)
Employment Grade (%)	Administrative	46.05	18.81	26.58	27.22	27.39
	Prof/Executive	43.30	26.72	27.39	22.77	23.13
	Clerical/Support	10.64	43.23	26.90	16.33	13.54
Alcohol consumption (units/wk)		13.92 (14.91)	12 (15)	13 (14)	14 (14)	16 (16)
Smoking Status (%)	Never	51.83	24.36	26.28	25.60	23.76
	Ex	38.16	24.59	28.62	23.32	23.47
	Current	10.01	27.95	24.12	19.69	28.15
Self-rated health (%)	Very Good	52.70	25.63	27.80	24.12	22.46
	Good	37.16	23.42	25.37	24.68	26.53
	Fair or Poor	10.14	25.58	28.46	22.31	23.65

Table 5.2. All-cause mortality risk according to categories of sitting behaviours between Phase 5 (1997-99) and August 31st 2012

	Person yrs (x1000)	N/Deaths	Rate/1000 person-yrs	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Work sitting (hrs/wk)					
≥0 & <8	18.64	1338/134	7.19	1	1
≥8 & <25	15.74	1121/92	5.85	1.02 (0.78, 1.33)	1.00 (0.76, 1.31)
≥25 & <40	20.45	1438/70	3.42	0.90 (0.65, 1.24)	0.90 (0.66, 1.25)
≥40	14.82	1039/39	2.63	0.78 (0.52, 1.16)	0.77 (0.52, 1.14)
P_{trend}				0.57	0.57
TV sitting (hrs/wk)					
≥0 & <8	6.97	491/30	4.30	1	1
≥8 & <15	11.77	833/56	4.76	1.01 (0.65, 1.58)	0.88 (0.56 (1.38)
≥15 & <16	17.98	1276/83	4.62	0.97 (0.64, 1.47)	0.88 (0.58, 1.35)
≥16	14.08	1009/92	6.54	1.21 (0.80, 1.83)	1.02 (0.67, 1.56)
P_{trend}				0.49	0.73
Non-TV Leisure Time Sitting (hrs/wk)					
≥0 & <4	11.36	803/52	4.58	1	1
≥4 & <9	12.95	917/66	5.10	1.04 (0.72, 1.50)	1.09 (0.76, 1.57)
≥9 & <16	11.83	840/64	5.41	1.10 (0.76, 1.59)	1.12 (0.77, 1.62)
≥16	11.75	835/60	5.11	0.97 (0.67, 1.42)	0.92 (0.63, 1.34)
P_{trend}				0.92	0.70
Leisure Time Sitting (hrs/wk)					
≥0 & <15	19.88	1400/81	4.07	1	1
≥15 & <18	16.29	1154/72	4.42	1.11 (0.80, 1.52)	1.09 (0.79, 1.50)
≥18 & <26	18.08	1282/82	4.54	1.04 (0.77, 1.42)	1.03 (0.75, 1.40)
≥26	16.89	1211/117	6.93	1.37 (1.03, 1.83)	1.26 (0.94, 1.69)
P_{trend}				0.12	0.37
Total sitting (hrs/wk)					
≥0 & <26	17.81	1273/116	6.51	1	1
≥26 & <41	19.38	1384/119	6.14	1.07 (0.83, 1.38)	1.11 (0.86, 1.44)
≥41 & <55	17.66	1239/54	3.06	0.74 (0.53, 1.03)	0.74 (0.53, 1.03)
≥55	17.48	1236/69	3.95	1.04 (0.76, 1.43)	0.97 (0.70, 1.33)
P_{trend}				0.14	0.12

Model 1 adjusted for age, gender, employment grade and ethnicity. Model 2 additionally adjusted for smoking status, alcohol consumption, fruit and vegetable consumption, BMI, walking time and MVPA. Bold typeface = statistically significant $P \leq 0.05$

Table 5.3. Coronary heart disease mortality risk according to categories of sitting behaviours between Phase 5 (1997-99) and August 31st 2012

	Person yrs (x1000)	N/Deaths	Rate/1000 person-yrs	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Work sitting (hrs/wk)					
≥0 & <8	18.64	1338/16	0.86	1	1
≥8 & <25	15.74	1121/13	0.83	1.22 (0.58, 2.57)	1.23 (0.58, 2.59)
≥25 & <40	20.45	1438/6	0.29	0.74 (0.27, 2.06)	0.71 (0.26, 1.95)
≥40	14.82	1039/4	0.27	0.85 (0.25, 2.85)	0.81 (0.25, 2.68)
P_{trend}				0.79	0.74
TV sitting (hrs/wk)					
≥0 & <8	6.97	491/5	0.72	1	1
≥8 & <15	11.77	833/4	0.34	0.44 (0.12, 1.64)	0.42 (0.11, 1.60)
≥15 & <16	17.98	1276/7	0.39	0.50 (0.16, 1.60)	0.53 (0.16, 1.75)
≥16	14.08	1009/13	0.92	1.03 (0.36, 2.93)	0.99 (0.33, 2.92)
P_{trend}				0.27	0.31
Non-TV Leisure Time Sitting (hrs/wk)					
≥0 & <4	11.36	803/5	0.48	1	1
≥4 & <9	12.95	917/4	0.34	0.88 (0.25, 3.06)	0.91 (0.26, 3.18)
≥9 & <16	11.83	840/6	0.54	1.38 (0.43, 4.39)	1.34 (0.42, 4.33)
≥16	11.75	835/7	0.66	1.30 (0.41, 4.14)	1.14 (0.35, 3.73)
P_{trend}				0.86	0.92
Leisure Time Sitting (hrs/wk)					
≥0 & <15	19.88	1400/8	0.40	1	1
≥15 & <18	16.29	1154/10	0.61	1.68 (0.66, 4.29)	1.69 (0.66, 4.35)
≥18 & <26	18.08	1282/8	0.44	1.16 (0.43, 3.11)	1.16 (0.43, 3.16)
≥26	16.89	1211/15	0.89	1.87 (0.77, 4.54)	1.83 (0.74, 4.53)
P_{trend}				0.46	0.50
Total sitting (hrs/wk)					
≥0 & <26	17.81	1273/12	0.67	1	1
≥26 & <41	19.38	1384/16	0.83	1.55 (0.73, 3.32)	1.65 (0.76, 3.58)
≥41 & <55	17.66	1239/4	0.23	0.66 (0.20, 2.12)	0.67 (0.21, 2.19)
≥55	17.48	1236/8	0.46	1.46 (0.56, 3.81)	1.35 (0.51, 3.56)
P_{trend}				0.37	0.34

Model 1 adjusted for age, gender, employment grade and ethnicity. Model 2 additionally adjusted for smoking status, alcohol consumption, fruit and vegetable consumption, BMI, walking time and MVPA. Bold typeface = statistically significant $P \leq 0.05$

Table 5.4. Cardiovascular disease mortality risk according to categories of sitting behaviours between Phase 5 (1997-99) and August 31st 2012

	Person yrs (x1000)	N/Deaths	Rate/1000 person-yrs	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Work sitting (hrs/wk)					
≥0 & <8	18.64	1338/34	1.82	1	1
≥8 & <25	15.74	1121/22	1.40	1.00 (0.58, 1.73)	0.98 (0.57, 1.70)
≥25 & <40	20.45	1438/11	0.54	0.63 (0.30, 1.31)	0.64 (0.30, 1.34)
≥40	14.82	1039/6	0.41	0.58 (0.22, 0.48)	0.58 (0.23, 1.47)
P_{trend}				0.46	0.50
TV sitting (hrs/wk)					
≥0 & <8	6.97	491/10	1.43	1	1
≥8 & <15	11.77	833/9	0.76	0.50 (0.20, 1.24)	0.43 (0.17, 1.08)
≥15 & <16	17.98	1276/15	0.83	0.55 (0.25, 1.23)	0.46 (0.20, 1.06)
≥16	14.08	1009/23	1.63	0.90 (0.43, 1.92)	0.71 (0.32, 1.55)
P_{trend}				0.21	0.18
Non-TV Leisure Time Sitting (hrs/wk)					
≥0 & <4	11.36	803/15	1.45	1	1
≥4 & <9	12.95	917/11	0.93	0.72 (0.34, 1.50)	0.75 (0.36, 1.57)
≥9 & <16	11.83	840/12	1.08	0.80 (0.38, 1.68)	0.79 (0.37, 1.66)
≥16	11.75	835/9	0.84	0.60 (0.27, 1.33)	0.56 (0.25, 1.26)
P_{trend}				0.63	0.57
Leisure Time Sitting (hrs/wk)					
≥0 & <15	19.88	1400/22	1.11	1	1
≥15 & <18	16.29	1154/16	0.98	0.97 (0.51, 1.86)	0.89 (0.46, 1.71)
≥18 & <26	18.08	1282/17	0.94	0.86 (0.45, 1.63)	0.76 (0.40, 1.45)
≥26	16.89	1211/25	1.48	1.13 (0.63, 2.04)	0.96 (0.53, 1.76)
P_{trend}				0.86	0.84
Total sitting (hrs/wk)					
≥0 & <26	17.81	1273/31	1.74	1	1
≥26 & <41	19.38	1384/27	1.39	1.01 (0.60, 1.70)	1.02 (0.60, 1.74)
≥41 & <55	17.66	1239/10	0.57	0.62 (0.29, 1.30)	0.61 (0.29, 1.28)
≥55	17.48	1236/11	0.63	0.76 (0.37, 1.57)	0.68 (0.33, 1.41
P_{trend}				0.54	0.42

Model 1 adjusted for age, gender, employment grade and ethnicity. Model 2 additionally adjusted for smoking status, alcohol consumption, fruit and vegetable consumption, BMI, walking time and MVPA. Bold typeface = statistically significant $P \leq 0.05$

Chapter 6

Sedentary behaviour and cardiovascular disease risk

6.1. Introduction

Cardiovascular disease (CVD) is a group of disorders including coronary heart disease (CHD), cerebrovascular disease, and diseases of the central and peripheral vasculature which are commonly associated with the development of atheroma and thrombosis, causing narrowing and blockages of blood vessels.[323] Functioning endothelial cells resist thrombosis by releasing anti-clotting factors and platelet inhibitors. They also help regulate blood flow by secreting vasodilators and they inhibit the proliferation of smooth muscle cells.[324] Injury to the endothelial cells comprising the intima of blood vessels caused by elevated blood glucose or blood pressure leads to the accumulation of molecules at the injury site. The intima enlarges due to accumulation of lipids and the proliferation of smooth muscle cells. Monocytes adhere to the endothelium and cross into the media layer (becoming macrophages) where they ingest oxidised lipid molecules. Macrophages and smooth muscle cells continue to proliferate, the latter producing collagen which increase the bulk of the lesion and further reduce blood flow. Lesions can also become calcified which reduce arterial elasticity. Symptoms usually begin when a lesion restricts blood flow and oxygen delivery by around 45%, a clinical horizon after which the disease progression begins to limit normal functioning.[324] Complications of atherosclerosis can also derive from sudden events such as the rupture of vulnerable plaques causing thrombus formation which can lead to heart attack or stroke. Arteries weakened by atherosclerosis are also susceptible to rupture.

Such conditions accounted for 17.5 of the 58 million all-cause deaths worldwide in 2005, three times more than were caused by infectious diseases such as HIV/AIDS tuberculosis and malaria combined.[283] In 2010, CVD led to nearly 180 thousand deaths in England accounting for 34% of total mortality.[325] Moreover, it is estimated that 2.3 million men and 2.3 million women in the United Kingdom are currently living with CVD[325] reportedly costing the UK economy £30 billion annually.[326]

The association between physical activity and CVD was first highlighted in the 1950's when Professor Jerry Morris observed a two-fold increase in the risk of myocardial infarction in London bus drivers compared to bus conductors whose occupational physical activity was far greater.[4] Since such early observations moderate to vigorous physical activity (MVPA) has been repeatedly demonstrated to reduce cardiovascular risk[327] and to benefit a range of disease markers in people on all stages of the atherogenic pathway.[328] The last 10 years has also seen the examination of associations between sitting time and a number of cardiovascular outcomes, independent of MVPA.

While there is evidence for positive associations between time spent sitting and cardiovascular mortality,[55 62 70 148 154] relationships between sitting and CVD incidence is less clear and requires further research attention.[27 329] With more people surviving myocardial infarctions (death rates from cardiovascular incidents in England have halved since 2002)[325] it is important to examine associations between sitting and cardiovascular disease morbidity as well as mortality. To date only six prospective studies have examined

associations between indicators of sitting time and incidence of CVD.[65 67 164-167] Three of these studies focussed solely on TV viewing or screen-based leisure-time entertainment and have observed significant positive associations with risk for cardiovascular events that are independent of MVPA.[65 67 164]In a study of 4512 Scottish adults, Stamatakis et al[67] observed an odds ratio of 2.30 (95% CI 1.33, 3.96) for cardiovascular events for those who reported more than 4 hours per day of screen time, relative to those who reported less than 2 hours per day.

As discussed previously indicators such as TV viewing or screen time, while representing a prevalent leisure-time sedentary behaviour have been found to be a poor indicator of total sitting time.[72] The three studies which have examined total sitting time from all domains[165-167] have reported mixed results. Over approximately 233000 person years of follow up Manson et al[166] observed an odds ratio for cardiovascular events of 1.68 (95%CI 1.07, 2.64) for women who reported sitting for longer than 16 hrs per day compared to those who sat for less than 4 hrs per day. These analyses were adjusted for age and leisure-time energy expenditure only. The omission of a range of potentially important covariates allows for the possibility of a degree of residual confounding. Chomistek et al[167] observed a significant increase in risk for cardiac events in those sitting for >10 hrs/day compared to those who sit for <5hrs/day following adjustment for a broad range of covariates. Conversely, in a recent analysis of 10 years of data from the Australian Longitudinal Study on Women's Health (ALSWH), Herber-Gast et al[165] observed no associations between self-reported total sitting time and CVD incidence following adjustment for covariates

including age, education, smoking, alcohol consumption, smoking status, physical activity and BMI.[165]

Due to the increasing prevalence[283 323] and therefore disease burden of cardiovascular disease[283 326] a comprehensive understanding of its potential determinants including sitting behaviours is essential. As discussed previously (chapter 2) sitting may occur in a range of occupational and leisure time contexts and may be subject to different influences, which will dictate the duration and pattern of the behaviour. As evidence suggests that the pattern of sitting behaviour may determine the magnitude of any deleterious effects on health markers[109 273] again it follows that sitting in different contexts may have differential associations with health outcomes[120 163 190 191] including CVD and should be examined separately. However, no previous studies have sought to separately examine the associations between cardiovascular disease incidence and both total sitting time and different sitting types in the same cohort.

This study aims to enhance the evidence base by drawing on 15 years of data from the Whitehall II cohort study to examine the type-specific associations of five different sitting indicators and risk for incident cardiovascular disease.

6.1.2. Hypotheses

Based on the current available evidence it is reasonable to hypothesise that:

i. Each of the five indicators of sitting time will be positively associated with cardiovascular disease incidence

ii. These associations will be independent of time spent in moderate to vigorous physical activity

6.2. Methods

6.2.1. Determination of sedentary behaviours and cardiovascular disease

The five sedentary behaviour exposures were determined from Phase 5 data as described previously (4.7).

Incident cardiovascular disease (hereafter to be described as cardiovascular events) comprised coronary death, first non-fatal myocardial infarction (MI) or first definite angina. Deaths from cardiovascular disease and coronary heart disease were determined using International Classification of Disease (ICD) codes (ICD-9, 390.0-458.9; ICD-10, 100-199), recorded on death certificates. Non-fatal MI was defined using the World Health Organisation (WHO) MONICA project criteria[330] and ascertained using data from 5 yearly resting electrocardiograms (ECGs) recorded as part of the Whitehall II study clinical examinations, and from ECGs and cardiac enzyme levels obtained from records during hospitalisation for acute MI. Definite angina was defined by clinical records, ECG abnormalities or coronary angiogram and nitrate medication use, but excluded self-reports which were not clinically verified. Three separate analyses examined associations between sitting and: 1) all

incident cardiovascular events, 2) fatal CHD and non-fatal incident MI, and 3) fatal CHD and incident non-fatal MI including self-reported MI.

6.2.2. Covariates

The sociodemographic covariates included in the current analysis were age, gender, ethnicity and employment grade. Employment grade (3 levels: clerical and support, professional and executive, senior administrative) in the Whitehall II Study is a comprehensive marker of socioeconomic circumstance relating to social status, salary and level of responsibility[307] For retired participants, their last reported employment grade was considered. Health related covariates included self-rated health (reported as; excellent, very good, good, fair, or poor), smoking status (current, previous, or never a smoker), alcohol consumption, diet quality, body mass index (BMI) and physical functioning. Participants reported the number of 'measures' of spirits, 'glasses' of wine, and 'pints' of beer consumed in the previous seven days, and this was then converted to units (1 unit = 8g) of alcohol. Diet quality was represented by frequency of fruit and vegetable consumption and was assessed using an eight point scale ranging from: 1) *"seldom or never",* to 8) *"two or more portions per day*". Height (m) and weight (kg) were recorded during clinical examination and BMI calculated using a standard formula. To assess perceptions of physical functioning the SF-36 questionnaire was used and scored with the Medical Outcomes Study scoring system.[308] The SF-36 assesses the extent to which participant's health limits their ability to perform physical activities, ranging in intensity from vigorous (sporting and volitional exercise activities) to light (day-to –day tasks) using the responses *"a lot", "a little",* and *"not at all"*. Responses

were scored, summed and transformed to scale from 0 (limited a lot in performing all types of physical activities) to 100 (able to perform all types of physical activity without limitation). This scale has been demonstrated to have high internal consistency. [309]

Physical activity covariates included daily walking time (minutes/day), and time spent in moderate to vigorous physical activity (hrs/wk). Physical activity was assessed using a modified version of the Minnesota leisure-time physical activity questionnaire which assesses both occupational and leisure-time physical activities, and which has been validated previously.[299] Twenty items (including 5 open-text responses) assessed time spent engaged in walking, sports and games, gardening activities, housework and do-it-yourself building/maintenance projects, in hours over the previous four week period. Each activity was subsequently assigned an energy expenditure value in metabolic equivalents (METs: where 1 MET is equal to energy expenditure at rest) using a compendium of activity energy expenditures.[302] Moderate intensity activities were classified as those eliciting an energy expenditure of 3-5.9 METs and vigorous intensity activities from 6 METs and upwards. The energy expenditure of walking activity is dependent on walking pace and could therefore not be determined from the Phase 5 questionnaire. As a result, while in some instances walking may have met the required energy expenditure, for the purposes of the present analysis walking did not contribute to the measure of MVPA but daily walking time (minutes per day) was included as a separate covariate.

6.2.3. Statistical analyses

Due to low numbers in the original eight response categories for sitting time, these were collapsed into four categories of as near equal numbers as the data would allow. Exact quartiles were not possible due to the non-normal distribution of the data.

To examine cardiovascular disease risk, across categories of the five sitting indicators Cox proportional hazards models were fitted.[310] Survival time was measured from the date of measurement at Phase 5 to the date of a cardiovascular event or the censor point (the earliest of the date of withdrawal from the study or the Phase 9 assessment in 2009. Hazard ratios and 95% confidence intervals were estimated for each sitting category with the lowest group serving as the reference category. The proportional hazards assumptions were checked using Schoenfeld residuals and Nelson-Aelen cumulative hazards plots for analyses of associations between five sitting indicators and the three mortality outcomes. The Schoenfeld residuals did not suggest evidence for any deviations from proportionality in any of the Cox models and this was consistent with observations from the Nelson-Aelen plots.

Cox models were initially adjusted for age, gender, employment grade and ethnicity (model 1) and subsequently for smoking status, alcohol consumption, physical functioning, fruit and vegetable consumption, BMI, walking time and MVPA (model 2). Wald chi-square tests were used to test for linear relationships in individual parameters and likelihood-ratio chi-square tests

for non-linear relationships. Analyses were limited to those free from cardiovascular disease at Phase 5.

To examine whether the associations between sitting indicators and incident cardiovascular disease outcomes differed between a priori defined subgroups, interaction terms were fitted for each sitting indicator with gender, age (in ten year age groups), BMI (in categories according to WHO classifications of underweight, normal weight, overweight and obese),[311] and physical activity (according to adherence to the Department of Health guidelines for MVPA).[13] Likelihood-ratio tests were used to determine whether each interaction term improved the fit of the models.

To minimise the potential confounding effect of occult disease at baseline, analyses were repeated after additionally excluding those who suffered cardiovascular events prior to Phase 6 (2001: 14892.8 person years of follow up excluded), and then Phase 7 (2003-04: 26707.05 person years of follow up excluded). In order to examine the possibility of bias due to differential loss from the original 1985 cohort, baseline age, gender, employment grade, alcohol consumption and the likelihood of being obese and of being a current smoker were compared between those who did and those who did not respond to questionnaire items relating to occupational and leisure time sitting behaviour. Pearson's product-moment correlations were used to examine the relationship between the five sitting indicators and weekly MVPA. Analyses were conducted in 2013 using STATA version 11.2.

6.3. Results

The final sample consisted of 5132 participants who had complete data for sitting time and all covariates, and were free from any cardiovascular or coronary heart disease at Phase 5. Sample characteristics are described in table 6.1. A total of 343 cardiovascular events of any type were recorded over 55567.61 person-years of follow-up (mean follow up time 10.83 ± 2.46yrs). This included 135 cases of either fatal CVD or non-fatal MI (123 with the exclusion of self-reported cases). Compared to those who completed questionnaire items related to sitting at Phase 5, those lost to follow-up between the studies inception in 1985 and the Phase 5 were slightly older at date of screening (0.42 yrs; 95%CI 0.17, 0.67: p=0.001) consumed slightly less alcohol 1.19 units/wk; 95%CI 0.64, 1.73: p<0.001) and had a greater likelihood of being male (OR 0.11; 95%CI 0.09, 0.13), obese (OR 0.04 95%CI 0.03, 0.05), and in a higher employment grade (OR 0.05 95%CI 0.03, 0.07) in 1985. Inclusion in the current analysis was not associated with smoking behaviour in 1985. There was very little evidence of a correlation between weekly MVPA with Work sitting (r=-0.15), TV viewing (r=0.02), Non-TV leisure time sitting (r=-0.04), Leisure time sitting (r=0.38), and Total sitting (r=-0.09).

Hazard ratios and 95% confidence intervals for incident cardiovascular risk are described in tables 6.2 (for any cardiovascular event), 6.3 (for fatal CVD and non-fatal MI), and 6.4 (for fatal CVD and non-fatal MI including self-reported cases). Unadjusted incidence rates are also presented (per 1000 person years) for each of the three cardiovascular outcomes in the corresponding tables. There were no associations between any of the five sitting indicators at Phase 5

and all risk for any cardiovascular disease event over the follow up period in either model 1 or 2. There were also no associations with risk of fatal CVD or non-fatal MI either including or excluding self-reported cases. In addition, no significant interaction effects were observed between the five sitting indicators and gender, age, adherence to public health guidelines for MVPA, or BMI classification.

6.4. Discussion

These analyses tested the hypothesis that sitting time would predict risk of incident cardiovascular events, including cardiovascular death first non-fatal MI and first angina episode, independently of moderate to vigorous intensity physical activity. This is the first study to examine associations between incident CVD and both total and type specific sitting time. Over 10 years of follow up there were no prospective associations observed between five separate indicators of sitting time and incident cardiovascular disease.

Previous prospective studies examining associations between indicators of sitting time and incident CVD risk have reported mixed results. Three previous studies have examined the associations between total self-reported sitting time and incident CVD. Chomistek et al[167] observed a significant increase in risk of cardiac events in participants who reported sitting for greater than 10 hrs per day compared to those who sit for less than five hours per day. Similarly, Manson et al reported that sitting for 16 hrs per day or more increased CVD risk by 68% compared with sitting for less than 4 hrs per day, while the

study by Herber-Gast et al observed no association. The current analyses accounts for a range of important covariates including age, socioeconomic status, ethnicity, smoking status, weekly alcohol consumption, BMI, physical activity and fruit and vegetable intake, all of which could potentially confound the association between sitting time and CVD incidence. Manson et al adjusted only for age and leisure-time physical activity. By not accounting for other factors which may be associated with both sitting and CVD it is possible that the observed associations may be due to residual confounding. For example if sitting time was socially patterned the apparent association between sitting and CVD may simply reflect the social gradient in CVD incidence. It is also important to note that in the studies by both Chmoistek et al and Manson et al, while the risk of CVD for those in the highest sitting group (who sat more than 10 hrs and 16hrs per day respectively) was significantly greater than the reference group (who sat less than 5 hrs and 4 hrs per day respectively), no other durations of sitting were associated with an increase in risk of CVD.

In addition the sitting time values reported in the current analyses and those by Herber-Gast et al are lower than those reported by Manson et al, Cholmistek et al and in some other study populations where associations between sitting and cardiovascular health outcomes have been observed.[53 62 150] The mean total sitting time was 5.6 ± 2.63 hrs per day (5.4 ± 2.6 hrs per day in Herber-Gast et al) and the mean for the highest sitting group only 9.05 ± 1.25 hrs per day. It is therefore possible that in both these studies reported volume of sitting time was insufficient to detect an association with cardiovascular disease risk in the current cohort during the follow-up period. It is also possible that the

durations of periods of sitting were shorter in the current study and that an association with CVD incidence is only associated with extended periods of sitting. This may also explain the contrast between the current analysis and the three prospective studies which have demonstrated significant positive associations between self-reported television viewing[65 164] and screen time[67] with risk of cardiovascular events as it would also appear that the current sample reportedly watched less TV than in these studies.[65]

It is also possible that the relatively low number of CVD events in the current analysis, particularly in analysis of non-fatal MI only, prevented the detection of an association with any of the sitting indicators. However the study by Herber-Gast et al observed fewer events (in a larger sample, over a similar follow-up period, in participants of a similar age) and had power enough to detect a minimum relative risk of 1.17[165] which is far smaller than that observed in studies of sitting and cardiovascular mortality.[55 62]

Another possible reason for the absence of an association between any of the 5 sitting indicators and risk for cardiovascular events are the high levels of walking reported by the current sample. As discussed previously, the public transport infrastructure in central London coupled with traffic congestion and the absence of parking for employees working in area such as Whitehall, mean that people are more likely to walk or stand (on buses and trains, or to and from stations and bus stops) than those residing outside of London.[313] This is reflected by the reported daily walking time which, in the current sample, is

more than twice the reported national average reported in the UK time use survey.[314]

The study by Manson et al[166] demonstrated significant negative associations between both total weekly energy expenditure from walking and walking pace with risk for cardiovascular events following adjustment for age, smoking status, ethnicity, level of education, annual household income, BMI, waist circumference, waist-to-hip ratio, alcohol intake, family history of heart disease and a number of dietary covariates including fat, fibre and fruit and vegetable intake. [166] Observation studies have consistently demonstrated a protective effect of walking against cardiovascular disease[331] and cardiovascular risk factors.[332] It is therefore possible that a protective effect of high levels of walking reported by the current sample may have counteracted against any increased cardiovascular risk attributable to sitting time. If the whole sample has a high residual level of walking then statistical adjustment for walking cannot address this possibility.

6.4.2. Strengths and limitations

In the current study the associations between an objective measure of CVD incidence and sitting time were examined in a large sample who were regularly assessed over a decade. As discussed, the richness and breadth of information on health behaviours available from the Whitehall II questionnaire allowed adjustment for a broad range of potential confounding factors. The independent nature of the associations between sitting time and MVPA with

CVD risk was a central question for the current analysis and this necessitated detailed information on habitual physical activity. As discussed previously, the questionnaire items employed in the Whitehall II study allowed comprehensive assessment of a broad range of physical activities using reference energy expenditure values rather than self-reported exertion.

A number of limitations must also be acknowledged. The Whitehall II study is an occupational cohort of white collar workers. As such, not only are all participants healthy enough to be in active employment but the use of a single industry sector, albeit one that includes a broad socioeconomic range,[307] limits the ability to generalise the findings to the general population. However, present findings remain relevant given the increasing proportion of workers in affluent societies employed in white-collar occupations.[320] As per the previous chapter it is also necessary to mention the underrepresentation of the lowest employment grade in the current sample and also that the relatively small proportion of women relative to men working in the British Civil Service is reflected in these analyses.

The use of self-report measures is an important feature of these analyses as they provide the contextual information necessary to examine different sitting types (work sitting versus TV viewing or non-TV leisure time sitting) which is not possible when using objective device-based measures such as accelerometers. Nevertheless any self-report measure of sitting may introduce bias if measurement error is related to the outcome or to membership of any particular population subgroup. In the current analysis it is likely that

measurement error was random and any resulting misclassification of sitting time would be non-differential and would simply lead to an underestimation of any association with CVD. However, as discussed the questionnaire items pertaining to sitting time have been validated[303] and used previously in studies where positive associations have been observed between sitting and health outcomes.[190 191] As discussed previously (3.8), it has been postulated that the pattern of sitting (in terms of the number of breaks or interruptions in a given period) might be an important factor in determining the magnitude of associations with health outcomes. It is therefore important to acknowledge that the wording of the questionnaire items related to sitting behaviour in the Whitehall II study does not allow for identification of the duration of individual periods of sitting. Therefore if it is only prolonged periods of sitting that infer a risk to health then the current classification may mask important associations.

Again it must be acknowledged that a degree of residual confounding may have contributed to the null findings in these analyses. The associations between sitting time and health outcomes may be influenced by environmental factors associated with the specific sitting activity and the context in which it occurs. These specific factors, such as back pain caused by poor desk set-up or the influence of food advertising on TV, which may confound associations with health outcomes, could not be accounted for in the current analyses. In addition, while the current analyses are adjusted for frequency of fruit and vegetable intake, a comprehensive account of diet and energy balance could not be made. As differences in energy balance may be an important factor in

the associations between sitting time and health markers[109 273] it is possible that the omission of such a measure from these analyses is significant.

As discussed in the previous chapter, it is also possible that due to differences in baseline characteristics between those who completed questionnaire items on sitting behaviour at Phase 5 and those who dropped out prior to Phase 5 that a degree of bias may have influenced the current findings, i.e. the current sample may have been disproportionally healthy compared to the original cohort. However, these baseline differences although statistically significant were, in absolute terms, relatively small. In addition not all of the observed significant baseline differences would logically indicate a reduced risk of CVD incidence.

6.5. Conclusions

In the Whitehall II cohort the volume of sitting overall or in specific types of sitting was not associated with incident CVD mortality or morbidity.

Evidence for an association between sitting time and incident cardiovascular disease is limited. Existing studies have either focussed on TV viewing or screen time or have provided weak or no evidence for an association between total sitting and CVD risk. The current study is the first to examine the relationship between five separate sitting time indicators and cardiovascular disease incidence. The findings may be due to in part to a protective effect of a higher than average energy expenditure due to the habitual active transport and associated with working in central London. It is also possible that the volume of

recorded sitting in the present sample is insufficient to detect an effect of sitting on CVD risk. Finally it is possible that only certain patterns of sitting are associated with CVD risk and future studies should develop measures that can quantify both volume and pattern of sitting.

Table 6.1.Subject characteristics at baseline (Phase 5 1997-99). Data are mean (SD)

		Whole sample		Sitting Group (Total from work and leisure time)							
				1		2		3		4	
n (cases)		4698 (323)		1120	(88)	1245	(96)	1665	(72)	1168	(67)
Age (yrs)		55.40	(5.96)	58.00	(5.8)	57	(6.10)	54	(5.30)	53	(5.00)
Male (%)		73.03		21.31		26.61		25.82		26.26	
BMI		25.92	(3.89)	26	(3.80)	26	(3.60)	26	(3.80)	26	(4.00)
Waist Circumference (cm)		89.16	(11.45)	87	(12.00)	88	(11.00)	88	(11.00)	89	(12.00)
Weight (Kg)		77.41	(13.21)	75.00	(13.00)	77.00	(13.00)	78.00	(13.00)	79	(14.00)
Walking (mins/d)		46.70	(36.06)	44.91	(24.87)	44.59	(22.53)	41.50	(21.52)	40.55	(21.03)
MVPA (hrs/wk)		14.26	(11.90)	15.31	(12.97)	15.95	(13.01)	13.09	(10.39)	12.75	(10.71)
Employment Grade (%)	Administrative	46.64		17.89		26.38		27.70		28.02	
	Prof/Executive	43.10		25.73		26.77		23.56		23.95	
	Clerical/Support	10.26		42.95		25.93		16.80		14.32	
Alcohol consumption (units/wk)		13.91	(14.78)	12.00	(15.00)	14.00	(14.00)	14.00	(14.00)	16	(16.00)
Smoking Status (%)	Never	52.53		23.46		25.77		26.22		24.55	
	Ex	38.17		23.70		28.28		24.09		23.93	
	Current	9.30		26.54		23.34		19.68		30.43	
Self-rated health (%)	Very Good	53.07		24.87		27.56		24.71		22.86	
	Good	37.25		22.40		24.97		25.23		27.37	
	Fair or Poor	9.68		23.74		26.59		23.52		26.15	

Table 6.2. Risk of any cardiovascular events according to categories of sitting behaviours between Phase 5 (1997-99) and Phase 9 (2008-09)

	Person yrs (x1000)	N/Events	Rate/1000 person-yrs	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Work sitting (hrs/wk)					
≥0 & <8	14.12	1338/109	7.72	1	1
≥8 & <25	11.93	1121/95	7.96	1.21 (0.91, 1.60)	1.18 (0.89, 1.57)
≥25 & <40	15.87	1438/74	4.66	1.08 (0.78, 1.51)	1.07 (0.77, 1.49)
≥40	11.57	1039/53	4.58	1.18 (0.82, 1.71)	1.20 (0.83, 1.75)
P_{trend}				0.58	0.61
TV sitting (hrs/wk)					
≥0 & <8	5.31	491/39	7.35	1	1
≥8 & <15	9.06	833/48	5.30	0.66 (0.43, 1.01)	0.61 (0.40, 0.93)
≥15 & <16	13.95	1276/77	5.52	0.69 (0.47, 1.01)	0.64 (0.44, 0.96)
≥16	10.74	1009/79	7.36	0.81 (0.55, 1.20)	0.74 (0.50, 1.10)
P_{trend}				0.18	0.10
Non-TV Leisure Time Sitting (hrs/wk)					
≥0 & <4	8.06	803/51	6.32	1	1
≥4 & <9	9.23	917/54	5.85	0.84 (0.58, 1.22)	0.86 (0.59, 1.24)
≥9 & <16	8.56	840/53	6.19	0.99 (0.68, 1.43)	0.99 (0.69, 1.43)
≥16	8.29	835/44	5.31	0.69 (0.47, 1.03)	0.69 (0.46, 1.02)
P_{trend}				0.22	0.21
Leisure Time Sitting (hrs/wk)					
≥0 & <15	15.21	1400/98	6.44	1	1
≥15 & <18	12.56	1154/70	5.57	0.88 (0.65, 1.20)	0.90 (0.66, 1.23)
≥18 & <26	13.98	1282/81	5.79	0.85 (0.63, 1.14)	0.84 (0.62, 1.13)
≥26	12.91	1211/88	6.82	0.87 (0.65, 1.16)	0.84 (0.63, 1.13)
P_{trend}				0.69	0.61
Total sitting (hrs/wk)					
≥0 & <26	13.43	1273/98	13.43	1	1
≥26 & <41	14.85	1384/107	14.85	1.07 (0.81, 1.41)	1.07 (0.81, 1.41)
≥41 & <55	13.76	1239/71	13.76	1.02 (0.74, 1.40)	1.01 (0.73, 1.39)
≥55	13.54	1236/67	13.54	1.04 (0.75, 1.45)	1.02 (0.73, 1.42)
P_{trend}				0.97	0.96

Model 1 adjusted for age, gender, employment grade and ethnicity. Model 2 additionally adjusted for smoking status, alcohol consumption, fruit and vegetable consumption, BMI, walking time and MVPA. Bold typeface = statistically significant $P \leq 0.05$

Table 6.3. Risk of non -fatal myocardial infarction (excluding self-report) according to categories of sitting behaviours between Phase 5 (1997-99) and Phase 9 (2008-09)

	Person yrs (x1000)	N/Events	Rate/1000 person-yrs	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Work sitting (hrs/wk)					
≥0 & <8	14.51	1338/37	2.55	1	1
≥8 & <25	12.26	1121/38	3.10	1.41 (0.89, 2.23)	1.39 (0.87, 2.20)
≥25 & <40	16.12	1438/21	1.30	0.85 (0.47, 1.52)	0.82 (0.46, 1.48)
≥40	11.73	1039/22	1.88	1.35 (0.74, 2.47)	1.35 (0.74, 2.47)
P_{trend}				0.19	0.18
TV sitting (hrs/wk)					
≥0 & <8	5.41	491/19	3.51	1	1
≥8 & <15	9.20	833/20	2.17	0.58 (0.31, 1.09)	0.54 (0.28, 1.02)
≥15 & <16	14.20	1276/27	1.90	0.51 (0.28, 0.92)	0.50 (0.28, 0.93)
≥16	11.00	1009/25	2.27	0.53 (0.29, 0.98)	0.50 (0.27, 0.93)
P_{trend}				0.12	0.10
Non-TV Leisure Time Sitting (hrs/wk)					
≥0 & <4	8.21	803/20	2.44	1	1
≥4 & <9	9.41	917/16	1.70	0.63 (0.34, 1.17)	0.66 (0.36, 1.24)
≥9 & <16	8.75	840/16	1.83	0.72 (0.39, 1.33)	0.74 (0.40, 1.36)
≥16	8.42	835/17	2.02	0.65 (0.35, 1.21)	0.65 (0.35, 1.22)
P_{trend}				0.42	0.49
Leisure Time Sitting (hrs/wk)					
≥0 & <15	15.51	1400/38	2.45	1	1
≥15 & <18	12.80	1154/27	2.11	0.87 (0.53, 1.43)	0.90 (0.55, 1.48)
≥18 & <26	14.25	1282/25	1.75	0.68 (0.41, 1.13)	0.69 (0.41, 1.14)
≥26	13.20	1211/33	2.50	0.85 (0.53, 1.37)	0.82 (0.51, 1.34)
P_{trend}				0.52	0.53
Total sitting (hrs/wk)					
≥0 & <26	13.74	1273/40	2.91	1	1
≥26 & <41	15.25	1384/36	2.36	0.87 (0.55, 1.37)	0.87 (0.56, 1.39)
≥41 & <55	13.97	1239/23	1.65	0.76 (0.44, 1.31)	0.73 (0.43, 1.26)
≥55	13.75	1236/24	1.75	0.85 (0.49, 1.46)	0.81 (0.47, 1.40)
P_{trend}				0.79	0.72

Model 1 adjusted for age, gender, employment grade and ethnicity. Model 2 additionally adjusted for smoking status, alcohol consumption, fruit and vegetable consumption, BMI, walking time and MVPA. Bold typeface = statistically significant $P \leq 0.05$

Table 6.4. Risk of non-fatal myocardial infarction (including self-report) according to categories of sitting behaviours between Phase 5 (1997-99) and Phase 9 (2008-09)

	Person yrs (x1000)	N/Events	Rate/1000 person-yrs	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Work sitting (hrs/wk)					
≥0 & <8	14.45	1338/42	2.91	1	1
≥8 & <25	12.24	1121/40	3.27	1.29 (0.83, 2.00)	1.28 (0.82, 1.99)
≥25 & <40	16.09	1438/24	1.49	0.82 (0.47, 1.43)	0.81 (0.46, 1.40)
≥40	11.70	1039/23	1.94	1.19 (0.66, 2.12)	1.18 (0.66, 2.12)
P_{trend}				0.33	0.32
TV sitting (hrs/wk)					
≥0 & <8	5.40	491/19	3.52	1	1
≥8 & <15	9.19	833/22	2.40	0.64 (0.35, 1.19)	0.59 (0.31, 1.10)
≥15 & <16	14.18	1276/29	2.05	0.55 (0.31, 0.99)	0.54 (0.30, 0.97)
≥16	10.96	1009/30	2.74	0.65 (0.36, 1.68)	0.61 (0.34, 1.09)
P_{trend}				0.24	0.20
Non-TV Leisure Time Sitting (hrs/wk)					
≥0 & <4	8.21	803/20	2.44	1	1
≥4 & <9	9.41	917/16	1.70	0.62 (0.34, 1.16)	0.66 (0.35, 1.23)
≥9 & <16	8.73	840/18	2.06	0.84 (0.46, 1.50)	0.85 (0.47, 1.54)
≥16	8.40	835/19	2.26	0.72 (0.39, 1.32)	0.72 (0.39, 1.32)
P_{trend}				0.48	0.55
Leisure Time Sitting (hrs/wk)					
≥0 & <15	15.49	1400/40	2.58	1	1
≥15 & <18	12.78	1154/29	2.27	0.88 (0.55, 1.43)	0.90 (0.56, 1.47)
≥18 & <26	14.23	1282/27	1.90	0.70 (0.43, 1.14)	0.70 (0.42, 1.14)
≥26	13.15	1211/38	2.89	0.94 (0.60, 1.48)	0.90 (0.57, 1.42)
P_{trend}				0.52	0.54
Total sitting (hrs/wk)					
≥0 & <26	13.69	1273/45	3.29	1	1
≥26 & <41	15.24	1384/37	2.43	0.78 (0.50, 1.22)	0.79 (0.51, 1.23)
≥41 & <55	13.93	1239/27	1.94	0.78 (0.47, 1.28)	0.75 (0.45, 1.24)
≥55	13.72	1236/26	1.90	0.79 (0.47, 1.33)	0.75 (0.45, 1.27)
P_{trend}				0.66	0.59

Model 1 adjusted for age, gender, employment grade and ethnicity. Model 2 additionally adjusted for smoking status, alcohol consumption, fruit and vegetable consumption, BMI, walking time and MVPA. Bold typeface = statistically significant $P \leq 0.05$

Chapter 7

Sedentary behaviour and diabetes risk

7.1. Introduction

The most prevalent form of diabetes mellitus is type II diabetes, comprising around 90% of diagnosed cases in the UK.[284] The underlying metabolic causes of type II diabetes are the combination of impairment in insulin-mediated glucose disposal (insulin resistance) and defective secretion of insulin by pancreatic β-cells.[333] Insulin resistance develops from lifestyle factors including poor diet, obesity and low levels of physical activity and is exacerbated by genetic susceptibility[334] and increasing age.[335] The onset of type II diabetes is commonly accompanied by other lifestyle related risk factors including hypertension, dyslipidaemia and prothrobotic factors. In 2011 it was estimated that diabetes affects 366 million people worldwide, a figure that, based on current trends, is predicted to rise to 552 million by 2030.[284] There are 2.9 million people with diagnosed diabetes in the UK and it is estimated that a further 850 000 have undiagnosed diabetes. It is expected that by 2025, 5 million UK citizens will have been diagnosed with diabetes.[284]

There is a large body of both epidemiological and pathological evidence that points to diabetes as an independent risk factor for cardiovascular disease in both men and women.[336] [337] Cardiovascular disease accounts for around 65% of deaths in diabetic patients. In addition, diabetic patients who develop clinical CVD have a worse prognosis for survival than CVD patients without diabetes. [338] [339]

Physical activity has been demonstrated to improve insulin sensitivity and as such has an established protective effect against diabetes. It is also of significant benefit to those already suffering with the condition.[340 341]

In the last 10 years a number of prospective studies have examined the associations between sedentary behaviour and incident type II diabetes although the majority have focussed on TV viewing rather than all types of sedentary behaviour. Significant positive associations have been observed between TV viewing time and risk of developing type II diabetes that are independent of moderate to vigorous physical activity in large scale population studies from Europe,[56] the US[190-192] and Australia.[81] As discussed previously, TV viewing, while a very prevalent sedentary leisure time activity is only one constituent of total sitting time and cannot be used as an effective marker of a broader pattern of sitting behaviour.[72] Currently there are no prospective studies which have directly examined the association between risk of type II diabetes and total sitting time and only one previous prospective study has investigated associations with multiple sitting behaviours.[191] Hu et al[191] examined incidence of type II diabetes over 6 years of follow up across quintiles of three different domains of sitting: TV viewing, sitting at work or during commuting, and other (non-TV) leisure-time sitting. They observed significant positive associations with diabetes risk for TV viewing and sitting at work but not for non-TV leisure-time sitting.

Due to the global burden of disease attributable to diabetes, its increasing prevalence and its role in the development of cardiovascular disease

a clear understanding of the potential contribution of sitting in the development of diabetes is essential. As discussed previously, while total sitting time is important, the nature of the specific activity and the context in which it is taking place will affect the pattern of sitting time, which has been demonstrated to influence the association with other health outcomes.[109 273] It is therefore necessary to examine the associations between diabetes incidence and both total sitting time and a range of sitting behaviours within the same cohort.

In addition, the role of obesity in the association between sitting and health risk is unclear. There is evidence that markers of adiposity explain a significant proportion (between 27.3% and 95.9%) of the association between sitting time and a range of metabolic risk markers[252] and a recent longitudinal study of early adulthood TV viewing and middle age cardiometabolic risk observed that once analyses were adjusted for baseline BMI the positive associations attenuated to the null.[197] As obesity is central to the development of type II diabetes[333] it is logical to include it in any analysis of sitting and diabetes risk as a potential confounder. Of the existing prospective studies examining sitting and diabetes only three studies[56 190 192] have included a marker of adiposity as a covariate. In all of these studies the positive associations were significantly attenuated following adjustment for baseline BMI and in one the association was attenuated to the null.[56] It is therefore important to examine the role of obesity in the relationship between sitting time and risk for type II diabetes.

This study aims to enhance the evidence base by drawing on 15 years of data from the Whitehall II cohort study to examine the type-specific associations of five different sitting indicators and risk for type II diabetes.

7.1.2. Hypotheses

Based on the current available evidence it is reasonable to hypothesise that:

i. Each of the 5 sitting time indicators will be positively associated with risk of developing type II diabetes
ii. These associations will be independent of moderate to vigorous physical activity
iii. These associations may be attenuated following adjustment for BMI

7.2. Methods

7.2.1. Determination of Sedentary Behaviours and Type II Diabetes

The five sedentary behaviour exposures were determined from Phase 5 data as described previously (4.7.2).

Cases of diabetes were identified by doctor's self-reported diagnosis and diabetic medication, and by 2 hour 75g oral glucose tolerance test conducted during clinical examinations at Phases 5, 7 and 9.[342 343] Following a baseline plasma glucose measurement, participants ingested a solution containing 75g of glucose. Plasma glucose concentration was then assessed at 10, 20, 30, 60 and 120 minutes. Diabetes was then determined using the 1999 World Health

Organisation classification.[168] Participants classified as having diabetes at Phase 5 were excluded from the analysis of incident diabetes between Phases 5 and 9.

7.2.2. Covariates

The sociodemographic covariates included in the current analysis were age, gender, ethnicity and employment grade. Employment grade (3 levels: clerical and support, professional and executive, senior administrative) in the Whitehall II Study is a comprehensive marker of socioeconomic circumstance relating to social status, salary and level of responsibility[307] For retired participants, their last reported employment grade was considered. Health related covariates included self-rated health (reported as; excellent, very good, good, fair, or poor), smoking status (current, previous, or never a smoker), alcohol consumption, diet quality, body mass index (BMI) and physical functioning. Participants reported the number of 'measures' of spirits, 'glasses' of wine, and 'pints' of beer consumed in the previous seven days, and this was then converted to units (1 unit=8g) of alcohol. Diet quality was represented by frequency of fruit and vegetable consumption and was assessed using an eight point scale ranging from: 1) *"seldom or never",* to 8) *"two or more portions per day*". Height (m) and weight (kg) were recorded during clinical examination and BMI calculated using a standard formula. To assess perceptions of physical functioning the SF-36 questionnaire was used and scored with the Medical Outcomes Study scoring system.[308] The SF-36 assesses the extent to which participant's health limits their ability to perform physical activities, ranging in intensity from vigorous (sporting and volitional exercise activities) to light (day-to –day tasks) using the responses *"a lot", "a little",* and *"not at all"*. Responses

were scored, summed and transformed to scale from 0 (limited a lot in performing all types of physical activities) to 100 (able to perform all types of physical activity without limitation). This scale has been demonstrated to have high internal consistency.[309]

Physical activity covariates included daily walking time (minutes/day), and time spent in moderate to vigorous physical activity (hrs/wk). Physical activity was assessed using a modified version of the Minnesota leisure-time physical activity questionnaire which assesses both occupational and leisure-time physical activities, and which has been validated previously.[299] Twenty items (including 5 open-text responses) assessed time spent engaged in walking, sports and games, gardening activities, housework and do-it-yourself building/maintenance projects, in hours over the previous four week period. Each activity was subsequently assigned an energy expenditure value in metabolic equivalents (METs: where 1 MET is equal to energy expenditure at rest) using a compendium of activity energy expenditures.[302] Moderate intensity activities were classified as those eliciting an energy expenditure of 3-5.9 METs and vigorous intensity activities from 6 METs and upwards. The energy expenditure of walking activity is dependent on walking pace and could therefore not be determined from the Phase 5 questionnaire. As a result, while in some instances walking may have met the required energy expenditure, for the purposes of the present analysis walking did not contribute to the measure of MVPA but daily walking time (minutes per day) was included as a separate covariate.

7.2.3. Statistical analysis

Due to low numbers in some of the eight categories of sitting time, they were collapsed into four categories of near equal numbers as the data permitted. Exact quartiles were again not possible due to the distributions of sitting time.

Separate multiple logistic regression models were fitted to examine the prospective associations between each of the five sitting exposures and type II diabetes incidence between Phases 5 (1997-99) and 9 (2008-09). Odds ratios for type II diabetes and 95% confidence intervals were estimated for each category of the five sitting exposures with the lowest group the reference category. Analyses were limited to those who were free from diabetes and who had not suffered any form of heart disease prior to Phase 5

Logistic regression models were first adjusted for age, gender, ethnicity and employment grade (model 1) and then additionally for smoking status, alcohol consumption, physical functioning, frequency of fruit and vegetable intake and self-rated health (model 2). In order to address the central hypothesis that sitting is a risk factor for diabetes that acts independent of physical activity, weekly MVPA and daily walking time were added in model 3. In order to examine the possibility that obesity may confound the relationship between sitting time and diabetes risk, those sitting models which showed a significant association between sitting and diabetes risk were repeated with additional adjustment for BMI (model 4). In order to examine the possibility of bias due to differential loss from the original 1985 cohort, baseline age, gender,

employment grade, alcohol consumption and the likelihood of being obese and of being a current smoker were compared between those who did and those who did not respond to questionnaire items relating to occupational and leisure time sitting behaviour. Pearson's product-moment correlations were used to examine the relationship between the five sitting indicators and weekly MVPA. Analyses were conducted in 2013 using STATA version 11.2.

7.3. Results

The final sample consisted of 4851 participants who had complete data for sitting time and all covariates and who were free from diabetes or coronary heart disease at Phase 5. Baseline sample characteristics are described in table 7.1. A total of 387 new cases of diabetes were recorded over a 10 year follow up period. Compared to those who completed questionnaire items related to sitting at Phase 5, those lost to follow-up between the studies inception in 1985 and the Phase 5 were slightly older at date of screening (0.42 yrs; 95%CI 0.17, 0.67: *P*=0.001) consumed slightly less alcohol 1.19 units/wk; 95%CI 0.64, 1.73: *P* <0.001) and had a greater likelihood of being male (OR 0.11; 95%CI 0.09, 0.13), obese (OR 0.04 95%CI 0.03, 0.05), and in a higher employment grade (OR 0.05 95%CI 0.03, 0.07) in 1985. Inclusion in the current analysis was not associated with smoking behaviour in 1985. There was very little evidence of a correlation between MVPA and Work sitting (r=-0.16), TV sitting (r=0.02), Non-TV leisure time sitting (r=-0.03), Leisure time sitting (r=0.04), and Total sitting (r=-0.09).

Odds ratios and 95% confidence intervals for diabetes risk across four categories of the five sitting indicators are described in table 7.2. There was a significant positive association between weekly TV sitting and diabetes risk which remained significant following adjustment for age, gender, ethnicity, self-rated health, smoking status, alcohol consumption MVPA, and daily walking time. Those who reported watching more than 16 hours of television per week were 73% more likely to develop diabetes than those who watched less than 8 hours per week following adjustment for covariates. Total sitting was not significantly associated with diabetes risk in model 1. However there was a significant association in model 2 (following adjustment for self-rated health, physical functioning, smoking status and alcohol consumption), and this persisted following subsequent adjustment for MVPA and daily walking time in model 3. Those in the highest total sitting group were 31% more likely to develop diabetes over the follow-up period than those in the reference category. Leisure time sitting was associated with diabetes risk in model 1 but was attenuated in the subsequent models. Work sitting and non-TV leisure-time sitting were not associated with diabetes risk in any of the models.

When the analyses for TV sitting, and total sitting time were further adjusted for BMI at baseline the positive associations were attenuated to null (odds ratios and 95% confidence intervals are described in table 7.3)

7.4. Discussion

These analyses tested the hypotheses that sitting time would predict risk of incident type II diabetes independently of moderate to vigorous intensity

physical activity and that BMI may attenuate these associations. This is the first study to examine associations between incident diabetes and both total and type specific sitting time. Sitting while watching television and total sitting time from work and leisure time were positively associated with risk of developing type II diabetes during the follow-up period while sitting at work and non-TV leisure time sitting were not. Leisure time sitting was significantly associated with diabetes risk in model 1 only. These associations remained significant following adjustments for a range of covariates including MVPA but were attenuated to null following adjustment for BMI (Table 7.3).

This is the first study to examine the relationships between total weekly sitting time, including both occupational and leisure time sitting, with type II diabetes risk. The current findings suggest that total sitting from all domains may be an important risk factor for type II diabetes, independent of moderate to vigorous physical activity. The differential associations observed between the five sitting indicators with diabetes risk also highlights the importance of examining sitting behaviour in different contexts separately.

The present findings are consistent with a number of previous prospective studies which have observed significant positive associations between TV viewing time and type II diabetes incidence.[56 65 190-192] The observation that non-TV leisure time sitting showed no association with diabetes risk is also consistent with the only previous study which has examined this exposure.[191] There are a number of possible explanations for these differential associations. Both epidemiological[109] and experimental[273 275]

evidence suggests that the pattern of sitting behaviour, in terms of the number of breaks or interruptions in a given period, can determine the magnitude of any negative health consequences. It is possible that when sitting to watch a TV programme or a film (which may last a matter of hours) people are less likely to get up and move around, engage in another activity, or otherwise interrupt prolonged sitting than during reading or talking on the phone, activities which may be shorter in duration or more sporadic. It has also been suggested that TV viewing may illicit a slightly lower energy expenditure than other sitting behaviours,[302] and may therefore contribute to the development of a positive energy balance to a greater degree.

It is also possible that TV viewing, unlike other sedentary behaviours may contribute to a higher overall energy intake leading to adiposity and subsequently to associated conditions including type II diabetes. This may happen either indirectly, by increased exposure to food advertising, or directly through the consumption of energy dense snack foods or beverages during TV viewing. In an investigation of the priming effects of television food advertising on eating behaviour Harris et al[74] observed that adults consumed more food following exposure to snack food advertising irrespective of their reported hunger and that these effects were not limited to the products being advertised. Cleland et al[321] also reported that the association between TV viewing time and waist circumference was significantly attenuated following adjustment for food and beverage consumption. While the current analyses were adjusted for frequency of fruit and vegetable consumption to try and account for differences in diet quality, differences in snacking behaviour and energy intake from calorie

rich foods and beverages could not be accounted for. It is therefore possible that TV food advertising and related changes in dietary behaviours may have contributed to the differential associations observed between TV viewing and non-TV leisure time sitting with diabetes risk in the current analysis.

There are also a number of methodological factors which must be considered. As discussed previously (2.2.4) it is possible that TV viewing is easier for participants to accurately recall than other leisure-time sitting behaviours which may occur less often, less regularly, and for shorter periods. TV viewing is a very prevalent leisure time behaviour and recall may also be aided by regular programming and TV schedules. As non-differential misclassification of the exposure will attenuate any true association with the outcome towards the null, if there is more error in the reporting of non-TV leisure time sitting than in TV viewing then observing an association with TV viewing is more likely.

The absence of an association between sitting at work and risk for type II diabetes is not consistent with the one previous prospective study to examine differences in diabetes risk across 5 categories of occupational weekly sitting time.[191] Hu et al observed a significant positive association between diabetes incidence and work sitting time following adjustment for a range of covariates including age, hormone use, alcohol consumption, smoking, family history of diabetes, physical activity and a range of dietary factors.[191] One possible explanation for the absence of an association with work sitting is the homogeneity of work patterns within the civil service. It may be that the use of

employees of a single industry sector does not allow sufficient variance in sitting time to be able to detect an association with diabetes risk. Alternatively, if sitting pattern is important, there may be differences in the patterns of occupational sitting between the two cohorts.

The last part of these analyses examined the effect of additionally adjusting the analyses for baseline BMI (model 4). Following this adjustment, the remaining associations between both TV viewing and total sitting time with diabetes risk were attenuated to the null. This is consistent with previous prospective studies which have reported significant attenuation of associations between sitting time and diabetes risk following adjustment for baseline BMI,[56] [190] [192] although in only one of these previous studies was the association attenuated to null.[56] It is also consistent with the findings by Stamtakis et al[197] who used prospective data from nearly 6000 participants from the 1958 British Birth Cohort Study to examine associations between TV viewing at age 23 and cardiovascular risk at age 44. The range of measured risk factors included plasma triacylglycerol, total and HDL cholesterol, systolic and diastolic blood pressure, waist circumference and glycated haemoglobin (HBA_{1c}) which is a marker of diabetes status. Following adjustment for baseline BMI associations between TV viewing with these risk markers and total cardiometabolic risk score were attenuated to null. In a separate cross-sectional analysis of 5067 people representative of the UK population, Stamatakis et al[252] observed that measures of adiposity explained significant proportions of the associations between both TV viewing and total sitting with a range of non-adiposity related cardiometabolic risk markers. Body mass index explained up to 95.9% of the

association between total sitting and risk markers (range for individual markers 33% to 95.9%: described previously (3.7). Waist circumference explained a slightly lower proportion of the association between total sitting time and risk markers (range for individual markers 38%-90%). A smaller but still considerable proportion of the associations between TV viewing and these risk markers were explained by BMI (range 28.6-60.3%) and waist circumference (27.3-60.7%). The findings of this study and those of others suggest that obesity may lead to greater volumes of sitting during non-work time (where there is greater choice) and subsequently increased risk rather than the other way round.

The direction of the association between sitting and obesity is unclear (it is plausible that obesity is both a cause and a consequence of sitting behaviour) [83 250] and further research is required to clarify this association and examine its contribution to the relationships between sitting and other disease outcomes.

One of the important aspects of the definition of sedentary behaviour is that little is required in the way of energy expenditure above resting levels. Unless energy intake is adjusted accordingly, this reduced energy expenditure would lead to a surplus of energy intake over expenditure. A recent experimental study observed that, compared to a more active day, the acute detrimental effects of a full day of uninterrupted sitting on insulin action were largely attenuated if energy intake was reduced to match the reduced energy expenditure[274] It is well established that energy surplus reduces insulin action[344 345] and evidence suggests that there is no compensatory decline in ad libitum

food intake in response to large reductions in energy expenditure.[346] Therefore it is reasonable to conclude that energy surplus and sedentary behaviour may often coexist. As well as acutely affecting insulin action, chronic exposure to a positive energy balance through repeated high volumes of daily sitting would also contribute to additional adiposity which in itself would contribute to insulin resistance and increased risk of diabetes. Therefore it may be that the association between sitting time and diabetes risk is due, at least in part, to the acute and chronic effects of a positive energy balance brought about by prolonged periods of time spent at a lower energy expenditure that are not compensated for by relatively short, occasional bouts of MVPA.

The measure of diet quality in the current analysis is not sufficient to account for differences in total daily energy intake or energy balance so this may be a source of residual confounding. Further epidemiological and experimental studies, with sensitive measures of diet, and energy intake versus expenditure, are needed to clarify the contribution of dietary behaviours and energy balance to the associations between sitting and health outcomes.

7.4.2. Strengths and limitations

The large sample size and 10 year follow-up period are strengths of the current analysis, as is the broad ranging information on physiological risk markers and health behaviours which allowed adjustment for large number of potential confounding factors. The benefits of physical activity on metabolic health, insulin sensitivity and diabetes risk are well established so the question of whether sitting time influences diabetes risk independently of physical activity

is an important one. The detailed assessment of a broad range of physical activities in the Whitehall II questionnaire is another significant strength.

A number of limitations must also be acknowledged. As discussed previously the Whitehall II study is an occupational cohort study, and as such all participants were healthy enough to be in active employment when recruited. This limits the ability to generalise the present findings to the wider population, as does the use of a single industry sector. However, given the increasing proportion of workers in affluent societies employed in white-collar occupations these findings remain very relevant.[320]

Measurement error associated with the use of self-report measures may lead to misclassification of sitting time. Any systematic measurement error could potentially have introduced bias to the analyses. However in the current study it is likely that any measurement error is random and resulting misclassification non-differential, which would simply result in an attenuation of any true associations between sitting and diabetes risk towards the null. In addition the questionnaire items related to occupational and leisure time sitting have been used previously in prospective studies examining associations between sitting time and health outcomes[190 191] and have been previously validated. [303]It must also be recognised that the use of self-report measures is an important strength of these analyses as objective measures of sedentary time such as accelerometers cannot provide the important contextual information which allows the separate examination of sitting in different domains. The differential associations between diabetes risk and the different sitting indicators observed

in these analyses highlight the importance of this. It is also possible that some misclassification of the outcome may have arisen from cases where the classification of diabetes was reliant on self-report of either a doctor's diagnosis of diabetes or the prescription of diabetes drugs.

7.4.3. Conclusions

The results of this study and others suggest TV viewing time, sitting during leisure time and total sitting from work and leisure time combined are associated with risk for type II diabetes independent of moderate to vigorous physical activity. These findings are also consistent with previous prospective studies that have demonstrated that associations between sitting and diabetes are significantly attenuated following adjustment for baseline BMI. As sitting behaviours require and energy expenditure of ≤1.5 METs it is logical that prolonged sitting could simply be a marker for low daily energy expenditure that could contribute to a positive energy balance. It is therefore possible that the association between sitting and diabetes incidence may be attributable at least in part to a positive energy balance rather than sitting per se, which would contribute to increased adiposity and subsequent reduced insulin sensitivity. Further experimental research is needed to determine the association between sitting and adiposity and the role of diet, energy expenditure and energy balance in the associations between sitting and health outcomes.

Table 7.1. Subject characteristics at baseline (Phase 5 1997-99)

		Whole sample	Sitting Group (Total from work and leisure time)			
			1	2	3	4
n (cases)		4851 (387)				
Age (yrs)		55.38 (5.93)	58.00 (5.80)	57.00 (6.00)	54.00 (5.30)	53.00 (5.00)
Male (%)		66.82	21.44	27.03	25.72	25.81
BMI		25.68 (3.77)	26.00 (3.70)	26.00 (3.60)	26.00 (3.80)	26.00 (4.00)
Waist Circumference (cm)		89.06 (11.36)	87.00 (11.00)	88.00 (11.00)	88.00 (11.00)	89.00 (12.00)
Weight (Kg)		77.00 (13.00)	76.00 (13.00)	77.00 (13.00)	78.00 (13.00)	79.00 (14.00)
Walking (mins/d)		42.71 (22.66)	44.49 (24.76)	44.30 (22.68)	40.98 (21.39)	40.91 (21.44)
MVPA (hrs/wk)		14.24 (11.89)	15.35 (12.81)	15.78 (13.06)	13.01 (10.40)	12.67 (10.62)
Employment Grade (%)	Administrative	47.00	18.68	26.49	27.24	27.59
	Prof/Executive	43.00	26.22	27.28	23.25	23.25
	Clerical/Support	10.00	40.82	27.42	17.32	14.43
Alcohol consumption (units/wk)		14.00 (15.00)	13.00 (15.00)	14.00 (14.00)	14.00 (14.00)	16.00 (16.00)
Smoking Status (%)	Never	52.05	23.41	26.26	26.10	24.24
	Ex	38.01	24.19	28.47	23.75	23.59
	Current	9.94	27.80	24.48	19.29	28.42
Self-rated health (%)	Very Good	53.43	25.08	27.70	24.31	22.92
	Good	37.04	22.70	25.43	25.15	26.71
	Fair or Poor	9.52	24.46	28.35	23.38	23.81

Data are mean (sd) unless otherwise stated.

Table 7.2.. Risk of type II diabetes according to categories of sitting behaviours between phases 5 and 9 (1997-99 and 2008-09)

		Model 1		Model 2		Model 3	
	N/Cases	**OR**	**(95% CI)**	**OR**	**95% CI**	**OR**	**95% CI**
Work sitting (hrs/wk)							
≥0 & <3	1240/105	1		1		1	
≥3 & <25	1046/91	1.08	(0.80, 1.46)	1.05	(0.77, 1.42)	1.05	(0.77, 1.42)
≥25 & <40	1381/109	1.11	(0.81, 1.52)	1.11	(0.81, 1.53)	1.10	(0.80, 1.51)
≥40	1002/65	0.96	0.67, 1.38	0.97	(0.68, 1.40)	0.96	(0.66, 1.38)
P_{trend}		0.79		0.84		0.84	
TV sitting (hrs/wk)							
≥0 & <8	469/27	**1**		**1**		**1**	
≥8 & <15	792/53	**1.26**	**(0.78, 2.05)**	**1.22**	**(0.75, 1.98)**	**1.23**	**(0.76, 2.01)**
≥15 & <16	1199/105	**1.67**	**(1.08, 2.61)**	**1.59**	**(1.02, 2.49)**	**1.62**	**(1.04, 2.53)**
≥16	953/93	**1.84**	**(1.17, 2.90)**	**1.70**	**(1.08, 2.70)**	**1.73**	**(1.10, 2.73)**
P_{trend}		**0.02**		**0.05**		**0.04**	
Non-TV Leisure Time Sitting (hrs/wk)							
≥0 & <8	748/60	1		1		1	
≥8 & <9	864/69	1.02	(0.71, 1.47)	0.99	(0.69, 1.43)	0.99	(0.69, 1.43)
≥9 & <16	800/53	0.84	(0.57, 1.23)	0.81	(0.55, 1.20)	0.82	(0.55, 1.21)
≥ 16	792/69	1.10	(0.76, 1.59)	1.04	(0.72, 1.50)	1.03	(0.70, 1.49)
P_{trend}		0.54		0.59		0.63	
Leisure Time Sitting (hrs/wk)							
≥0 & <11	1324/88	**1**		1		1	
≥11 & <18	1102/78	**1.14**	**(0.83, 1.57)**	1.11	(0.81, 1.53)	1.11	(0.81, 1.54)
≥18 & <26	1205/109	**1.47**	**(1.09, 1.98)**	1.43	(1.06, 1.94)	1.44	(1.07, 1.96)
≥26	1142/103	**1.41**	**(1.04, 1.91)**	1.29	(0.95, 1.76)	1.30	(0.95, 1.77)
P_{trend}		**0.04**		0.09		0.08	
Total sitting (hrs/wk)							
≥0 & <26	1171/96	1		**1**		**1**	
≥26 & <41	1306/105	1.08	(0.81, 1.46)	**1.08**	**(0.80, 1.45)**	**1.08**	**(0.80, 1.46)**
≥41 & <55	1190/83	1.04	(0.76, 1.44)	**1.14**	**(1.05, 1.43)**	**1.18**	**(1.04, 1.42)**
≥ 55	1184/103	1.36	(1.00, 1.87)	**1.32**	**(1.07, 1.82)**	**1.31**	**(1.05, 1.79)**
P_{trend}		0.18		**0.05**		**0.03**	

Model 1 adjusted for age, gender, employment grade and ethnicity. Model 2 additionally adjusted for smoking status, alcohol consumption, fruit and vegetable consumption, BMI, walking time. Bold typeface = statistically significant $P \leq 0.05$

Table 7.3. Risk of type II diabetes according to categories of sitting behaviours between phases 5 and 9 (1997-99 and 2008-09)

		Model 3		Model 4	
	N/Cases	**OR**	**(95% CI)**	**OR**	**95% CI**
TV sitting (hrs/wk)					
≥0 & <8	469/27	**1**		1	
≥8 & <15	792/53	**1.23**	**(0.76, 2.01)**	1.21	(0.74, 1.98)
≥15 & <16	1199/105	**1.62**	**(1.04, 2.53)**	1.54	(0.98, 2.43)
≥16	953/93	**1.73**	**(1.10, 2.73)**	1.60	(1.00, 2.54)
P_{trend}		**0.04**		0.13	
Leisure Time Sitting (hrs/wk)					
≥0 & <11	1324/88	1		1	
≥11 & <18	1102/78	1.11	(0.81, 1.54)	1.09	(0.79, 1.52)
≥18 & <26	1205/109	1.44	(1.07, 1.96)	1.37	(1.01, 1.86)
≥26	1142/103	1.30	(0.95, 1.77)	1.24	(0.91, 1.69)
P_{trend}		0.08		0.20	
Total sitting (hrs/wk)					
≥0 & <26	1171/96	**1**		1	
≥26 & <41	1306/105	**1.08**	**(0.80, 1.46)**	1.07	(0.79, 1.45)
≥41 & <55	1190/83	**1.18**	**(1.04, 1.42)**	0.99	(0.71, 1.38)
≥ 55	1184/103	**1.31**	**(1.05, 1.79)**	1.20	(0.87, 1.65)
P_{trend}		**0.03**		0.61	

Model 3 additionally adjusted for MVPA. Model 4 additionally adjusted for BMI. Bold typeface = statistically significant $P \leq 0.05$

Chapter 8

Sedentary Behaviour and Obesity

8.1. Introduction

The increasing prevalence of overweight and obesity is a global health concern. A recent systematic analysis of epidemiological studies from 199 countries estimated that in 2008 1.46 billion adults worldwide were overweight and 502 million were obese.[347] The effects of a chronically high prevalence of obesity on population health are far reaching. Obesity is an established risk factor for several major chronic conditions, including cardiovascular and metabolic diseases and certain cancers. The morbidity and premature mortality associated with such conditions drives the increasing health burden of overweight and obesity.[348 349] The acute and chronic conditions associated with obesity impact societies not just by detrimentally affecting the health related quality of life of individuals, [350 351] but also financially, through the increased healthcare costs and lost productivity. A 2007 report by the UK Office for Science Foresight Program projected that the continuing rise in obesity prevalence will add £5.5 billion in medical costs to the National Health Service by 2050[285] and although individual estimates vary, a number of studies have suggested that the monetary value of lost productivity is several times larger than the direct medical cost.[352 353] A comprehensive understanding of how health behaviours might affect the development of obesity is therefore essential.

Moderate to vigorous intensity physical activity (MVPA) has an established protective effect against a range of health outcomes and associated

risk factors, including obesity.[354 355] In addition an emerging body of evidence suggests that sitting may be linked to cardiometabolic risk independently of MVPA.[34 356] As discussed previously (chapter 3), prospective studies have demonstrated significant positive associations between indicators of sitting behaviour and mortality,[53 62 152 154] cardiovascular disease,[65 67] and metabolic disease including type 2 diabetes,[56 190-192] which are independent of MVPA. Cross-sectional studies have reported consistent associations between sitting behaviour and obesity prevalence [206 289] while some prospective studies have reported sitting to predict incident obesity or positive changes in bodyweight or adiposity.[66 191 217 246] Nevertheless, evidence for associations between sitting and obesity risk is equivocal: other studies have shown body weight status can predict sitting time,[83] sedentary lifestyle[250] and reduced levels of physical activity,[357 358] but sitting may not predict future obesity.[83]

A recent longitudinal study looking at the associations between TV viewing in early adulthood and cardio metabolic risk profiles in middle age also found that once the analyses were adjusted for baseline BMI there was little evidence of an association.[197] In a separate study BMI and waist circumference were found to explain most of the association between time spent sitting and cardiometabolic risk factors.[252]

Different types of sitting that vary in duration and pattern may have differential associations with health outcomes.[109] Despite this, only one previous prospective study has separately examined whether different types of sitting are differentially associated with obesity. Other studies have examined all sitting

behaviours combined or a single type of sitting, most commonly TV viewing and/or recreational screen time. Further, no studies have examined the prospective associations between obesity and time spent in different sitting types. This is important as if some sitting behaviours are associated with obesity and others aren't this might offer some insight as to the biological mechanism underlying the association.

The aim of this study was to add to the current literature by examining different types of sitting and the direction of any relationship with obesity. Drawing on data from two measurement phases of the Whitehall II cohort study the cross-sectional and prospective associations between 5 sitting exposures and obesity were examined. In addition, data from earlier measurement phases were used to examine the hypothesis that obesity may determine different types of sitting behaviour rather than sitting determining obesity.

8.1.2. Hypotheses

Based on the current available evidence it is reasonable to hypothesise that:

iv. Each of the 5 sitting time indicators will be positively associated with both prevalent and incident obesity

v. These associations will be independent of moderate to vigorous physical activity

vi. Obesity may also predict volume of sitting time

8.2. Methods

8.2.1. Determination of sedentary behaviours and obesity

The five sedentary behaviour exposures were determined from Phase 5 data as described previously (4.7.4).

The questionnaire included items related to both occupational and leisure time sitting behaviours. Participants were asked 'On average how many hours per week do you spend: sitting at work, driving or commuting?' and 'sitting at home e.g. watching TV, sewing, at a desk', and responded by selecting one of eight time categories (none, 1hr, 2-5, 6-10, 11-20, 21-30, 31-40, >40hrs). For sitting at home participants were given an open text response option to specify two types of sitting and then selected a time category for each. Using the midpoint of each time category, 5 indicators of sitting expressed as hours per week were computed: 1) work related sitting time, 2) TV viewing time, 3) Non-TV leisure sitting time, 4) Total leisure time (LT) sitting (sum of 2 and 3 above), and 5) Total sitting time (sum of 1-3 above). These items have been used previously[191] and their validity is described elsewhere.[303]

Height (metres) and weight (kg) were measured at the clinical examinations. Body Mass Index (BMI) was computed by dividing height^2 (m) by bodyweight (Kg). Obesity was defined as having a BMI of ≥30kg.m^2 and was recorded at baseline and at Phases, 3, 5 and 7. At baseline participants were asked to recall their weight at 25 years which was used with height at baseline to estimate BMI and obesity status at age 25 years.

8.2.2. Covariates

Sociodemographic covariates included age, gender, ethnicity and employment grade. Employment grade in the Whitehall II study is a comprehensive marker of socioeconomic circumstance related to salary, level of responsibility and social status.[307] Health behaviours included smoking status (current, previous, or never a smoker), alcohol consumption (units per week), self-rated health (excellent, very good, good, fair, or poor). Perceived physical functioning was assessed using the SF-36 and scored with the Medical Outcomes Study scoring system.[308] The scale requires participants to consider the extent to which their health limits their ability to perform 10 physical activities ranging from vigorous intensity sporting activities to light intensity day to day tasks using the responses 'a lot', 'a little', and 'not at all'. These scores are summed and transformed to scale from 0 (limited a lot in performing all ten types of physical activities) to 100 (performs all ten types of physical activities without limitation). This scale has high internal consistency.[309]

Physical activity covariates included daily walking time (mins/day), time spent in light intensity activity (LPA) and moderate to vigorous intensity physical activity (MVPA) in hrs/wk. The questionnaire asked about occupational, domestic and leisure time physical activities. Twenty items assessed time spent engaged in walking, cycling, stair-climbing, sports and games, domestic activity including gardening, housework and DIY. Participants reported the number of occasions and total number of hours spent engaged in each activity over the previous 4-week period. Each activity was then assigned an energy expenditure value using a compendium of physical activity energy costs.[359] Physical

activities were classified by metabolic equivalents (MET) with moderate intensity activities (e.g. heavy gardening, heavy household maintenance activities, some sports,) ranging from 3-5.9 METS and vigorous intensity activities (e.g. sports) 6 METS or greater. As the energy cost of walking is dependent on walking pace and could not be determined from the Phase 5 questionnaire, walking time did not contribute to either the MVPA or LPA variables. Therefore LPA included all other activities up to 3 METS (light housework and chores).

8.2.3. Statistical analyses

Due to low numbers in some of the eight categories of sitting time, they were collapsed into four categories of near equal numbers as the data permitted (see Table 2). Exact quartiles were not possible due to non-normal distributions. Participants were classified as obese (1) or not (0) depending on their BMI for each phase. Pearson's product-moment correlations were used to examine the relationship between the five sitting indicators and weekly MVPA.

Separate multiple logistic regression models were fitted to examine the cross-sectional associations between each of the five sitting exposures and obesity at Phase 5. Odds ratios and 95% confidence intervals were estimated for each category of sitting time, by type, with the lowest group the reference category. Cross-sectional analyses were limited to those who had completed both the survey and clinical examination, who were still working in the civil service or elsewhere, and who had not suffered any form of heart disease prior to the survey/examination. Analysis of incident obesity between Phases 5 and 7

was restricted to the same sample as cross-sectional analyses but in addition participants who were obese at Phase 5 were excluded.

To investigate the effect of antecedent obesity on sitting behaviour at Phase 5 participants were characterised as obese/non-obese at baseline, Phase 3 and at age 25. The sum of values from these 3 variables indicated the number of occasions an individual was obese prior to the measurement of sitting at Phase 5.

Ordinary least squared linear regression models were fitted to examine the association between occasions of obesity prior to Phase 5 (a categorical exposure variable with scores 0-3) and time spent in each of the five types of sitting at Phase 5 (as the outcomes). Models were first adjusted for age and gender (Model 1) and then further adjusted for employment grade, ethnicity, smoking status, weekly alcohol intake, self-rated health, physical functioning, daily walking time and MVPA (Model 2). The light intensity physical activity (LPA) variable was not included in the final models as it did not significantly improve model fit. To test for linear trends in individual parameters the Wald chi-squared test was used and the Likelihood-ratio chi-squared test was used for non-linear relationships. In order to examine the possibility of bias due to differential loss from the original 1985 cohort, baseline age, gender, employment grade, alcohol consumption and the likelihood of being obese and of being a current smoker were compared between those who did and those who did not respond to questionnaire items relating to occupational and leisure

time sitting behaviour. Analyses were conducted in 2012 using STATA version 11.2 (StataCorp, College Station, TX).

8.3. Results

Participant characteristics are shown in Table 8.1. Logistic regression analyses showed that participants who provided complete data for the Phase 5 measurement only did not differ significantly in baseline characteristics to those who provided complete data for both Phases 5 and 7 ($p>0.05$ for all). Compared to those who completed questionnaire items related to sitting at Phase 5, those lost to follow-up between the studies inception in 1985 and the Phase 5 were slightly older at date of screening (0.42 yrs; 95%CI 0.17, 0.67: $p=0.001$) consumed slightly less alcohol 1.19 units/wk; 95%CI 0.64, 1.73: $p<0.001$) and had a greater likelihood of being male (OR 0.11; 95%CI 0.09, 0.13), obese (OR 0.04 95%CI 0.03, 0.05), and in a higher employment grade (OR 0.05 95%CI 0.03, 0.07) in 1985. Inclusion in the current analysis was not associated with smoking behaviour in 1985. There was no evidence of a correlation between weekly MVPA and Work sitting ($r=0.04$), TV viewing ($r=-0.04$), Non-TV leisure sitting ($r=-0.02$), Leisure time sitting ($r=-0.01$), and Total sitting ($r=0.02$).

8.3.2. Cross-sectional and Prospective analyses

No cross-sectional associations between different sitting indicators and prevalent obesity were observed (Table 8.2). Between Phases 5 and 7, ninety-eight new cases of obesity were recorded. None of the five sitting exposures were associated with incident obesity between Phases 5 and 7 (Table 8.2).

8.3.3. Antecedent obesity analysis

The results of linear regression analyses of the effect of prior obesity on Phase 5 sitting time are shown in Table 3. The group of participants classified as being obese at all three time points prior to Phase 5 watched an average of nearly 9 hours of TV per week more than the reference category (never obese at any measurement prior to Phase 5). Being obese on 3 occasions prior to Phase 5 was also associated with a 6hrs/wk increase in total leisure time sitting (Model 1) relative to the reference category. These effects were only slightly attenuated in the fully adjusted Model 2. Being obese at one measurement phase prior to Phase 5 was associated with around 2.5 hrs/wk higher TV viewing time at Phase 5 but not total LT sitting. There were no associations between prior obesity and work sitting, non-TV LT sitting, or total sitting.

8.4. Discussion

The current study is the first to examine the nature and direction of cross-sectional and prospective associations between type specific sitting time and obesity. No evidence of cross-sectional or prospective associations between the five sitting time indicators and prevalent or incident obesity were found. Conversely, prior obesity was associated with higher levels of TV viewing time at Phase 5.

The absence of any associations between sitting time and obesity in this study is not consistent with a number of previous studies which have demonstrated positive prospective associations between sitting time and obesity,[66 191] markers of body composition,[217] and weight gain.[246] One possible

explanation for the lack of an apparent association between sitting time and obesity in the present data is a higher than average energy expenditure accrued as a consequence of walking and standing for transport in the Whitehall II cohort. The mean reported walking time for the whole sample was 40.71 (±20.83) mins/day, which is considerably higher than the population average reported in the 2005 UK Time Use Survey (17 mins/day).[314] This difference may reflect the commuting habits of London professionals who, due to the public transport infrastructure, may be more likely to walk and stand (on buses and trains) on their journey to work, than people residing and working in other areas of the country who may be more accustomed to commuting by car.[313] Hu et al[191] observed that while sitting time was positively associated with obesity risk, time spent standing or walking around was associated with a significant reduction in obesity risk. In addition, it has previously been demonstrated that habitual active transport may moderate the association between TV viewing and obesity.[199 360] The volume of MVPA reported by this cohort is also high in comparison with other prospective studies. It has been observed previously that London civil servants report higher levels of physical activity than the age matched wider population.[319] One possible explanation for why the results in the current study differ from previous prospective studies is that the total daily energy expenditure attributable to habitual active commuting and leisure time physical activity is higher than that observed in other cohorts and sufficient to counter the risk of obesity due to prolonged sitting.

In the current analysis obesity prior to Phase 5 was associated with TV viewing at Phase 5, although the association was not linear. The strongest

association was in participants who were obese at all time points. These observations are consistent with findings from previous studies which have also reported that measures of body weight and composition were prospectively associated with sitting time,[83] having a sedentary lifestyle[250] and reduced physical activity levels,[357] [358] while reporting no association in the other direction. One such study[83] observed that after adjustment for covariates, baseline sedentary time was not predictive of changes in body weight, BMI, fat mass or waist circumference at follow-up. However, when the adiposity outcomes were modelled as exposure variables, all four significantly and independently predicted sitting time at follow-up. In the same study, changes in body weight, BMI and fat mass between baseline and follow-up were predictive of sitting time at follow-up. Of the previous studies that have shown an association between indicators of sitting time and markers of obesity, only one adjusted for earlier BMI.[66] A recent report of a UK birth cohort also found that following adjustment for baseline BMI, observed positive associations between TV viewing frequency at age 23 and cardiovascular risk factors and waist circumference at age 44 were attenuated to null.[197]

The finding that an effect of prior obesity was only associated with time spent watching television and leisure time sitting is logical as arguably people can exert more control over how much time they spend sitting at home compared to at work. Also, as discussed previously TV viewing may be easier to recall than other sitting behaviours which may be more sporadic, and the greater recall error associated with these behaviours may attenuate any true association towards null. Sitting at work may also be less prone to recall error,

but this study has limited ability to detect associations between work sitting and obesity due to the lack of variance in work related sitting amongst employees of the civil service.

8.4.2. Strengths and limitations

The large sample size and prospective design are major strengths of this study, as is the objective measurement of BMI by trained professionals. It was also possible to take account of a number of important confounding factors, notably employment grade, alcohol intake, self-rated health, physical activity, and physical functioning. Physical functioning could significantly impact upon sitting time as physical limitation could dictate an individual's choice of leisure time activity. Periods of limited physical functioning due to injury or ill health may somewhat artificially inflate an individual's reported sitting behaviour and if not considered could be a source of confounding. This is the first study to account for a measure of physical functioning when examining prospective associations between sitting time and obesity. The availability of multiple measures of BMI which precede data on sitting time allowed for the examination of reverse causality in the relationship between sitting and obesity and is another significant strength of the study.

The present study is not without limitation. Occupational cohort participants are by definition sufficiently healthy to be in active employment which may reduce the extent to which conclusions may be generalised to a wider population. Although participants who were obese or who had previous

history of cardiovascular disease were excluded from the prospective analysis it was not possible to assess health status during the follow-up period. It is therefore possible that underlying illness during follow-up may have caused weight loss in some participants and this may have contributed to the null findings in the present analyses.

Women are underrepresented in this cohort, comprising approximately a quarter of the analysis groups. Individuals in the lowest employment grade were also underrepresented in this sample comprising only 11% in the cross-sectional analysis group, and only 9% in the prospective analysis group, with the remainder split approximately equally between the higher two employment grades. A recent prospective analysis of data from this cohort demonstrated that over a ten year follow up period, individuals in higher employment grades showed significantly smaller increases in waist circumference and BMI.[320] Therefore it is possible that the underrepresentation of the lower employment grades may have disproportionally reduced the incidence of obesity observed in the current sample.

The reliance on self-report measures may have led to misclassification of sitting which, if non-differential, would attenuate the association between sitting and obesity risk toward the null. A more precise measure of sitting time may have led to stronger associations. As BMI is a more precise measure than sitting in the current study it is possible that a significant association was more likely to be observed when obesity was modelled as an exposure. However, items used to construct the sitting variables in the current study have been used

elsewhere,[191] and validated.[303] In addition, previous Whitehall II publications have shown associations between self-reported health behaviours, including physical activity, and obesity suggesting that questionnaire items on health behaviour have predictive validity.[361]

Previous studies have shown beneficial effects of LPA on obesity risk[191] which are not evident in this cohort and may in part be due to the omission of walking from the computation of LPA. Although analyses were adjusted for walking time how much of it was light or moderate intensity is unknown.

The results of this study and those of others suggest a complex relationship in which the direction of the association between adiposity and sitting time is not entirely certain. Uncertainty also remains as to whether time spent sitting is simply a proxy for low total daily energy expenditure[274] or whether sitting itself represents an independent risk for obesity. Further prospective or experimental research, with more precise measurement of time spent in specific sitting behaviours, is required to better determine if adiposity or weight gain leads to more sitting or vice-versa. Future studies also need a precise measurement of the potential confounding effect of energy balance.

8.5. Conclusions

This is the first study to examine the cross-sectional and prospective associations between five different sitting types with obesity. Time spent sitting

while at work, television viewing, and non-TV leisure time sitting were not associated with incident or prevalent obesity in this occupational cohort. Obesity was associated with the amount of time an individual spent sitting while watching television suggesting that the relationship between sedentary behaviour and obesity may be more complex than has been suggested previously. The possibility of reciprocal or reverse causality in this association requires further research attention.

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Table 8.1. Subject characteristics at baseline (Phase 5 1997-99)

		Whole sample	Sitting Group (Total from work and leisure time)			
			1	2	3	4
n		1971	1 (n= 408)	2 (n=562)	3 (n=496)	4 (n=505)
Age (yrs)		52.00 (4.10)	53.00 (4.70)	52.00 (3.70)	52.00 (3.70)	52.00 (4.00)
Male (%)		72.81	17.77	28.85	26.13	27.25
BMI		26.00 (4.10)	26.00 (4.10)	26.00 (3.80)	26.00 (3.80)	26.00 (4.10)
Waist Circumference (cm)		88.69 (11.63)	88.20 (12.44)	88.19 (11.43)	88.78 (11.34)	89.57 (11.38)
Weight (Kg)		78.00 (14.00)	77.00 (14.00)	77.00 (13.00)	78.00 (13.00)	79.00 (14.00)
Walking (mins/d)		41.39 (20.32)	42.50 (20.96)	42.09 (20.12)	39.82 (20.01)	41.28 (20.28)
MVPA (hrs/wk)		11.83 (9.86)	10.86 (9.88)	12.10 (9.87)	12.42 (10.08)	11.74 (9.59)
Employment Grade (%)	Administrative	44.09	12.66	31.53	28.88	26.93
	Prof/Executive	44.80	23.33	26.95	23.78	25.93
	Clerical/Support	11.11	42.01	22.83	15.98	19.18
Alcohol consumption (units/wk)		14.00 (15.00)	12.00 (14.00)	14.00 (14.00)	15.00 (15.00)	15.00 (16.00)
Smoking Status (%)	Never	54.85	19.98	28.68	25.62	25.72
	Ex	34.70	21.78	29.39	24.42	24.42
	Current	10.45	20.87	24.76	25.24	29.13
Self-rated health (%)	Very Good	48.55	19.33	30.83	26.85	22.99
	Good	40.49	20.93	26.32	24.94	27.82
	Fair or Poor	10.96	25.93	26.39	18.52	29.17

Data are mean(sd) unless otherwise stated.

Table 8.2. Obesity risk according to categories of sitting behaviours from cross-sectional and prospective analyses

Analysis	Sitting Type	N (Cases)	Referent	2		3		4	
			OR	OR	CI	OR	CI	OR	CI
Cross sectional	Work	1954 (252)	1	1.21	0.77, 1.88	1.02	0.68, 1.55	1.03	0.68, 1.55
Phase 5 (97-99)	TV	1359 (183)		1.22	0.70, 2.13	1.35	0.80, 2.28	1.35	0.77, 2.38
	Non TV LT	1200 (143)		1.05	0.63, 1.74	1.52	0.93, 2.49	0.80	0.43, 1.46
	LT	1937 (251)		1.32	0.91, 1.90	0.94	0.65, 1.37	1.27	0.83, 1.95
	Total	1971 (256)		0.79	0.53, 1.18	0.89	0.60, 1.34	0.83	0.56, 1.25
Prospective	Work	1545 (97)	1	0.87	0.43, 1.75	0.85	0.44, 1.62	1.10	0.59, 1.96
Phase 5-7 (97-04)	TV	1071 (66)		0.99	0.43, 2.24	1.04	0.48, 2.25	0.97	0.41, 2.29
	Non TV LT	959 (65)		1.07	0.54, 2.11	0.97	0.48, 1.99	0.88	0.40, 1.95
	LT	1534 (96)		0.94	0.53, 1.67	1.03	0.58, 1.83	1.28	0.67, 2.47
	Total	1559 (98)		0.55	0.30, 1.03	0.79	0.44, 1.43	0.95	0.51, 1.74

Adjusted for age, gender, ethnicity, employment grade, smoking status, weekly alcohol intake, self-rated health, physical functioning, daily walking time, and time spent in moderate to vigorous physical activity. Bold typeface= statistical significance ($P \leq 0.05$

Analysis Groups: Cross-sectional and prospective analyses; Work 1=0-20hrs.wk, 2=21-30hrs.wk, 3= 31-39hrs.wk, 4=≥40hrs.wk; TV 1=0-6hrs.wk, 2=7=11hrs.wk, 3=12-18hrs.wk, 4= ≥19hrs.wk; Non-TV LT 1=0-6hrs.wk, 2=7-11hrs.wk, 3=12-16hrs.wk, 4=≥17hrs.wk. Cross-sectional analysis; LT 1=0-11hrs.wk, 2=12-15hrs.wk, 3=16-25hrs.wk, 4=≥25hrs.wk; Total 1=0-33hrs.wk, 2=34-48hrs.wk, 3=49-56hrs.wk, 4=≥57hrs.wk. Prospective analysis; LT 1=0-9hrs.wk, 2=10-15hrs.wk, 3=16-25hrs.wk, 4=≥26hrs.wk

Table 8.3. Hours per week of sitting at Phase 5 according to occasions of prior obesity

	Sitting type									
Obesity	Work Sitting (n=1858)		TV Viewing (n=1286)		Non-TV Leisure Time Sitting (n=1146)		Leisure Time Sitting (n=1843)		Total Sitting (n=1874)	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
0	0	0	0	0	0	0	0	0	0	0
1	-1.96 (-4.55,0.61)	-2.13 (-4.66, 0.38)	**2.72 (0.36, 5.08)**	**2.43 (0.07, 4.78)**	-1.81 (-4.68,1.06)	-2.07 (-4.98,0.83)	0.39 (-1.98,2.77)	0.06 (-2.32, 2.44)	-1.89 (-5.67,1.87)	-2.45 -6.21,1.31
2	-0.18 (-3.18, 2.81)	0.70 (-2.22, 3.63)	-0.33 (-2.71, 2.64)	-0.62 (-3.29, 2.04)	-0.82 (-4.37, 2.72)	-1.13 (-4.74, 2.47)	-0.92 (-3.72,1.88)	-1.46 (-4.27,1.34)	-0.87 (-5.30, 3.56)	-0.74 -5.16, 3.68
3	0.99 (-4.82, 6.82)	2.57 (-3.11, 8.25)	**8.78 (3.73, 13.84)**	**7.41 (2.36, 12.46)**	-2.76 (-9.35, 3.82)	-2.87 (-9.49,3.76)	**5.91 (0.51,11.31)**	**5.20 (0.19, 10.6)**	7.47 (-1.14,16.08)	8.24 (-0.33,16.82)

Obesity was classified from recalled weight at age 25 (from Phase 1 questionnaire), and BMI at Phase 1, and 3. Coefficients are sitting time (hrs/wk) with 95%CI. Model 1 - adjusted for age and sex only Model 2 – additionally adjusted for employment grade, ethnicity, smoking status, weekly alcohol intake, self-rated health, physical functioning, daily walking time, and time spent in moderate to vigorous physical activity. Bold typeface= statistical significance ($P \leq 0.05$)

Chapter 9

The prevalence of self-reported sitting and accelerometer derived sedentary time in England

9.1. Introduction

As described in chapter 3 there is a body of evidence suggesting that sitting represents an independent risk to health. It is unclear whether the mechanism underpinning these associations relates to sitting behaviour itself or the displacement of physical activity, particularly that of light intensity. Once the exact physiological and temporal aspects of the effect of high volumes of sitting (or low levels of light intensity activity) on disease risk have been established the logical next step would be to design targeted behavioural interventions to reduce this risk. In order to effectively target and deliver such interventions accurate estimates of the prevalence of sitting across different population subgroups is vital. While a number of UK based cohort studies have examined the associations between sitting and health outcomes [55 65 66 68 83 117 216 268], no population based estimates of sitting time from representative samples have been reported for England.[362]

Specific sitting behaviours have different correlates and determinants and have differential associations with health outcomes (chapters 7 and 8). It is therefore necessary to examine the population prevalence of common specific sitting behaviours as well as the total volume of sitting. In light of the limitations and potential for misclassification associated with the measurement of sitting using both objective and self-report measures it is also necessary to separately

examine data from questionnaires and device based measures to assess potential differences in associations and population estimates. The following chapter aims to examine the prevalence of both self-reported leisure time sitting behaviours and accelerometer defined sedentary behaviour and their associations with a range of sociodemographic and health related factors, using data from the 2008 Health Survey for England.

9.2. Methods

The Health Survey for England (HSE) comprises a series of annual surveys of which the 2008 survey is the eighteenth. The HSE is part of a range of surveys currently commissioned by the NHS Information Centre for Health and Social Care (before 2005 commissioned by the Department of Health). Each survey features an interview and a nurse's visit that provide core data on demographic characteristics, health behaviours, anthropometric measurements and analysis of blood and saliva samples with the overall aims to;

1. Provide annual data from nationally representative samples to monitor trends in the nation's health;
2. Estimate the proportion of people in England who have specified health conditions;
3. Estimate the prevalence of certain risk factors associated with these conditions;
4. Examine differences between subgroups of the population (by age, sex or income) in their likelihood of having specified conditions or risk factors;

5. Assess the frequency with which particular combinations of risk factors are found and in which groups these combinations commonly occur;
6. Monitor progress towards selected health targets
7. (Since 1995) measure the height of children at different ages, replacing the National Study of Health and Growth; and
8. (Since 1995) monitor the prevalence of overweight and obesity in children

The primary focus of the 2008 HSE was physical activity and fitness and this included assessment of sitting using both self-report and accelerometry. Self-report information on physical activity and sedentary behaviour was collected in the 2008 survey using the enhanced long version of the HSE physical activity questionnaire.[363] The questions for the HSE were originally derived from the English National Fitness Survey, a major national study of physical activity and fitness which was carried out in 1990.[364] These questions were first used in the 1991 HSE and were repeated until 1994 after which various revisions produced a shorter and longer version of the questionnaire (the short version was last used in 2006). In 2008 the enhanced version of the long questionnaire was used in the main HSE for the first time. Importantly it included questions related to sedentary behaviour due to the emerging evidence regarding the importance of sedentary behaviour as a risk factor for disease. These items included a short set of questions relating to television viewing and other time spent sitting down in leisure time activities during weekdays and on weekends. These questions were validated in 2007.[365]

9.2.2. Participants and sampling

The core sample of the Health Survey for England 2008 was designed to be representative of the population living in private households in England. Like previous HSE surveys, the 2008 survey adopted a multistage stratified probability sampling design. To maximise the precision of the sample, primary sampling units (PSUs) (based on postcode sectors) were ordered by local authority and within each local authority, by the percentage of households in the 2001 Census with a head of household in a non-manual occupation (NS-SEC groups 1-3). Primary sampling units were then selected from this list by sampling at fixed intervals from a random starting point. A total of 1176 PSUs were selected with the probability of selection proportional to the number of addresses within each PSU. Within each selected PSU a random sample of postal address (delivery points) was drawn. For the HSE core sample all adults aged 16 years or over at each household were selected for interview (up to a maximum of 10 adults). A subsample of PSUs were selected to participate in accelerometer data collection. In the selected addresses up to two adults were selected to take part with 4507 adults invited in total. [363]

9.2.3. Outcome measures

9.2.3.1. Self-reported sitting time

In the 2008 HSE participants were asked to report their average TV viewing and other sitting behaviour during leisure time for weekend and weekdays separately, using the following questions;

In the last four weeks, how much time did you spend sitting down watching TV (including DVD's and videos on an average weekday (that is Monday to Friday)? Please do not include time spent doing these activities while at work.

The same question was used for weekend days (that is Saturday and Sunday)

In the last four weeks, how much time did you spend sitting down doing any other activity on an average weekday (that is Monday to Friday)? Please do not include time spent doing these activities while at work.

Again the same question was used for weekend days.

Example activities included reading, eating, studying, drawing, using a computer, and playing video games. For each question participants recorded a value in hours and minutes which was subsequently converted to total minutes of TV viewing or sitting (excluding TV - from this point to be described as non-TV sitting) for the purposes of analyses. Total leisure time sitting (in minutes) was computed as the sum of TV viewing and non-TV sitting.[366] Sitting while at work could not be considered in the analyses as the questionnaire item referring to occupational sitting asks for a combined estimate of time spent sitting and standing at work. As the specific posture of sitting behaviour is an important part of its definition, a combined measure of sitting and standing would not provide an accurate estimate of sitting prevalence.

9.2.3.2. Accelerometer defined sedentary time

A randomly selected subsample of participants were asked to wear a uniaxial accelerometer (Actigraph GT1M) on their hip during all waking hours for seven consecutive days. Participants were also provided with a log book to document their accelerometer wear time including instances when the monitor was removed for bathing, swimming, contact sports, and for periods of cycling or rowing (due to the movement patterns of these activities this type of accelerometer may underestimate their intensity). Data was summarised in one minute epochs and non-wear time was considered as periods of 60 consecutive minutes of zero accelerometer counts with allowance of up to two consecutive minutes of 1-100 counts per minute. Specialist data reduction software (Kinesoft version 3.0.98, New Brunswick, Canada) was used to quantify sedentary time (defined as time spent below 200 counts per minute) for each valid measurement day. In order for a day to be valid for inclusion in the analyses, participants had to have worn the monitor for a minimum of 600 minutes. Sedentary time in minutes was then averaged across valid days.

9.2.4. Explanatory variables

The sociodemographic covariates included in this analysis were age, gender, employment grade and index of multiple deprivation (IMD) score. Age was reported in 10 year age categories from 16 upwards (16-24, 25-34, 35-44, 45-54, 55-64, ≥65yrs). Participant's employment grade was classified into three groups (managerial and professional occupations, intermediate occupations and routine and manual occupations) according to the three level version of the National Statistics Socioeconomic Classification (NS-SEC). Index of multiple

deprivations is a relative measure of overall neighbourhood deprivation based on seven separate dimensions: income, employment, health and disability, education, crime, barriers to housing and services, and living environment. A higher score based on ranking in these seven dimensions indicate a higher level of area deprivation.[367] IMD score in current analyses is divided into quintiles.

Health related covariates included self-reported general health (reported as (very good/ good, fair, or bad/very bad), BMI classification and physical activity level. Participants were classified according to their BMI as underweight (BMI< 18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-30 kg/m^2) obese (30-39.9 kg/m^2) and morbidly obese (≥ 40kg/m^2). In the 2008 HSE physical activity was self-reported using a validated questionnaire.[365] Over 40 items assessed participants occupational, lifestyle and leisure time activities including, walking, housework, gardening and manual work and participation in a wide range of sport and exercise activities. Based on this information the number of days on which a participant achieved 30 minutes of moderate to vigorous physical activity was calculated and their overall activity level was classified as either low (less than day per week), medium (less than four days per week) or high (five or more days per week).[366]

These explanatory variables were chosen as sitting time and accelerometer defined sedentary behaviour have been previously demonstrated to vary across gender and age categories[32 61] and with various indicators of socioeconomic position.[198] Overall physical activity level[362], BMI[200], and general

health status including presence of longstanding illness[67] have also previously been associated with volume of sitting time.

9.2.5. Statistical analyses

Analysis of both self-reported leisure-time sitting and accelerometer defined sedentary time was limited to adults (over the age of 16yrs) who are in full-time employment and provided complete data for all covariates. Limiting the analysis to those in fulltime employment is important as people who are retired, unemployed or who work part time may have more discretionary time and this may bias comparisons of leisure time sitting behaviour. Analysis of self-reported leisure time sitting was additionally limited to those who had complete data on both TV viewing and sitting time. Analysis of accelerometer defined sedentary time was additionally limited to those who provided seven valid days (≥60 minutes of wear time). By using less than seven days the computation of average values for physical activity and sedentary behaviour is complicated. For if inclusion was determined by having only four valid days then the number of weekdays (when participants are more likely to be at work) or weekend days (when more activity will be discretionary) included within those four days will affect the activity recorded within them, and therefore the estimates of average sedentary behaviour.

Within the sample data was weighted to account for varying probabilities of selection and to reduce bias caused by non-response. A comprehensive description of the sample design[363] and information regarding the weighting strategy [366] for the 2008 survey is available elsewhere.

Ordinary least squares regression analysis was used to examine self-reported TV viewing time, mean non-TV leisure time sitting and total leisure time sitting, and accelerometer defined inactivity across gender, age, employment grade and IMD categories. Due to low numbers in the youngest and oldest age groups, age categories were collapsed to the following (16-34, 35-44, 45-54, ≥55yrs). For the same reason the lowest two categories of general health (fair, and bad/very bad) were combined. The youngest age group (16-34 yrs), men, the highest employment grade (managerial and professional) the lowest IMD score (least deprived), the most active group, the normal weight group (BMI 18.5-25.0 kg/m^2) and those whose general health was very good/good served as reference categories for the analyses. In order to examine the possibility of selection bias due to the exclusion of those with missing data or those who did not meet accelerometer wear criteria, age, gender, employment grade IMD score and other covariates were compared between those who were included in the analyses and the wider HSE sample. In order to compare sedentary behaviour estimates between the analysis group and the wider HSE sample, self-reported leisure time sitting time for all participants who provided data (n=15102), and accelerometer defined sedentary time for all participants with at least one valid measurement day (n=2356) were summarised by age and gender.

All analyses were carried out in 2014 using STATA SE version 13 and significance was set at 0.05. Data are presented as mean (± standard error) unless stated otherwise.

9.3. Results

The final sample for the analysis of self-reported sitting consisted of 5255 participants who had complete data for both TV viewing and non-TV leisure time sitting and covariates. Compared to the wider HSE population, inclusion in the analysis of self-reported sitting was associated with being male, slightly older, from a higher employment grade, living in an area with a lower multiple deprivation score, having a higher BMI, poorer general health and a higher activity level (P<0.001 for all).

The final sample for analysis of accelerometer defined sedentary time included 466 people who had seven valid days of accelerometer wear time and complete data for all covariates. Compared to the whole HSE accelerometer sample, the current sample were more likely to be male, slightly older, from a higher employment grade, living in an area with a lower multiple deprivation score, with a higher BMI, slightly worse self-rated general health and a higher activity level (p<0.001 for all). Compared to those included in the accelerometer sample, weekday TV viewing was significantly lower in those who did not meet the inclusion criteria (p=0.05) although the magnitude of the difference was relatively small (< 7 minutes per day). None of the other self-reported sitting indicators differed significantly between those who did and those who did not meet the inclusion criteria for the accelerometer sample. Characteristics of the samples for both self-reported sitting and accelerometer defined sedentary time analyses are described in table 9.1.

Table 9.1. Sample characteristics for analysis of self-reported sitting and accelerometer defined sedentary time.

		Self-Reported Sitting Group	Accelerometer Group
		N=5255	N=466
Age (%)	16-34 yrs	32.06	20.60
	35-44 yrs	27.05	24.89
	45-54 yrs	24.70	27.04
	≥55 yrs	16.19	27.47
Gender (%)	Male	61.85	64.16
	Female	38.15	35.84
Employment Grade (%)	Managerial and Professional	47.07	47.42
	Intermediate	22.38	22.96
	Routine and Manual	30.55	29.61
IMD Group (%)	1 - Least Deprived	23.49	28.97
	2	20.93	24.68
	3	20.82	19.10
	4	19.49	16.31
	5 - Most Deprived	15.28	10.94
BMI (%)	<18.5 kg/m^2	0.86	1.29
	18.5-24.9 kg/m^2	33.94	28.97
	25-29.9 kg/m^2	40.04	45.71
	30-39.9 kg/m^2	23.68	22.75
	≥40 kg/m^2	1.49	1.29
General Health (%)	Very Good/Good	86.51	85.19
	Fair/Bad/Very Bad	13.49	14.81
Physical activity level (%)	Low	21.94	20.82
	Medium	31.01	35.84
	High	47.05	43.35

Self-reported leisure time sitting time for all participants who provided data (n=15102), and accelerometer defined sedentary time for all participants with at least one valid measurement day (n=2356) are summarised in tables 9.2, 9.3 and 9.4. Mean self-reported TV viewing time in current sample was

135.08 mins (±1.75) on weekdays and 168.62 (±2.18) mins on weekend days which is lower than the values reported in the wider HSE sample of 171.62 mins (± 0.95) and 185.70 (± 0.99) respectively. Similarly, mean values for self-reported daily non-TV leisure time sitting and total leisure sitting were lower than those reported in the wider sample (non-TV sitting: 99.68 [±1.55] mins for weekdays and 124.76 [±3.93] mins for weekend days compared to 132.79 [± 0.89] and 142.31 [± 0.91] minutes respectively for the wider sample; Total sitting: 234.76 [±2.35] mins for weekdays and 293.38 [±2.99] mins for weekend days compared to 304.58 [± 1.32] and 328.25 [± 1.36] respectively for the wider sample). Mean daily accelerometer defined sedentary time was slightly higher in the current sample compared with the wider HSE accelerometer group (593. 23 [±7.19] compared to 578.14 [±1.94] mins).

9.3.2. Gender differences

Mean (and standard error) values for self-reported weekday TV viewing, non-TV sitting and total sitting are described in table 9.5. Women reported watching significantly less TV and sitting less in total than men during weekdays in model 1 (P=0.001 and P=0.002 respectively) and these differences persisted in the fully adjusted model (P=0.005 and P=0.002). There were no significant gender differences in weekday non-TV sitting in either model 1 or model 2.

On weekend days women again reported watching significantly less TV than men and also reported less total sitting time in model 1 (P<0.001 for both) and model 2 (P=0.0002 and P=0.0001 respectively). Non TV sitting time was slightly lower in women than in men on weekend days although this was not

significant in the age adjusted analysis. However this difference did become significant following adjustment for all covariates in model 2 (P=0.05). Mean (SE) values for domain specific weekend sitting is described in table 9.6.

In the accelerometer sample mean sedentary minutes per day did not differ significantly between men and women in either model 1 (P=0.11) or model 2 (P=0.67). Mean (SE) values for accelerometer defined sedentary time are described in table 9.7.

9.3.3. Age group differences

TV viewing, non-TV sitting and total sitting on weekdays across age groups is described in table 9.8. In comparison with the reference category, weekday television viewing increased significantly with increasing age following adjustment for gender (P_{trend}<0.001), and also in the fully adjusted model (P_{trend}=0.035). Conversely the youngest age group reported more non-TV sitting on weekdays than the older age groups. This difference was significant in model 1 (P_{trend} =0.03) but was attenuated following adjustment for covariates. Total weekday sitting was significantly higher in the oldest group compared to the youngest in both model 1 (P_{trend}=0.001) and the fully adjusted model (P_{trend}=0.004).

On weekend days TV viewing time did not differ significantly across age categories in model 1 (P_{trend}=0.58) or model 2 (P_{trend}=0.16). However the youngest age group reported more minutes of non-TV sitting than any of the

other age groups following adjustment for gender (P_{trend}<0.001) and this persisted following adjustment for other covariates (P_{trend}<0.001) . Similarly total sitting was highest in the youngest age group (p_{trend}=0.004) and this persisted in the fully adjusted model (p_{trend}<0.001). Mean (SE) values for domain specific weekend sitting is described in table 9.9.

In the accelerometer sample mean sedentary minutes per day did not differ significantly across age groups in either model 1 (p_{trend} =0.57) or model 2 (p_{trend} =0.39). Mean (SE) values for accelerometer defined sedentary time are described in table 9.10.

9.3.4. Socioeconomic differences: Employment grade and area deprivation

Associations between weekday TV viewing, non-TV sitting and total sitting and employment grade are described in table 9.11 and associations with IMD score are described in table 9.14. There was a significant inverse association between weekday TV viewing and employment grade after initial adjustment for age and gender (P_{trend}<0.001) and in the fully adjusted model (P_{trend}<0.001). There was also a significant increase in weekday TV viewing across quintiles of increasing multiple deprivation score in model 1 (P_{trend}<0.001) which persisted following adjustment for covariates (P_{trend}=0.03).

Conversely, there was a significant positive association between weekday non-TV sitting and employment grade in both model 1 (P_{trend}<0.001)

and model 2 (P_{trend}=0.002). However, there was no significant association between non-TV sitting and IMD score. Total weekday sitting did not differ significantly across employment grades and although there was a significant increase in total sitting across quintiles of increasing area deprivation score in model 1 (P_{trend}=0.004), this association was attenuated to null in the fully adjusted model (P_{trend}=0.10).

Associations between weekday TV viewing, non-TV sitting and total sitting and employment grade are described in table 9.12 and associations with IMD score are described in table 9.15. Weekend day TV viewing was inversely associated with employment grade in both model 1 and model 2 (P_{trend}<0.001 for both) and positively associated with area deprivation in model 1 only (P_{trend} =0.03). As on weekdays, weekend day non-TV sitting was positively associated with employment grade in both model 1 and model 2 (P_{trend}<0.001 for both) and there was no association with area deprivation score. There were also no significant associations between total weekend day sitting time and either employment grade or area deprivation score.

In the accelerometer sample there was a significant inverse association between accelerometer defined sedentary time and employment grade in both model 1 and model 2 (P_{trend}<0.001 for both) with those in the lowest employment grade recording on average over 90 minutes less sedentary time per day than those in managerial and professional occupations. Accelerometer defined sedentary time was not significantly associated with IMD score. Associations between accelerometer defined sedentary time and employment

grade are described in table 9.13 and associations with IMD score are described in table 9.16.

9.3.5. Health related differences: BMI, general health and activity level

Associations between weekday self-reported sitting indicators with BMI, general health and activity level are described in tables 9.17, 9.20, and 9.23 respectively. Body mass index was positively associated with both weekday TV viewing and total weekday sitting in both models 1 and 2 (P_{trend} <0.001 for all) although there were no evident associations with weekday non-TV sitting. General health status was positively associated with both weekday TV viewing and total weekday sitting in model 1 and in model 2 (P_{trend}<0.001 for all). Weekday non-TV sitting was not associated with general health status. Activity level was inversely associated with weekday TV viewing (P_{trend}<0.001 for models 1 and 2), weekday non-TV sitting (P_{trend}=0.002 for model 1 and 0.006 for model 2), and total weekday sitting (P_{trend}<0.001 for models 1 and 2).

Associations between weekend day self-reported sitting indicators with BMI, general health and activity level are described in tables 9.18, 9.21, and 9.24 respectively. Body mass index was also positively associated with both weekend day TV viewing and total weekend day sitting in both models 1 and 2 (P_{trend} <0.001 for all) although again there were no evident associations with weekday non-TV sitting. General health status was positively associated with weekend TV (P_{trend}<0.001 in model 1 and 0.002 for model 2) and total weekend day sitting (P_{trend}<0.001 in model 1 and 0.013 for model 2). Activity level was inversely associated with weekend day TV viewing (P_{trend}<0.001 for model 1

and 0.002 for model 2), weekday non-TV sitting (P_{trend}<0.001 for model 1 and 0.002 for model 2), and total weekday sitting (P_{trend}<0.001 for models 1 and 2).

Associations between accelerometer defined sedentary time and BMI, general health and activity level are described in tables 9.19, 9.22, 9.25 respectively. Activity level was inversely associated with accelerometer defined total sedentary time in both model 1 (P_{trend} <0.001) and in model 2 (P_{trend} =0.002). Body mass index and general health status were not significantly associated with accelerometer defined sedentary time.

9.4. Discussion

The aim of this study was, for the first time, to examine the prevalence of specific self-reported leisure time sitting behaviours and average accelerometer defined sedentary time across age, gender and categories of selected socioeconomic and health related variables in an English population sample.

Mean daily TV viewing time in the current sample was 135.08 mins (±1.75) on weekdays and 168.62 (±2.18) mins on weekend days. These figures are slightly higher than those in previous analysis from the Whitehall II cohort (121.2 ± 2.02) (8.3.2) but lower than those reported in previous UK cohorts: EPIC-Norfolk (188.4 ± 0.78 mins),[55] and the Scottish Health Survey (203.21 ± 1.45 minutes).[198] This may reflect differences in TV viewing time between the various regions of the UK examined in these studies and the English population. It must also be acknowledged that the measure used in the Scottish Health

Survey was of screen time, including both TV viewing and computer use which may also in part explain the higher values observed compared to the current analysis which focussed on TV viewing alone. The English prevalence of leisure time sitting excluding TV viewing has not been examined previously although the values of 99.68 (±1.55) mins for weekdays and 124.76 (±3.93) minutes for weekends are only slightly lower than the mean value observed in the previous analysis of data from the Whitehall II data (129.60 ±2.53 minutes) (8.3.2).

Mean accelerometer defined sedentary time in the current analysis (593.23 ± 7.19 minutes) is higher than that recorded in population studies from both the US (478.90 ± 2.6 minutes, NHANES 2005-06)[368] and Australia (504 ± 7.41 minutes, AusDiab 2004-05).[369] These studies included participants who wore an accelerometer for at least ten hours on at least one [368] and five [369] days out of 7. As the current analysis included only those with at least ten hours on seven days of the week it is possible that these differences might be due to the daily averages in these studies being computed from a greater proportion of weekend days (rather than two out of seven in the present analysis). If people sit less at the weekends for example, the fewer working days that are included in the averages the less sedentary time will be measured and the lower the average value will be. These differences not only limit comparability between studies, but also undermine comparisons of average sedentary time between individuals and groups. In order to accurately determine the differences in sedentary time between groups it is important to either consider different segments of the day (i.e. occupational, and leisure time) separately, or ensure

that the proportions of measured work and leisure time are the same for all participants.

Although the estimates reported in this chapter show small differences between the sample selected and the wider HSE sample they still suggest that on average that adults in England report spending approximately five hours per day sitting during the weekend and nearly four hours sitting on a weekday during non-work time. It is also likely that, given the previously discussed difficulties with accurately reporting common everyday behaviours such as sitting, this may be an underestimate of the true prevalence of sitting. It must also be considered that these estimates do not include occupational sitting and that an increasing proportion of the population in developed countries such as the UK are engaged in largely inactive occupations.[320] This is reflected in the accelerometer defined sedentary time values (that capture all sedentary behaviour) which suggest that on average participants were sedentary for almost 10 hrs of the day. If, as postulated within the current literature, sitting time represents an independent risk to health the present analyses highlight the potential scale of the problem within the English population.

9.4.2. Associations with gender

Women reported sitting less during leisure time than men on both weekdays and weekend days. As there were no differences in non-TV leisure time sitting on either weekdays or weekend days this can be largely attributed to differences in TV viewing time. This finding is consistent with previous UK time-use surveys[314] and population based epidemiological studies from the UK,[198]

the US[368] and Australia.[370] The magnitude of the gender differences in daily TV viewing (between 10 and 15 minutes) is also comparable with data from Australia[370] and the UK (Pulsford et al 2013 – unpublished data). While all participants in the current study were in full-time employment it is conceivable that the relatively small difference in TV viewing time might reflect women undertaking a greater proportion of domestic household tasks than men outside of working hours. Conversely there were no observable gender differences in accelerometer defined sedentary time in the current analysis, which is in contrast to previous findings.[32 61] These studies both required participants to wear accelerometers for a minimum of 10 hrs per day although they were only required to have one[32] or four[61] valid measurement days in order to be included in the analyses. Both these studies observed higher levels of daily sedentary time in women although it is possible that differences in accelerometer wear patterns between genders i.e. weekdays versus weekend days, may have contributed to these findings. The difference in findings between self-reported sitting and accelerometer defined sedentary time will be discussed later in the chapter.

9.4.3. Associations with age

In the current study, the youngest age group watched less TV and reported sitting less overall during leisure time than the older age groups although the absolute differences were very small (<8 minutes in fully adjusted analyses). This is in contrast with a previous population study from Australia which observed differences of close to 60 minutes per day between participants aged 25-44 and those aged over 65.[370] However the study in question included

people who were unemployed, retired and in part time work which may have allowed for higher volumes of weekday TV viewing. As employment status is a strong correlate of TV viewing time[201 370] and given that the probability of being retired or semi-retired would be greater after the age of 65, this may explain the larger age related increases in TV viewing compared to the current study. At weekends the youngest age group reported sitting a lot more than the older age groups. It is likely that as there was no reported difference in weekend day TV viewing across age categories, that the difference in total leisure time sitting simply reflects differences in non-TV leisure time sitting activities such as computer use which have been demonstrated to be inversely associated with age.[61]

Accelerometer defined sedentary time was not associated with age which is inconsistent with previous findings.[32 61] In an analysis of data from NHANES from 2003-04 Matthews et al [32] observed a significant reduction in accelerometer defined sedentary time between the youngest age group (20-29 yrs) and the next group (30-39 yrs) after which sedentary time increased with increasing age. This trend remained when the findings were extended by Healy et al[61] who combined data from the 2003-04 and 2005-06 surveys. However as discussed, it is possible that due to the inclusion of participants with only one valid day of accelerometer wear, differences in accelerometer wear patterns, rather than actual volume of sitting may have contributed to these findings. For example if participants in the younger age groups were more likely to wear their accelerometer at the weekend, when their time was more discretionary and they

could potentially be more active, then this could explain the lower sedentary time values recorded in these groups.

9.4.4. Associations with socioeconomic position

The observed inverse relationship between both weekday and weekend day TV viewing with employment grade, and the positive association with area deprivation score is consistent with previous findings.[69 179 198 230] Stamatakis and co-workers[198] observed similar associations between a combined measure of TV viewing and screen time with social class, as defined by occupational classification, and quintiles of area deprivation score, along with two other indicators of socioeconomic position. It is possible that people engaged in more manual occupations compensate by sitting more outside of work. However a number of studies have found no evidence of such compensatory behaviour. Mummery et al found no difference in leisure time activity across levels of occupational sitting.[69] In addition if compensatory sitting is a factor then according to the current findings it extends only to TV viewing, as non-TV leisure time sitting was positively associated with employment grade. It is also possible that people from lower employment grades watch more television as they have less expendable income to engage in active leisure activities.[198] Conversely participants from higher employment grades may place greater value on sitting behaviours such as reading or have more disposable income for computers. The increase in weekday TV viewing with increasing area deprivation suggests that neighbourhood and environmental factors such as access to active leisure facilities or perceptions of safety may also influence choice of leisure activity. Physical activity facilities are fewer in less affluent

neighbourhoods which may reduce opportunities for active leisure activities[371] [372] in favour of sedentary activities such a TV viewing. Concerns about personal safety in the neighbourhood environment are greater in lower SEP groups and are also associated with lower levels of physical activity.[198] [373]

The positive association between accelerometer defined sedentary time and employment grade would logically reflect the differences in occupational sitting between routine/manual professions and managerial professions. This is because the accelerometer wear period is likely to include a greater proportion of time at work compared to leisure time.

The differential associations observed between sitting and sedentary time with employment grade and area deprivation score illustrate the multifaceted nature of socioeconomic position. It is therefore important to consider precisely how different aspects of socioeconomic position, which may variously reflect differences in the home and neighbourhood environment or the access and affordability of active leisure time activities, can influence sitting behaviour. The different associations with TV viewing and non-TV leisure time sitting on weekdays and weekend days again highlights the importance of examining discrete sitting behaviours separately in the contexts in which they occur. A measure of total sedentary time, however precise, may mask these important differential associations.[68]

9.4.5. Associations with health indicators

The observed positive association between both weekday and weekend day TV viewing time and total leisure time sitting with BMI is consistent with a number of cross sectional studies which have observed associations between BMI,[198 223 241] waist circumference[223 241] body composition,[223] and obesity[193] and self-reported sitting. Cross-sectional analyses do not provide insight into the direction of the association and evidence from prospective studies is equivocal.[68 69 83 250] As discussed previously it is plausible that obesity could be both a cause and a consequence of high volumes of sitting. While low energy expenditure during sitting might contribute to a positive energy balance and subsequently to weight gain, people who are overweight and obese may choose sedentary activities such as TV viewing over more active leisure activities.

Although a similar pattern was evident in the accelerometer data it was not statistically significant. As participants were instructed to wear the accelerometer during all waking hours, accelerometer defined sedentary time would include occupational activity while the self-report measures focus exclusively on leisure time activity. Accelerometer defined sedentary time would therefore contain large parts of the day during which behaviour is less discretionary (during working hours) and this would perhaps reduce the variance in the sample. It is possible that the homogeneity in overall accelerometer defined sedentary time within the sample and the reduced power due to the small sample, may have reduced the ability to detect differences in recorded volitional sedentary time across BMI classification groups.

The inverse association between self-reported general health status and TV viewing and total leisure time sitting is logical as people who perceive their health to be less than optimal would be more likely to choose less active leisure time activities. This is consistent with a number of previous studies which have reported cross-sectional associations between self-reported sitting and both general health status and specific disease outcomes.[29 172 181]

Self-reported physical activity was inversely associated with accelerometer defined sedentary time. Evidence as to the association between sitting time and physical activity is mixed and may reflect the physical activity measure used. A number of studies have focussed on moderate to vigorous physical activity (MVPA), or adherence to public health guidelines relating to MVPA and findings are equivocal.[198 368 370] Stamatakis et al[198] reported that within the Scottish Health Survey screen time was inversely associated with likelihood of meeting current government guidelines of 150 minutes per week of MVPA, although no such association was observed in the Ausdiab cohort where daily TV viewing did not differ in those who did and did not adhere to public health recommendations regarding physical activity.[370] While it is possible that high volumes of sitting time might displace some MVPA, the proportion of the day engaged in activity of this intensity is relatively small compared to light intensity activity. Therefore you would not necessarily expect differences in MVPA to be reflected in differences in sitting time.

In the current analysis physical activity was examined using a summary measure that incorporates MVPA including sports and volitional exercise

participation, but also occupational and lifestyle physical activities which are important contributors to total physical activity. It is therefore logical that the observed inverse association would be due to sitting behaviours displacing some of these physical activity behaviours. When associations between sitting and total physical activity or physical activity energy expenditure have been considered similar inverse associations to those observed in the present analysis have been reported. Parsons et al observed a significant linear decrease in total physical activity energy expenditure across increasing categories of increasing TV viewing.[374]

When sedentary time and physical activity are assessed by accelerometer only as duration in different intensity categories it is not possible to examine the association between sedentary time and all physical activity (including light moderate and vigorous intensity activity). The sum of the durations spent in these activity categories will account for 100% of accelerometer wear time so an increase in sedentary time would logically cause a reduction in time spent at other intensity categories. Due to this issue of collinearity, light intensity physical activity is often excluded from these analyses (as it is often almost the perfect inverse of sedentary time)[54] and adjustment is only made for MVPA. The true association between physical activity and sedentary behaviour may therefore be masked.[375] However the use of a comprehensive self-report measure of physical activity in the current analysis, allowed the examination of the association between accelerometer determined sedentary time and overall physical activity level.

9.4.6. Strengths and limitations

A major strength of this study is the use of data from the HSE which provides a large, randomly selected, nationally representative and geographically heterogeneous sample with which to examine habitual sitting behaviour in England.[363] The richness of the HSE data also allowed the examination of associations between sitting and a range of relevant sociodemographic and health related covariates. Another strength of this study is the examination of three separate self-report measures of leisure time sitting as well as an objective measure of overall sedentary time. The differential associations observed between the various sociodemographic and health covariates and the three self-reported sitting indicators again highlights the importance of examining different sitting activities separately.

This study is not without limitation. The analyses are cross-sectional and as such it is impossible to establish a causal relationship between sociodemographic and health related variables and the four sitting indicators. In the current analyses it was also not possible to examine self-reported occupational sitting, which is an important contributor to total daily sitting time. In the 2008 HSE the questionnaire item relating to occupational sitting asked participants to quantify the amount of time they spent sitting or standing at work. As the distinction between sitting and standing is an important feature of the definition of sedentary behaviour (i.e. behaviours involving sitting or reclining) this measure could not be included in the current analyses. As the questionnaire items relating to leisure time sitting focussed on sitting only, data

on occupational sitting and standing could not be effectively combined with leisure time sitting as a measure of total daily sitting.

As discussed previously the use of both self-report measures of sitting and accelerometers to define sedentary time are not without limitation. Ubiquitous day to day activities such as sitting are difficult to accurately recall and quantify.[93] The use of self-report measures can therefore lead to misclassification of sitting which if non-differential could attenuate the associations with exposures towards the null.[92] Television viewing might also be easier to report accurately than non-TV sitting which may occur sporadically and for shorter periods. The difference in the precision of these measures may partially explain why in the current study TV viewing was more commonly associated with sociodemographic and health related exposures than non-TV sitting. Conversely if misclassification was systematic it may have influenced the findings of the present analysis. For example if participants who reported their general health as being good or very good were more likely to under-report their daily sitting behaviour this could artificially inflate the difference in sitting observed across general health categories. Nevertheless self-report measures are vital in allowing the examination of specific sitting behaviours, in the contexts in which they occur. Although accelerometers provide objective assessment of sedentary time and as such are not affected by problems of reporting error or bias, they cannot accurately distinguish between postures, and the assumption that time spent below an arbitrary threshold value in movement acceleration represents sitting time can also lead to misclassification. It has been demonstrated previously that some standing activities return accelerometer count values below the 200cpm threshold

applied to the current data.[115] It is also possible that some sitting behaviour might cause sufficient movement acceleration to be classified as light intensity activity.[42] As discussed previously, a combination of both device based and self-report measures of sedentary behaviour, the use of inclinometer based devices which can distinguish between sitting and standing, or the use of pattern recognition approaches to accurately and objectively identify specific behaviours could resolve these limitations in future population based cohort studies.

Comparison of associations between accelerometer defined sedentary time and self-reported sitting are also problematic as the accelerometer data was collected over seven consecutive days while the self-report measures ask participants to describe typical sitting behaviours over the previous four weeks. While the differential associations observed in the current analysis between self-reported sitting time and accelerometer defined sedentary time may have been attributable in part to differences in what is being measured (leisure time sitting versus total sedentary time in both work and leisure time) they may also reflect differences between typical behaviour and actual measured behaviour during different measurement periods.

In light of the differences between the study sample and total HSE sample the possibility of selection bias must also be acknowledged. For example, inclusion in the study was associated with being from a higher employment grade and living in a less deprived area. As both of these characteristics are associated with lower levels of sitting, general estimates of

sitting behaviour taken from the current study sample would likely be lower than the true population value.

Self-reported weekday and weekend day sitting were lower in the study sample than in the total HSE sample, although the difference in weekend day sitting was far less pronounced. In addition, accelerometer defined sedentary time was slightly higher than in the whole HSE accelerometer subsample. Limiting the analysis of both the self-report sitting data and accelerometer data to those who are in fulltime employment, and further limiting the accelerometer data analysis to those who provided seven valid measurement days would certainly lead to a more homogenous study sample which may have limited the ability to detect important differences in sitting time between different population subgroups. Table 9.25 below compares the mean (SD) values for accelerometer defined sedentary time and self-reported siting for weekdays and weekend days between those included in the current accelerometer sample (who have seven days of valid wear time) and those who have up to three valid days of accelerometer wear. A variance ratio test was carried out to examine the difference in the magnitude of the variance between groups.

Table 9.26. Mean (SD) self-reported sitting and accelerometer defined sedentary time in those with seven days (at over 10 hrs) of valid accelerometer wear and those with up to three valid days.

	≤ 3 valid days		7 valid days		p
n	117		466		
Accelerometer defined sedentary time	523.37	(119.44)	594.10	(93.19)	**0.01**
SR - Weekday					
TV viewing	146.07	(78.86)	142.82	(78.39)	0.91
Non-TV leisure sitting	102.64	(77.95)	99.27	(72.27)	0.28
Total sitting	248.72	(113.58)	241.83	(105.56)	0.30
SR- Weekend day					
TV viewing	161.66	(89.68)	175.73	(92.20)	0.73
Non-TV leisure sitting	125.09	(87.73)	124.44	(86.94)	0.88
Total sitting	286.75	(121.12)	299.59	(133.40)	0.21

Size of the variance in each group for each measure compared using variance ratio test. Bold typeface indicates statistically significant difference between groups ($p<0.05$)

In the self-report data the size of the variance did not differ significantly between those with seven and those with up to three valid days of accelerometer wear. However the mean accelerometer defined sedentary time is less, and the variance is significantly greater in those with up to three valid days. It is possible that the reduced variance in the accelerometer data in the study sample contributed to some of the null findings in the current analyses and may explain why associations that are present in in the self-report data are not present in the accelerometer data.

However it must also be considered that associations observed in the self-report data may be due to differential levels of social desirability bias and reporting bias across categories of the various explanatory variables. For example it is possible that the observed positive association between self-reported TV viewing and area deprivation is due to people from less deprived areas under reporting their TV viewing more than those in more deprived areas. This association could therefore simply reflect differences in reporting due to greater or lesser negative connotations placed on TV viewing at different levels of the social strata, rather than any actual difference in behaviour. These associations would be lost when sedentary behaviour is measured objectively.

While a more homogenous sample may in part explain some of the null findings in the current study, the inclusion of only people in full time employment is an important feature of these analyses as it prevented comparisons of leisure time sitting being made between people with vastly different amounts of leisure time (i.e. time away from work). For example, women, and those in the oldest age category are less likely to be in fulltime employment and therefore would have more leisure time. Estimates of daily non-occupational sitting for these groups may therefore be inflated and associations with other sociodemographic or health related factors biased by these differences in employment status. Similarly, while inclusion in the accelerometer sample of people who are not in full time employment or those with fewer than seven valid days of accelerometer wear would have allowed for a larger sample size, it also allows for variation between participants in the number of working and non-working days included in the computation of their average sedentary time values

(minutes per valid day of measurement). Those people with relatively sedentary occupations who only wore the accelerometer on working days would have more measured sedentary time (and therefore more sedentary time per valid measurement day) than people with the same occupations who wore the monitor only at weekends. As discussed previously the use of waterproof, wrist worn accelerometers which needn't be taken off at any point during a seven day measurement period could allow for 24 hour measurement which would eliminate the problematic effects of differences in wear time for future population based measurement of physical activity and sedentary behaviour.

9.5. Conclusions

In conclusion, the current study aimed to examine both self-reported leisure time sitting and accelerometer defined sedentary time within a representative sample of the UK population according to a number of sociodemographic and health related variables. Findings suggest that overall, adults in the UK spend around 10 hrs per day on average engaged in sedentary behaviours including around two and a quarter hours on weekdays and 3 hrs at weekends watching television although these values vary between population subgroups. Associations with sociodemographic and health related factors also differed between leisure time sitting behaviours which demonstrates the need to examine these behaviours separately. Had the current analysis relied on either self-reported total sitting or accelerometer defined sedentary time these important differential associations would have been missed. While the current findings cannot address the causes of these associations they do provide original descriptive data on variations in volumes of sitting and sedentary behaviour between population subgroups in the UK. As described previously, it

is unclear whether high volumes of sitting have been associated with adverse health consequences as a result of a specific mechanism attributable to sitting itself or whether it is due to the displacement of light intensity physical activity. In either event there is a case for increasing total physical activity (and in doing so displacing sitting) as part of a strategy to improve population wide health. These findings have the potential to inform such initiatives by identifying population groups in which high volumes of sitting are most prevalent.

Table 9.2. Self-reported TV viewing, non-TV leisure time sitting and total leisure time sitting (minutes per day)on weekdays for all HSE participants by age and gender. Data are mean (standard error)

	Weekday TV Sitting (mins/day)			Weekday Non-TV Sitting			Total Weekday Sitting		
	Men	**Women**	**Total**	**Men**	**Women**	**Total**	**Men**	**Women**	**Total**
16-34 yrs	146.67 (2.55) N= 1729	150.55 (2.24) N=2140	148.81 (1.68) N=3869	145.36 (2.95) N= 1729	133.48 (2.38) N=2140	138.79 (1.86) N=3869	292.05 (3.90) N= 1729	283.91 (3.39) N=2140	287.55 (2.56) N=3869
35-44 yrs	149.02 (3.17) N=1222	136.46 (2.45) N=1514	142.07 (1.97) N=2736	104.69 (2.47) N=1222	105.49 (2.23) N=1514	105.49 (1.65) N=2736	253.49 (4.13) N=1222	241.75 (3.40) N=1514	246.99 (2.64) N=2736
45-55 yrs	158.33 (3.39) N=1101	151.01 (2.76) N=1374	154.26 (2.15) N=2475	106.71 (2.65) N=1101	109.86 (2.41) N=1374	108.46 (1.78) N=2475	265.06 (4.44) N=1101	260.47 (3.79) N=1374	262.51 (2.89) N=2475
55+	206.16 (2.44) N=2708	207.39 (2.10) N=3314	206.83 (1.59) N=6022	85.25 (2.26) N=2708	90.54 (2.01) N=3314	150.66 (2.07) N=6022	353.91 (3.18) N=2708	359.52 (2.87) N=3314	356.99 (2.13) N=6022
Overall	172.82 (1.46) N=6760	170.65 (1.24) N=8342	171.62 (0.95) N=15102	132.86 (1.35) N=6760	132.13 (1.18) N=8342	132.45 (0.89) N=15102	305.46 (1.99) N=6760	302.44 (1.76) N=8342	303.79 (1.32) N=15102

Table 9.3. Self-reported TV viewing, non-TV leisure time sitting and total leisure time sitting (minutes per day)on weekend days for all HSE participants by age and gender. Data are mean (standard error)

	Weekend day TV Sitting (mins/day)			Weekend day Non-TV Sitting			Total Weekend day Sitting		
	Men	**Women**	**Total**	**Men**	**Women**	**Total**	**Men**	**Women**	**Total**
16-34 yrs	172.81 (2.95) N=1729	165.40 (2.43) N=2140	168.71 (1.88) N=3869	159.91 (3.03) N=1729	139.39 (2.44) N=2140	148.56 (1.92) N=3869	332.41 (4.24) N=1729	304.64 (3.53) N=2140	317.05 (2.72) N=3869
35-44 yrs	181.97 (3.50) N=1222	159.07 (2.64) N=1514	169.30 (2.15) N=2736	123.27 (2.76) N=1222	114.07 (2.26) N=1514	118.18 (1.72) N=2736	304.93 (4.53) N=1222	272.75 (3.57) N=1514	287.12 (2.84) N=2736
45-55 yrs	186.82 (3.78) N=1101	165.22 (2.83) N=1374	174.38 (2.31) N=2475	123.15 (2.93) N=1101	126.98 (2.62) N=1374	125.24 (1.95) N=2475	308.83 (4.79) N=1101	291.75 (3.89) N=1374	299.38 (3.04) N=2475
55+	213.01 (2.51) N=2708	205.19 (2.13) N=3314	208.71 (1.63) N=6022	152.70 (2.28) N=2708	156.94 (2.05) N=3314	155.04 (1.52) N=6022	365.13 (3.30) N=2708	361.65 (3.02) N=3314	363.21 (2.23) N=6022
Overall	193.25 (1.54) N=6760	180.46 (1.26) N=8342	186.19 (0.98) N=15102	144.99 (1.39) N=6760	140.18 (1.20) N=8342	142.34 (0.91) N=15102	338.08 (2.06) N=6760	320.45 (1.79) N=8342	328.34 (1.35) N=15102

Table 9.4. Accelerometer defined sedentary time (average minutes per valid measurement day at <200 counts per minute) for all HSE participants with ≥ 1 day of valid measurement day (≥ 600 minutes of wear) by age and gender. Data are mean (standard error)

	Accelerometer Defined Sedentary Time (time spent below 200 cpm, in mins per day)		
	Men	**Women**	**Total**
16-34 yrs (213 Male & 281 Female)	562.94 (7.18) n=213	546.03 (5.31) n=281	553.32 (4.34) n=494
35-44 yrs (164 male & 197 female)	575.61 (8.27) n=164	531.20 (6.58) n=197	551.37 (5.32) n=361
45-55 yrs (186 male & 217 female)	571.25 (7.46) n=186	559.99 (5.59) n=217	565.19 (4.58) n=403
55+ (501 male & 597 female)	614.52 (4.07) n=501	593.10 (3.23) n=597	602.87 (2.57) n= 1098
Overall	590.59 (3.09) n=1064	567.76 (2.43) n=1292	578.07 (1.94) n=2356

Table 9.5. Regression analyses for self-reported TV viewing, non-TV leisure time sitting and total leisure time sitting on weekdays with gender

	Sex	N	Weekday TV (mins)		Weekday non-TV sitting (mins)		Total weekday sitting (mins)	
Model			**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**
	Male	3251	139.44	1.55	100.33	1.34	239.76	2.09
	Female	2004	130.72	1.91	99.03	1.75	229.76	2.60
			Coefficient	**95% CI**	**Coefficient**	**95% CI**	**Coefficient**	**95% CI**
1	**Male**	3251	**0**		0	0	**0**	
	Female	2004	**-8.34**	**-13.12, -3.55**	-1.81	-6.15, 2.53	**-10.15**	**-16.67, -3.62**
	P_{trend}		**0.001**		0.414		**0.002**	
2	**Male**	3251	**0**		0	0	**0**	
	Female	2004	**-7.01**	**-11.92, -2.09**	-3.43	-7.93, 1.04	**-10.45**	**-17.15, -3.75**
	P_{trend}		**0.005**		0.13		**0.002**	

Bold typeface indicates significance (p<0.05). Analyses are limited to those in fulltime employment and with complete data for self-reported sitting and all covariates. Model 1 adjusted for age only, Model two adjusted for age, IMD, employment grade, BMI, habitual physical activity level and general health

Table 9.6. Regression analyses for self-reported TV viewing, non-TV leisure time sitting and total leisure time sitting on weekend days with gender

	Sex	N	Weekend day TV (mins)		Weekend day non-TV sitting (mins)		Total weekend day sitting (mins)	
Model			**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**
	Male	3251	175.43	2.00	125.44	1.73	300.87	2.72
	Female	2004	161.81	2.35	124.08	2.20	285.89	3.25
			Coefficient	**95% CI**	**Coefficient**	**95% CI**	**Coefficient**	**95% CI**
1	**Male**	3251	**0**		0		**0**	
	Female	2004	**-13.36**	**-19.41, -7.31**	-2.55	-8.04, 2.94	**-15.92**	**-24.24, -7.60**
	P_{trend}		**0.0001**		0.362		**0.0001**	
2	**Male**	3251	**0**		**0**		**0**	
	Female	2004	**-11.48**	**-17.55, -5.40**	**-5.58**	**-11.22, 0.05**	**-17.06**	**-25.50, -8.63**
	P_{trend}		**0.0002**		**0.05**		**0.0001**	

Bold typeface indicates significance (p<0.05). Analyses are limited to those in fulltime employment and with complete data for self-reported sitting and all covariates. Model 1 adjusted for age only, Model two adjusted for age, IMD, employment grade, BMI, habitual physical activity level and general health

Table 9.7. Regression analyses for accelerometer defined sedentary time (average minutes per valid measurement day at <200 counts per minute) with gender

Model	Sex	N	Average daily sedentary time (minutes at<200 cpm)	
			Mean	**SE**
	Male	299	595.18	7.29
	Female	167	591.29	7.08
			Coefficient	**95% CI**
1	**Male**	299	0	
	Female	167	14.66	-3.20, 32.53
	$\boldsymbol{P_{trend}}$		0.11	
2	**Male**	299	0	
	Female	167	3.24	-11.65, 18.31
	$\boldsymbol{P_{trend}}$		0.67	

Bold typeface indicates significance (p<0.05). Analyses are limited to those in fulltime employment and with complete data for self-reported sitting and all covariates. Model 1 adjusted for age and accelerometer wear time only, Model two adjusted for age, accelerometer wear time, IMD, employment grade, BMI, habitual physical activity level and general health

Table 9.8. Regression analyses for self-reported TV viewing, non-TV leisure time sitting and total leisure time sitting on weekdays with age

	Age Category	N	Weekday TV (mins)		Weekday non-TV sitting (mins)		Total weekday sitting (mins)	
Model			**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**
	16-34	1685	132.88	2.16	103.53	1.89	236.41	2.91
	35-44	1421	136.77	2.39	97.43	2.17	234.19	3.41
	45-54	1297	134.45	2.23	96.26	1.90	230.67	2.87
	55+	852	148.73	2.96	101.39	2.60	250.12	3.84
			Coefficient	**95% CI**	**Coefficient**	**95% CI**	**Coefficient**	**95% CI**
1	**16-34**	1685	**0**		**0**		**0**	
	35-44	1421	**3.89**	**-2.42, 10.20**	**-6.02**	**-11.66, -0.38**	**-2.08**	**-11.62, 5.94**
	45-54	1297	**2.65**	**-3.45, 8.74**	**-7.12**	**-12.42, -1.80**	**-6.13**	**-14.15, 1.89**
	55+	852	**17.03**	**9.81, 24.24**	**-2.02**	**-8.37, 4.33**	**12.85**	**3.38, 22.31**
	P_{trend}		**<0.0001**		**0.03**		**0.0009**	
2	**16-34**	1685	**0**		0		**0**	
	35-44	1421	**0.35**	**-6.06, 6.76**	-6.20	-11.87, -0.54	**-5.70**	**-14.53, 3.13**
	45-54	1297	**-2.73**	**-8.88, 3.41**	-7.32	-12.68, -1.96	**-9.48**	**-17.65, -1.31**
	55+	852	**7.76**	**0.51, 15.00**	-2.44	-8.88, 4.00	**6.54**	**3.15, 16.22**
	P_{trend}		**0.04**		0.33		**0.004**	

Bold typeface indicates significance (p<0.05). Analyses are limited to those in fulltime employment and with complete data for self-reported sitting and all covariates. Model 1 adjusted for gender only, Model two adjusted for gender, IMD, employment grade, BMI, habitual physical activity level and general health

Table 9.9. Regression analyses for self-reported TV viewing, non-TV leisure time sitting and total leisure time sitting on weekend days with age

	Age Category	N	Weekend day TV (mins)		Weekend day non-TV sitting (mins)		Total weekend day sitting (mins)	
Model			**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**
	16-34	1685	170.07	2.88	135.42	2.56	305.49	3.99
	35-44	1421	172.38	2.86	117.27	2.50	289.65	3.90
	45-54	1297	167.74	2.90	120.06	2.55	287.80	3.87
	55+	852	174.37	3.60	121.04	3.09	295.41	4.83
			Coefficient	**95% CI**	**Coefficient**	**95% CI**	**Coefficient**	**95% CI**
1	**16-34**	1685	0		**0**		**0**	
	35-44	1421	1.43	-6.52, 9.39	**-18.30**	**-25.31, -11.30**	**-16.87**	**-27.87, -5.96**
	45-54	1297	-2.90	-10.91, 5.12	**-15.46**	**-22.55, -8.35**	**-18.35**	**-29.27, -7.43**
	55+	852	3.10	-5.98, 12.18	**-14.59**	**-22.49, -6.69**	**-11.49**	**-23.82, -0.82**
	P_{trend}		0.58		**0.0001**		**0.004**	
2	**25-34**	1685	0		**0**		**0**	
	35-44	1421	-2.69	-10.64, 5.25	**-19.43**	**-26.49, -12.37**	**-22.13**	**-33.07, -11.18**
	45-54	1297	-8.73	-16.71, -0.75	**-16.79**	**-23.95, -9.62**	**-25.52**	**-36.51, -14.53**
	55+	852	-6.08	15.21, 3.06	**-16.43**	**-24.61, -8.25**	**-22.51**	**-35.17, -9.85**
	P_{trend}		0.16		**0.0001**		**0.0001**	

Bold typeface indicates significance ($p<0.05$). Analyses are limited to those in fulltime employment and with complete data for self-reported sitting and all covariates. Model 1 adjusted for gender only, Model two adjusted for gender, IMD, employment grade, BMI, habitual physical activity level and general health

Table 9.10. Regression analyses for accelerometer defined sedentary time (average minutes per valid measurement day at <200 counts per minute) with age

	Age Category	N	Average daily sedentary time (minutes at<200 cpm)	
Model			**Mean**	**SE**
	16-34	96	577.88	11.31
	35-44	116	594.17	12.33
	45-54	126	594.53	8.99
	55+	128	613.07	8.84
			Coefficient	**95% CI**
1	**16-34**	96	0	
	35-44	116	1.81	-23.49, 27.11
	45-54	126	-6.33	-32.03, 19.67
	55+	128	11.38	-14.88, 37.64
	$\boldsymbol{P_{trend}}$		0.57	
2	**16-34**	96	0	
	35-44	116	-13.16	-36.36, 10.04
	45-54	126	-14.18	-37.94, 9.58
	55+	128	-2.47	-28.22, 23.28
	$\boldsymbol{P_{trend}}$		0.39	

Bold typeface indicates significance (p<0.05). Analyses are limited to those in fulltime employment and with complete data for self-reported sitting and all covariates. Model 1 adjusted for gender, and accelerometer wear time only, Model two adjusted for gender, IMD, employment grade, BMI, habitual physical activity level and general health

Table 9.11. Regression analyses for self-reported TV viewing, non-TV leisure time sitting and total leisure time sitting on weekdays with employment grade

	Employment Grade	N	Weekday TV (mins)		Weekday non-TV sitting (mins)		Total weekday sitting (mins)	
Model			**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**
	Managerial and pro	2472	125.05	1.65	102.48	1.55	227.53	2.29
	Intermediate	1176	141.67	2.69	97.22	2.25	238.90	3.56
	Routine and man	1607	149.57	2.25	97.91	1.94	247.47	3.05
			Coefficient	**95% CI**	**Coefficient**	**95% CI**	**Coefficient**	**95% CI**
1	**Managerial and pro**	2472	**0**		**0**		**0**	
	Intermediate	1176	**14.85**	**8.63, 21.06**	**-6.12**	**-11.59, -0.66**	**8.72**	**0.33, 17.11**
	Routine and man	1607	**21.14**	**15.52, 26.77**	**-6.63**	**-11.49, -1.77**	**14.51**	**6.99, 22.03**
	P_{trend}		**<0.0001**		**0.01**		**0.0005**	
2	**Managerial and pro**	2472	**0**		**0**		**0**	
	Intermediate	1176	**14.50**	**8.30, 20.71**	**-5.93**	**-11.38, -0.49**	**8.57**	**0.21, 16.94**
	Routine and man	1607	**21.19**	**15.59, 26.78**	**-6.13**	**-11.05, -1.21**	**15.06**	**7.49, 22.63**
	P_{trend}		**<0.0001**		**0.02**		**0.0004**	

Bold typeface indicates significance (p<0.05). Analyses are limited to those in fulltime employment and with complete data for self-reported sitting and all covariates. Model 1 adjusted for age and gender only, Model two adjusted for age, gender, IMD, BMI, habitual physical activity level and general health

Table 9.12. Regression analyses for self-reported TV viewing, non-TV leisure time sitting and total leisure time sitting on weekend days with employment grade

	Employment Grade	N	Weekend day TV (mins)		Weekend day non-TV sitting (mins)		Total weekend day sitting (mins)	
Model			**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**
	Managerial and professional	2472	162.71	2.07	132.23	1.99	294.94	2.92
	Intermediate	1176	172.06	3.31	121.23	3.02	293.28	4.56
	Routine and manual	1607	181.65	3.03	116.85	2.36	298.49	4.00
			Coefficient	**95% CI**	**Coefficient**	**95% CI**	**Coefficient**	**95% CI**
1	**Managerial and professional**	2472	**0**		**0**			
	Intermediate	1176	**9.53**	**1.81, 17.25**	**-11.18**	**-18.26, -4.09**	-1.64	-12.34, 9.05
	Routine and manual	1607	**16.85**	**9.55, 24.15**	**-17.39**	**-23.71, -11.07**	-0.54	-10.52, 9.44
	P_{trend}		**<0.0001**		**<0.0001**		0.95	
2	**Managerial and professional**	2472	**0**		**0**			
	Intermediate	1176	**9.51**	**1.83, 17.18**	**-11.08**	**-18.14, -4.032**	-1.58	-12.20, 9.04
	Routine and manual	1607	**17.33**	**10.03, 24.63**	**-16.65**	**-22.99, -10.32**	0.68	-9.27, 10.62
	P_{trend}		**<0.0001**		**<0.0001**		0.93	

Bold typeface indicates significance (p<0.05). Analyses are limited to those in fulltime employment and with complete data for self-reported sitting and all covariates. Model 1 adjusted for age and gender only, Model two adjusted for age, gender, IMD, BMI, habitual physical activity level and general health

Table 9.13. Regression analyses for accelerometer defined sedentary time (average minutes per valid measurement day at <200 counts per minute) with employment grade

	Employment Grade	N	Average daily sedentary time (minutes at<200 cpm)	
Model			**Mean**	**SE**
	Managerial and professional	221	634.10	5.68
	Intermediate	107	591.41	12.78
	Routine and manual	138	536.03	9.48
			Coefficient	**95% CI**
1	**Managerial and professional**	221	**0**	
	Intermediate	107	**-34.59**	**-55.17, -14.00**
	Routine and manual	138	**-96.47**	**-114.43, -78.50**
	P_{trend}		**<0.0001**	
2	**Managerial and professional**	221	**0**	
	Intermediate	107	**-32.07**	**-51.95, -12.19**
	Routine and manual	138	**-92.11**	**-110.19, -74.03**
	P_{trend}		**<0.0001**	

Bold typeface indicates significance (p<0.05). Analyses are limited to those in fulltime employment and with complete data for self-reported sitting and all covariates. Model 1 adjusted for age, gender and accelerometer wear time only, Model two adjusted for age, gender, IMD, BMI, habitual physical activity level and general health

Table 9.14. Regression analyses for self-reported TV viewing, non-TV leisure time sitting and total leisure time sitting on weekdays with Index of Multiple Deprivation (IMD) Score

	IMD Quintile	N	Weekday TV (mins)		Weekday non-TV sitting (mins)		Total weekday sitting (mins)	
Model			**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**
	1 (Least deprived)	1236	129.08	2.28	100.00	2.14	229.08	3.10
	2	1100	135.91	2.66	97.84	2.38	233.75	3.69
	3	1094	135.10	2.54	99.50	2.251	234.59	3.48
	4	1023	137.87	2.73	101.67	2.44	239.53	3.61
	5 (Most deprived)	802	147.76	3.53	100.62	2.85	248.38	4.72
			Coefficient	**95% CI**	**Coefficient**	**95% CI**	**Coefficient**	**95% CI**
1	**1 (Least deprived)**	1236	**0**		0		**0**	
	2	1100	**7.18**	**0.36, 14.01**	-1.73	-7.95, 4.50	**5.46**	**-3.89, 14.80**
	3	1094	**6.55**	**-0.11, 13.21**	-0.34	-6.40, 5.71	**6.21**	**-2.88, 15.29**
	4	1023	**10.18**	**3.22, 17.14**	1.24	-5.11, 7.58	**11.42**	**2.13, 20.72**
	5 (Most deprived)	802	**20.22**	**12.00, 28.44**	0.21	-6.79, 7.20	**20.43**	**9.37, 31.48**
	P_{trend}		**0.0001**		0.94		**0.005**	
2	**1 (Least deprived)**	1236	**0**		0		0	
	2	1100	**6.11**	**-0.59, 12.82**	-1.09	-7.40, 5.19	5.06	-4.17, 14.30
	3	1094	**4.16**	**-2.41, 10.74**	-0.04	-6.10, 6.01	4.27	-4.76, 13.31
	4	1023	**6.17**	**-0.72, 13.06**	2.87	-3.36, 9.30	7.67	-1.57, 16.90
	5 (Most deprived)	802	**12.84**	**4.61, 21.08**	2.03	-5.06, 9.13	13.30	2.27, 24.34
	P_{trend}		**0.04**		0.78		0.10	

Bold typeface indicates significance (p<0.05). Analyses are limited to those in fulltime employment and with complete data for self-reported sitting and all covariates. Model 1 adjusted for age and gender only, Model two adjusted for age, gender, employment grade, BMI, habitual physical activity level and general health

Table 9.15. Regression analyses for self-reported TV viewing, non-TV leisure time sitting and total leisure time sitting on weekend days with Index of Multiple Deprivation (IMD) Score

	IMD Quintile	N	Weekend day TV (mins)		Weekend day non-TV sitting (mins)		Total weekend day sitting (mins)	
Model			**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**
	1 (Least deprived)	1236	166.93	2.87	127.64	2.72	294.57	3.98
	2	1100	165.63	3.26	119.63	2.83	285.26	4.49
	3	1094	169.61	3.19	126.31	3.00	295.92	4.50
	4	1023	172.20	3.50	127.20	3.26	299.40	4.82
	5 (Most deprived)	802	182.49	4.77	123.45	3.56	305.94	6.18
			Coefficient	**95% CI**	**Coefficient**	**95% CI**	**Coefficient**	**95% CI**
1	**1 (Least deprived)**	1236	**0**		0		0	
	2	1100	**-1.35**	**-9.85, 7.15**	-7.28	-14.96, 0.38	-8.63	-20.39, 3.11
	3	1094	**2.34**	**-6.04, 10.74**	-1.41	-9.34, 6.51	0.93	-10.80, 12.66
	4	1023	**5.51**	**-3.35, 14.38**	-2.05	-10.33, 6.23	3.47	-8.79, 15.72
	5 (Most deprived)	802	**15.74**	**4.80, 26.70**	-5.79	-14.62, 3.05	9.96	-4.53, 24.46
	$\boldsymbol{P_{trend}}$		**0.03**		0.34		0.15	
2	**1 (Least deprived)**	1236	0		0		0	
	2	1100	-2.36	-10.75, 6.03	-5.83	-13.44, 1.78	-8.19	-19.77, 3.39
	3	1094	0.55	-7.78, 8.88	0.62	-7.29, 8.54	1.18	-10.51, 12.87
	4	1023	2.46	-6.39, 11.31	1.45	-6.88, 9.78	3.91	-8.36, 16.19
	5 (Most deprived)	802	9.35	-1.59, 20.31	-1.49	-10.47, 7.48	7.86	-6.75, 22.48
	$\boldsymbol{P_{trend}}$		0.35		0.42		0.24	

Bold typeface indicates significance (p<0.05). Analyses are limited to those in fulltime employment and with complete data for self-reported sitting and all covariates. Model 1 adjusted for age and gender only, Model two adjusted for age, gender, employment grade, BMI, habitual physical activity level and general health

Table 9.16. Regression analyses for accelerometer defined sedentary time (average minutes per valid measurement day at <200 counts per minute) by quintiles with Index of Multiple Deprivation (IMD) Score

	IMD Quintile	N	Average daily sedentary time (minutes at<200 cpm)	
Model			**Mean**	**SE**
	1 (Least deprived)	135	609.86	7.90
	2	115	599.87	9.54
	3	89	576.44	12.09
	4	76	577.16	15.46
	5 (Most deprived)	81	594.61	21.90
			Coefficient	**95% CI**
1	**1 (Least deprived)**	135	0	
	2	115	-0.61	-22.20, 20.98
	3	89	-25.54	-48.31, -2.77
	4	76	-14.63	-43.54, 14.27
	5 (Most deprived)	81	-25.08	-57.13, 6.98
	$\boldsymbol{P_{trend}}$		0.14	
2	**1 (Least deprived)**	135	0	
	2	115	1.87	-15.89, 19.62
	3	89	-6.68	-26.97, 13.62
	4	76	1.29	-23.26, 25.83
	5 (Most deprived)	81	-0.97	-27.54, 20.02
	$\boldsymbol{P_{trend}}$		0.95	

Bold typeface indicates significance (p<0.05). Analyses are limited to those in fulltime employment and with complete data for self-reported sitting and all covariates. Model 1 adjusted for age, gender and accelerometer wear time only, Model two adjusted for age, gender, employment grade, BMI, habitual physical activity level and general health

Table 9.17. Regression analyses for self-reported TV viewing, non-TV leisure time sitting and total leisure time sitting on weekdays with BMI classification

	BMI	N	Weekday TV (mins)		Weekday non-TV sitting (mins)		Total weekday sitting (mins)	
Model			**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**
	<18.5	45	132.55	13.40	116.09	10.15	248.64	15.03
	18.5-25	782	126.03	2.04	101.72	1.88	227.75	2.78
	25-30	2106	137.09	1.90	96.72	1.69	233.81	2.62
	30-40	1244	149.25	2.52	102.07	2.08	251.32	3.31
	>40	78	165.33	9.67	97.55	9.55	262.88	13.84
			Coefficient	**95% CI**	**Coefficient**	**95% CI**	**Coefficient**	**95% CI**
1	**<18.5**	45	**7.15**	**-19.69, 33.99**	12.97	-6.47, 32.41	**20.11**	**-9.12, 47.35**
	18.5-25	782	**0**		0		**0**	
	25-30	2106	**9.88**	**4.27, 15.49**	-4.07	-9.09, 0.94	**5.80**	**-1.80, 13.40**
	30-40	1244	**21.96**	**15.49, 28.44**	1.79	-3.80, 7.37	**23.75**	**15.15, 32.35**
	>40	78	**39.97**	**20.46, 59.47**	-2.38	-21.61, 16.86	**37.59**	**9.44, 65.74**
	P_{trend}		**<0.0001**		0.11		**<0.0001**	
2	**<18.5**	45	**4.98**	**-20.66, 30.62**	13.03	-6.75, 32.81	**18.01**	**-9.59, 45.62**
	18.5-25	782	**0**		0		**0**	
	25-30	2106	**9.28**	**3.71, 14.84**	-4.24	-9.24, 0.75	**5.01**	**-2.53, 12.56**
	30-40	1244	**18.88**	**12.46, 25.29**	0.88	-4.78, 6.54	**19.77**	**11.17, 28.38**
	>40	78	**32.39**	**13.66, 51.12**	-4.45	-23.77, 14.87	**27.95**	**0.55, 55.36**
	P_{trend}		**<0.0001**		0.15		**<0.0001**	

Bold typeface indicates significance (p<0.05). Analyses are limited to those in fulltime employment and with complete data for self-reported sitting and all covariates. Model 1 adjusted for age and gender only, Model two adjusted for age, gender, IMD, employment grade, habitual physical activity level and general health

Table 18. Regression analyses for self-reported TV viewing, non-TV leisure time sitting and total leisure time sitting on weekend days with BMI classification

	BMI	N	Weekend day TV (mins)		Weekend day non-TV sitting (mins)		Total weekend day sitting (mins)	
Model			**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**
	<18.5	45	144.34	14.50	122.58	13.52	266.92	20.47
	18.5-25	782	157.58	2.55	127.00	2.36	284.58	3.56
	25-30	2106	171.11	2.46	121.94	2.14	293.05	3.33
	30-40	1244	189.42	3.21	125.81	2.71	315.23	3.33
	>40	78	192.53	12.91	148.20	15.73	340.72	21.64
			Coefficient	**95% CI**	**Coefficient**	**95% CI**	**Coefficient**	**95% CI**
1	**<18.5**	45	**-11.16**	**-40.11, 17.78**	-6.53	-33.05, 19.98	**-17.70**	**-57.83, 22.46**
	18.5-25	782	**0**		0		**0**	
	25-30	2106	**12.83**	**5.73, 19.94**	-2.24	-8.56, 4.07	**10.59**	**0.91, 20.27**
	30-40	1244	**32.06**	**23.90, 40.22**	3.14	-4.09, 10.37	**35.20**	**24.01, 46.40**
	>40	78	**37.55**	**11.72**	25.65	-5.56, 56.86	**63.20**	**19.77, 106.63**
	P_{trend}		**<0.0001**		0.26		**<0.0001**	
2	**<18.5**	45	**-13.17**	**-41.90, 15.55**	-5.36	-31.54	**-18.53**	**-57.95, 20.88**
	18.5-25	782	**0**		0		**0**	
	25-30	2106	**12.12**	**5.04, 19.20**	-2.39	-8.67, 3.90	**9.73**	**0.06, 19.41**
	30-40	1244	**29.36**	**21.13, 37.59**	2.16	-5.11, 9.43	**31.52**	**20.21, 42.82**
	>40	78	**30.57**	**4.90, 56.24**	23.14	-7.93, 54.22	**53.71**	**10.71, 96.71**
	P_{trend}		**<0.0001**		0.38		**<0.0001**	

Bold typeface indicates significance (p<0.05). Analyses are limited to those in fulltime employment and with complete data for self-reported sitting and all covariates. Model 1 adjusted for age and gender only, Model two adjusted for age, gender, IMD, employment grade, habitual physical activity level and general health

Table 9.19. Regression analyses for accelerometer defined sedentary time (average minutes per valid measurement day at <200 counts per minute) with BMI classification

	BMI Category	N	Average daily sedentary time (minutes at<200 cpm)	
Model			**Mean**	**SE**
	<18.5	6	587.25	67.79
	18.5-25	135	576.48	9.04
	25-30	213	599.23	8.60
	30-40	106	607.71	10.96
	>40	6	565.61	21.42
			Coefficient	**95% CI**
1	**<18.5**	6	25.80	-49.30, 100.91
	18.5-25	135	0	
	25-30	213	18.98	-3.00, 40.96
	30-40	106	28.54	0.85, 56.23
	>40	6	1.04	-50.21, 52.30
	$\boldsymbol{P_{trend}}$		0.28	
2	**<18.5**	6	11.96	-30.66, 54.58
	18.5-25	135	0	
	25-30	213	14.38	-2.99, 31.76
	30-40	106	19.25	-4.93, 43.44
	>40	6	0.32	-51.30, 51.94
	$\boldsymbol{P_{trend}}$		0.45	

Bold typeface indicates significance (p<0.05). Analyses are limited to those in fulltime employment and with complete data for self-reported sitting and all covariates. Model 1 adjusted for age, gender and accelerometer wear time only, Model two adjusted for age, gender, IMD, employment grade, habitual physical activity level and general health

Table 9.20. Regression analyses for self-reported TV viewing, non-TV leisure time sitting and total leisure time sitting on weekdays with self-rated general health status

	General Health	N	Weekday TV (mins)		Weekday non-TV sitting (mins)		Total weekday sitting (mins)	
Model			**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**
	Good/Very Good	4547	132.8	1.26	99.31	1.14	232.19	1.71
	Fair/ Bad/Very Bad	708	159.06	3.81	103.41	3.06	261.46	5.43
			Coefficient	**95% CI**	**Coefficient**	**95% CI**	**Coefficient**	**95% CI**
1	**Good/Very Good**	4547	**0**		0		**0**	
	Fair/ Bad/Very Bad	708	**25.65**	**17.74, 33.55**	4.59	-1.78, 10.59	**30.24**	**19.60, 40.88**
	$\boldsymbol{P_{trend}}$		**<0.0001**		0.18		**<0.0001**	
2	**Good/Very Good**	4547	**0**		0		**0**	
	Fair/ Bad/Very Bad	708	**18.30**	**10.28, 26.33**	3.67	-2.85, 10.19	**21.98**	**11.16, 32.80**
	$\boldsymbol{P_{trend}}$		**<0.0001**		0.49		**<0.0001**	

Bold typeface indicates significance (p<0.05). Analyses are limited to those in fulltime employment and with complete data for self-reported sitting and all covariates. Model 1 adjusted for age and gender only, Model two adjusted for age, gender, IMD, employment grade, BMI, and habitual physical activity level

Table 9.21. Regression analyses for self-reported TV viewing, non-TV leisure time sitting and total leisure time sitting on weekend days with self-rated general health status

	General Health	N	Weekend day TV (mins)		Weekend day non-TV sitting (mins)		Total weekend day sitting (mins)	
Model			**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**
	Good/Very Good	4547	167.39	1.63	124.96	1.46	292.35	2.23
	Fair/ Bad/Very Bad	708	191.31	4.58	124.86	3.82	316.17	6.26
			Coefficient	**95% CI**	**Coefficient**	**95% CI**	**Coefficient**	**95% CI**
1	**Good/Very Good**	4547	**0**		0		**0**	
	Fair/ Bad/Very Bad	708	**24.79**	**15.21, 34.36**	1.42	-6.57, 9.40	**26.46**	**13.40, 39.53**
	P_{trend}		**<0.0001**		0.73		**0.0001**	
2	**Good/Very Good**	4547	**0**		0		**0**	
	Fair/ Bad/Very Bad	708	**16.96**	**5.03, 25.31**	-0.23	-8.50, 8.05	**16.94**	**3.58, 30.30**
	P_{trend}		**0.002**		0.96		**0.013**	

Bold typeface indicates significance (p<0.05). Analyses are limited to those in fulltime employment and with complete data for self-reported sitting and all covariates. Model 1 adjusted for age and gender only, Model two adjusted for age, gender, IMD, employment grdae, BMI, and habitual physical activity level

Table 9.22. Regression analyses for accelerometer defined sedentary time (average minutes per valid measurement day at <100 counts per minute) with self-rated general health status

	Age Category	N	Average daily sedentary time (minutes at<200 cpm)	
Model			**Mean**	**SE**
	Good/Very Good	397	593.27	5.97
	Fair/ Bad/Very Bad	69	599.45	13.18
			Coefficient	**95% CI**
1	**Good/Very Good**	397	0	
	Fair/ Bad/Very Bad	69	8.68	-16.81, 34.16
	P_{trend}		0.50	
2	**Good/Very Good**	397	0	
	Fair/ Bad/Very Bad	69	10.44	-10.92, 31.80
	P_{trend}		0.29	

Bold typeface indicates significance (p<0.05). Analyses are limited to those in fulltime employment and with complete data for self-reported sitting and all covariates. Model 1 adjusted for age, gender and accelerometer wear time only, Model two adjusted for age, gender, IMD, employment grade, BMI, and habitual physical activity level

Table 9.23. Regression analyses for self-reported TV viewing, non-TV leisure time sitting and total leisure time sitting on weekdays with overall physical activity level

	Activity Level	N	Weekday TV (mins)		Weekday non-TV sitting (mins)		Total weekday sitting (mins)	
Model			**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**
	Low	1153	149.81	2.85	105.12	2.37	254.92	3.86
	Medium	1630	133.34	2.02	101.25	1.89	234.58	2.77
	High	2472	132.42	1.74	96.70	1.53	229.12	2.33
			Coefficient	**95% CI**	**Coefficient**	**95% CI**	**Coefficient**	**95% CI**
1	**Low**	1153	**0**		**0**		**0**	
	Medium	1630	**-15.90**	**-22.76, -9.05**	**-4.06**	**-10.05, 1.93**	**-19.99**	**-29.37, -10.63**
	High	2472	**-17.68**	**-24.30, -10.90**	**-9.51**	**-15.20, -3.84**	**-27.22**	**-36.27, -18.16**
	P_{trend}		**<0.0001**		**0.0023**		**0.0001**	
2	**Low**	1153	**0**		**0**		**0**	
	Medium	1630	**-11.15**	**-17.95, -4.34**	**-4.45**	**-10.43, 1.54**	**-15.62**	**-24.95, -6.30**
	High	2472	**-16.02**	**-22.53, -9.50**	**-9.08**	**-14.86, -3.30**	**-25.12**	**-34.19, -16.04**
	P_{trend}		**<0.0001**		**0.0064**		**0.0001**	

Bold typeface indicates significance (p<0.05). Analyses are limited to those in fulltime employment and with complete data for self-reported sitting and all covariates. Model 1 adjusted for age and gender only, Model two adjusted for age, gender, IMD, employment grade, BMI, and general health

Table 9.24. Regression analyses for self-reported TV viewing, non-TV leisure time sitting and total leisure time sitting on weekend days with overall physical activity level

	Activity Level	N	Weekend day TV (mins)		Weekend day non-TV sitting (mins)		Total weekend day sitting (mins)	
Model			**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**
	Low	1153	180.70	3.36	133.26	3.16	313.96	4.72
	Medium	1630	171.18	2.49	128.07	2.38	299.25	3.49
	High	2472	166.01	2.35	119.34	1.93	285.35	3.13
			Coefficient	**95% CI**	**Coefficient**	**95% CI**	**Coefficient**	**95% CI**
1	**Low**	1153	**0**		**0**		**0**	
	Medium	1630	**-10.14**	**-18.32, -1.97**	**-6.37**	**-14.13, 1.39**	**-16.51**	**-27.99, -5.03**
	High	2472	**-16.39**	**-24.42, -8.36**	**-16.61**	**-23.99, -9.23**	**-33.00**	**-44.19, -21.81**
	P_{trend}		**0.0003**		**<0.0001**		**<0.0001**	
2	**Low**	1153	**0**		**0**		**0**	
	Medium	1630	**-5.54**	**-13.67, 2.59**	**-7.88**	**-15.61, -0.15**	**-13.42**	**-24.87, -1.97**
	High	2472	**-13.48**	**-21.50, -5.47**	**-15.08**	**-22.39, -7.75**	**-28.56**	**-39.74, -17.37**
	P_{trend}		**0.003**		**0.0002**		**<0.0001**	

Bold typeface indicates significance (p<0.05). Analyses are limited to those in fulltime employment and with complete data for self-reported sitting and all covariates. Model 1 adjusted for age and gender only, Model two adjusted for age, gender, IMD, employment grade, BMI, and general health

Table 9.25. Regression analyses for accelerometer defined sedentary time (average minutes per valid measurement day at <200 counts per minute) with overall physical activity level

	Activity level	N	Average daily sedentary time (minutes at<200 cpm)	
Model			**Mean**	**SE**
	Low	97	614.05	15.78
	Medium	167	619.85	7.67
	High	202	565.80	7.19
			Coefficient	**95% CI**
1	**Low**	97	**0**	
	Medium	167	**-6.62**	**-33.20, 19.97**
	High	202	**-49.51**	**-75.73, -23.29**
	P_{trend}		**<0.0001**	
2	**Low**	97	**0**	
	Medium	167	**-18.39**	**-40.09, 3.31**
	High	202	**-42.78**	**-64.53, -21.02**
	P_{trend}		**0.0002**	

Bold typeface indicates significance (p<0.05). Analyses are limited to those in fulltime employment and with complete data for self-reported sitting and all covariates. Model 1 adjusted for age, gender, and accelerometer wear time only, Model two adjusted for age, gender, IMD, employment grade, BMI, and general health

Chapter 10.

The differential effects of sustained and interrupted sitting on glucose metabolism

10.1. Introduction

Over the last ten years there has developed a body of evidence reporting cross-sectional and longitudinal associations between sedentary behaviour and health outcomes that are not explained simply by a lack of MVPA. Extended periods of sitting are argued to represent an increased risk of future disease, irrespective of levels of reported MVPA. As discussed previously (3.10.3) the most consistent of these associations appears to be between sitting time and metabolic diseases such as Type 2 diabetes,[56 190 191] and prediabetes including abnormal glucose tolerance [34 35 173 288] and insulin resistance.[376]

In a cross-sectional study Healy et al [109] observed a negative association between the daily volume of accelerometer defined sedentary time and markers of insulin sensitivity and lipid metabolism in adults. Further, the 'breaks' in sedentary time were associated with a lower waist circumference, BMI, triglycerides and plasma glucose. The associations were independent of the total volume of sedentary time, duration and intensity of breaks, and total physical activity. In other words, breaking up long periods of sedentary time, for any length of time and any intensity of activity, appeared to be beneficial. As discussed (3.8) the results of Healy et al[109] suggest that extended uninterrupted periods of sedentary time may be more important than simply the total time

spent sedentary per day. Despite the growth in the evidence base, methodological limitations mean that uncertainty remains about causal associations between sedentary time and health and the mechanisms by which any associations occur. More specifically, key questions remain about the classification of sedentary time inferred from accelerometer data, discriminating between the effects of low/no movement and the posture of sitting, and the confounding effects of daily energy expenditure.

10.1.2. Insulin function and insulin resistance

Insulin is a major fuel-regulating hormone secreted by the pancreatic beta cells in response to food intake and whilst it enables adequate cellular energy supplies by allowing glucose to enter cells e.g. by Glucose Transporter Protein 4 (GLUT-4) translocation, it is also a regulator of circulating glucose levels. In skeletal muscle and adipose tissue, insulin stimulates the uptake of glucose from the blood by the translocation of GLUT-4 glucose transporter to the cell surface. In the skeletal muscle and liver tissue, insulin stimulates the synthesis of glycogen from glucose and inhibits glycogenolysis. In the liver insulin also decreases hepatic gluconeogenesis, preventing an influx of more glucose into the bloodstream. In adipose tissue, insulin promotes lipogenesis and stimulates glucose uptake. The net effect of all these functions is to enable glucose uptake to organs as a vital energy substrate and to reduce postprandial blood glucose.[267] In insulin resistance the insensitivity of muscle, adipose and liver cells to insulin causes increased insulin production from the pancreas in order to maintain the clearance of glucose from the blood. Continued insulin resistance can lead to elevated circulating glucose levels. These elevated

glucose concentrations are first noted postprandially but fasting glucose can also become elevated, which is a hallmark of Type 2 diabetes.

There is cross sectional evidence linking high volumes of sitting time with reduced insulin sensitivity[54] although the time scales over which these effects may take place has only recently been investigated using experimental manipulation of sitting. As discussed previously, due to the burden of disease attributable to diabetes, its increasing prevalence and its role in the development of cardiovascular disease, an understanding of modifiable lifestyle factors that lead to a reduction in insulin resistance has considerable potential for health gain.

10.1.3. Existing sitting intervention studies

A small number of randomised control trials have investigated the acute effects of continuous versus interrupted sitting on a number of metabolic outcomes including insulin sensitivity. Dunstan et al[273] compared the effects of three separate 7 hr sitting conditions on glucose and insulin levels following the ingestion of a mixed test drink in overweight and obese adults (aged 45-65yrs). One condition involved uninterrupted sitting, while during the other two, sitting was interrupted by repeated 2 minute bouts of either light (3.2km/h) or moderate (5.8-6.4km/h) intensity walking. All participants completed all conditions in a randomised cross-over design. They observed that compared to the uninterrupted sitting condition, interrupting sitting with walking reduced the glucose and insulin responses to the mixed test drink by 30% and 23%

respectively. A smaller and less prolonged increase in circulating glucose and insulin indicates a more sensitive and efficient response of body tissues to deal with the energy provided by the test meal. No difference was observed between the light and moderate intensity walking conditions indicating that regularly interrupting sitting with any intensity of walking has a beneficial effect on glucose and insulin metabolism. However, what is not clear from this study is whether the reductions in glucose and insulin concentrations were due to the act of disrupting sitting, or whether they were due to the higher total energy expenditure accumulated during the repeated walking bouts.

Stephens et al[274] used a similar three trial design to examine insulin action in a younger (aged 19-32yrs) population. The first two trials involved either a day of uninterrupted sitting (trial 1) or a day of activities designed to replicate the day to day movements of healthy adults in which sitting was restricted (trial 2). Meals were provided throughout and the energy content of these meals was constant across the first two trials. The third trial involved a day of uninterrupted sitting in which energy intake was reduced (by approximately 1000kcal) in order to balance the reduced energy demands of a completely sedentary day. It was observed that compared with the active trial, 1 day of sitting reduced insulin action (defined as whole body rate of glucose disappearance normalised to mean plasma insulin concentration) measured the following morning during a continuous infusion of (6,6-[2]H) glucose by 39%. Reducing energy intake to match the lower energy demands of sitting significantly attenuated (an absolute difference of 18% [*P*=0.07] compared to active trial) but did not completely prevent the decline in insulin action. It was

concluded that a positive energy balance (due to low energy expenditure during sitting) may account for a large proportion of the difference between uninterrupted and interrupted sitting patterns, but other factors specific to the prolonged sitting may be also involved.[274]

If an energy surplus is the predominant factor in the adverse health consequences associated with prolonged sitting then it could be argued that the posture of sitting is not the exposure but simply acts as a proxy for low energy expenditure. Interrupting sitting with walking therefore, may tell us more about the effect of increased energy expenditure rather than the effect of prolonged sitting.

However a study by Peddie et al[275] suggests that differences in total daily energy expenditure do not determine the beneficial effects of interrupting sitting. Peddie et al examined plasma glucose and insulin responses to three mixed test meals across three 9hr trial days in 70 adults (aged 25.9 ± 5.3 yrs). The first trial involved sustained sitting while during the second a single 30 minute bout of walking was undertaken at the start of the day (physical activity trial). During the third trial sitting was interrupted every 30 minutes with a walking bout lasting 1 minute 40 seconds (activity breaks trial). Incremental area under the curve for glucose was significantly reduced with activity breaks compared to the preload with a bout of morning physical activity (- 37% $P<0.001$) and sustained sitting (- 39% $P<0.001$). Incremental area under the curve for insulin was also significantly reduced in the activity breaks trial compared to the single bout of

physical activity (-18% *P*<0.001) and sustained sitting (-26% *P*<0.001). No differences were observed between the single bout of physical activity and sustained sitting intervention. The total duration of activity and average heart rate during both the activity breaks and single bout of physical activity were matched, suggesting that differences in total daily energy expenditure do not explain the reduction in glucose and insulin concentrations in the activity breaks trial relative to sustained sitting. Rather there are factors specifically related to the regular interruption of sitting which may be beneficial. However, although this study attempted to control for energy expenditure, it did so using estimates of energy expenditure rather than direct measurement. Also, the absence of a study arm that changed posture but not energy expenditure (e.g. standing) means that it is still not possible to determine that sitting itself is the cause of less healthy levels of insulin and glucose rather than energy expenditure.

More recently, Thorp and co-workers[377] examined whether alternating between 30 minute bouts of sitting and standing during 5 consecutive 8 hr working days (intervention condition) would reduce postprandial glucose, insulin and triglyceride responses to a mixed test drink, compared to 5 consecutive 8 hr days where sitting was sustained (control condition). Twenty-three overweight or obese middle-aged (48.2 ± 7.9 yrs) adults completed both intervention and control conditions in a randomised cross-over design. A modest reduction (11.1%) in postprandial glucose response was observed following the intervention condition although insulin and triglyceride responses did not differ between conditions. Although this seems to suggest that standing intervals may be of some benefit to glucose metabolism relative to sustained sitting, the

authors state that light ambulatory activity was permitted within the confines of the laboratory during these intervals. It is therefore likely that the observed effect may be attributable to the increased movement and energy expenditure during these intervals. This is especially true given the duration of the standing/walking periods which would allow significant accumulation of activity.

Understanding whether differences in glucose and insulin observed during sustained and interrupted sitting are due to the posture of sitting or differences energy expenditure is very important as future policy and behavioural advice that may follow could be misleading if based on assumptions about sitting rather than energy expenditure. Therefore, there is still a need for experimental investigation of the metabolic effects of prolonged sitting versus interruptions in sitting that do and do not alter energy expenditure.

10.1.4. Study aims and hypotheses

In light of the evidence reported above, the aim of the current study was to compare the effect of a) a 7hr period of uninterrupted sitting with b) a 7hr sitting period interrupted by a posture change without increased energy expenditure and (c) a 7hr sitting period interrupted by walking and therefore increased energy expenditure, on the plasma glucose and insulin responses to both an oral glucose tolerance test and a mixed test meal. All three day-long tests were designed to mimic an office based working day with telephone, computer and internet access. The study aimed to determine;

i) Whether any type of interruption in prolonged sitting has beneficial effects on glucose and insulin metabolism
ii) Whether interruptions need to result in an increase in energy expenditure above approximately 1.5 METs (the energy cost of standing) to have a beneficial effect on glucose and insulin metabolism

More specifically the study aimed to test the null hypotheses that;

i) there will be no differences in plasma glucose and insulin responses to an OGTT and a test meal between 7hrs of uninterrupted or interrupted sitting
ii) there will be no differences in plasma glucose and insulin responses to an OGTT and a test meal between 7hrs of sitting interrupted by regular standing breaks and 7hrs of sitting interrupted by regular walking breaks.

10.2. Methods

10.2.1 Study overview

This three-trial randomised, cross-over study of the differential metabolic effects of sustained and interrupted sitting was approved by the University of Exeter Sport and Health Sciences departmental ethics committee (approval number 2013/410) see appendix 2.1. Written informed consent was obtained from all participants prior to their first trial. Following an initial preliminary visit, participants attended the laboratory on three separate occasions to perform three trials (’SIT-ONLY’ ‘SIT-STAND’ and ‘SIT-WALK’). Each trial began at 8.30am and concluded at 5.00pm and involved participants remaining in a seated position for the duration of the day while blood samples were taken

periodically in order to analyse differences in glucose and insulin profiles between experimental conditions. During the SIT-STAND and SIT-WALK trials participants stood or walked for 2 minutes every 20 minutes before resuming a seated position. An oral glucose tolerance test (OGTT) was performed at 10.00am and a standardised test meal replacement drink consumed at 1.00pm. Following the collection of the last blood sample and removal of the cannula participants were able to help themselves from a selection of drinks and snacks. Preliminary testing and all 3 main trial days took place at a Sport and Health Sciences laboratory at the University of Exeter's St. Luke's campus.

10.2.2. Participants

Recruitment: Participants were recruited from an existing research volunteer database, the 'Exeter Ten-thousand' (Extend - http://www.exeter.crf.nihr.ac.uk/node/155) held by the Clinical Research Facility in Exeter, and from advertisements sent to staff at a number of University of Exeter departments via internal email.

Inclusion Criteria: Male participants aged 30-65yrs, who are non-smokers, who can walk without limitation and do not participate regularly in physical activity (≤ 4 occasions [1-60mins] of sport or exercise in the last 4 weeks).

Exclusion Criteria: hypertension (resting BP ≥160/90mmHg; on antihypertensive medication), known cardiovascular, diabetes or endocrine disorders (thyroid

disease), previous gastric surgery, requirement (at the present time or in the previous 6 months) of any medication or nutritional supplements known to effect lipid or carbohydrate metabolism, antidepressants, smoking < 5 years ago, passive smoking, history of heavy alcohol use (> 20 units a week) or recreational drug abuse.

Participants meeting the above criteria were contacted initially by letter and then, once they had expressed their interest, by telephone and invited to participate in the study. A participant information document (see appendix 2.2), detailing all procedures and requirements for the study was sent to their home address for consideration.

10.2.3. Preliminary Testing

Participants attended a preliminary visit at the Sport and Health Sciences department at the University of Exeter. Prior to the preliminary assessments a member of the research team read through the participant information with each person, reiterating the study objectives and the methods employed for the three trials, before addressing any questions they had. Written informed consent for the study was then obtained using the form detailed in appendix 2.3. Participants aged 46 or over also completed a physical activity readiness questionnaire (PAR-Q) (see appendix 2.4) in accordance with departmental policy. This questionnaire is routinely used to determine whether a person should consult a doctor prior to undertaking physical activity or increasing their

habitual activity level. Any participant failing to meet the criteria outlined in the assessment would be thanked for their time but take no further part in the study.

Following consent, a measurement of the resting metabolic rate was then obtained over a 45 minute period, using a portable gas analysis system (Cosmed K4b^2, Cosmed. U.K). In order to do so, participants remained in a seated position for 30 minutes after which they completed a period of 5 minutes of standing and 5 minutes of walking (at 2mph) separated by a 5 minute seated, rest period. The procedure allowed the attainment of steady state energy expenditure values for each individual while sitting, standing and walking.

Participant's height (in cm using a freestanding stadiometer), weight (in kg using a calibrated scale), waist circumference (in cm measured at the midaxillary line using a tape placed midway between the lower rib cage and the iliac crest), body fat percentage (using bi-electrical impedance) and resting blood pressure (in mmHg using an automated sphygmomanometer) were measured in triplicate and recorded. Before leaving the department, instructions for the days prior to the three trial days were explained to each participant and any questions addressed. The instructions were as follows;

- Participants were instructed to wear a GENEActiv accelerometer (ActivInsights, Kimbolton, United Kingdom) on their left wrist during all

waking hours for 2 days prior to each of the three trial days to assess physical activity.

- Throughout the day prior to the first trial, participants were required to record all food and drink consumed in the food diary provided. The diary would then be used to replicate food intake on the days prior to the second and third trial days.
- Participants were instructed to remain inactive (no volitional physical activity other than day to day tasks) for 48 hours prior to each trial day
- Participants were instructed to avoid alcohol for 24 hours and caffeine for 11 hours (from 9.30pm) preceding each trial day.
- Participants were asked to attend each trial in clothing and footwear that is both comfortable and suitable for slow walking on a walking platform.
- Participants were advised to attend the laboratory by car if at all possible on each trial day. If this was not possible a taxi would be provided.
- Participants were provided with a food record diary and the above instructions (appendices 2.5 and 2.6).

10.2.4. Trial allocation procedure

The order of the three trials was randomly allocated to each participant with the first being within 30 days of the preliminary visit. Following their preliminary screening visit participants were randomised to six possible trial orders by an impartial third party using sealed envelopes.

As acute exercise bouts have been shown to enhance insulin sensitivity over a number of days,[378] trials were separated by a minimum of six days to eliminate the possibility of any carryover effects of physical activity from the SIT-STAND or SIT-WALK trials. Participants received the accelerometer (initiated and programmed using GENEA software) at least two days prior to each trial day. They also received a reminder phone call at this time during which any questions regarding the written instructions for the subsequent two days could be addressed.

10.2.5. Trial day procedures

The main experimental protocol for the three trials is described in the participant timetable (appendix 2.7) and illustrated in the protocol diagram (figure 10.1). A full explanation of the interrupted and uninterrupted sitting trials is provided below.

10.2.5.2. Trial 1: SIT-ONLY

Participants attended the laboratory on each trial day at 8.30am following an overnight fast from 9.30pm (excluding water consumption), having not consumed any alcohol or undertaken any moderate to vigorous intensity physical activity (any volitional physical activity other than day to day tasks) in the previous 24 hrs and having not consumed any caffeine in the previous 10 hrs. Participants arrived by private car or taxi from their home to avoid additional energy expenditure from transportation. The experimental protocol, study

objectives and methods for trials 1, 2, and 3 were explained again and any further questions addressed. A measure of weight (in kg using a calibrated scale) was then taken. Participants were also encouraged to use the toilet at this time prior to the start of the trial protocol.

At 8.50am an indwelling cannula was inserted into an antecubital vein. By 9.00am participants had made themselves comfortable in a seated position at a desk where they remained for the duration of the trial. The first hour was treated as a rest period in order for metabolic rate to return close to resting levels following the journey to the laboratory and cannulation. At 10.00am a baseline blood sample was taken. Participants then completed an OGTT to measure insulin sensitivity and to provide some calories which would ordinarily be consumed during breakfast. For this, subjects were given a drink with a glucose content of 75g glucose (Lucozade) to consume as quickly as possible. A further eight blood samples (samples 2-9) were then collected at 10, 20, 30, 60, 90, 120, 150 and 180 minutes (up to 1.00pm).

At 1.00pm (180 minutes), immediately following blood sample 9, participants consumed a standardised mixed test meal in the form of an energy dense drink. Participants were encouraged to finish their test meal within 10 minutes (by 1.10pm). Blood samples 10-18 were then collected at 190, 200, 210, 240, 270, 300, 330, 360, and 390, minutes up until 4.30pm. A final blood sample (sample 19) was taken at 5.00pm (420 minutes), prior to the removal of the cannula. With the exception of the test meal provided no additional food was

consumed at any point during the intervention. Water was consumed ad libitum from a bottle of known volume. The total fluid consumed during the first intervention day was recorded for the participants to replicate during subsequent trials.

Throughout the entirety of the SIT-ONLY trial (from 9.00am until 5.00pm) participants remained seated quietly at a desk where they were allowed to work at the computer, watch DVDs, listen to music or read. Newspapers and a computer with a DVD player and internet access were provided. Participants were allowed comfort breaks as required although they were encouraged to visit the toilet prior to the start of the intervention at 10.00am. The number and duration of comfort breaks taken was then replicated in the subsequent interventions. Participants were observed throughout the majority of the trial to ensure that they remained seated, and accelerometer data was additionally checked following completion of the trial to ensure participants remained seated when they were not being directly observed.

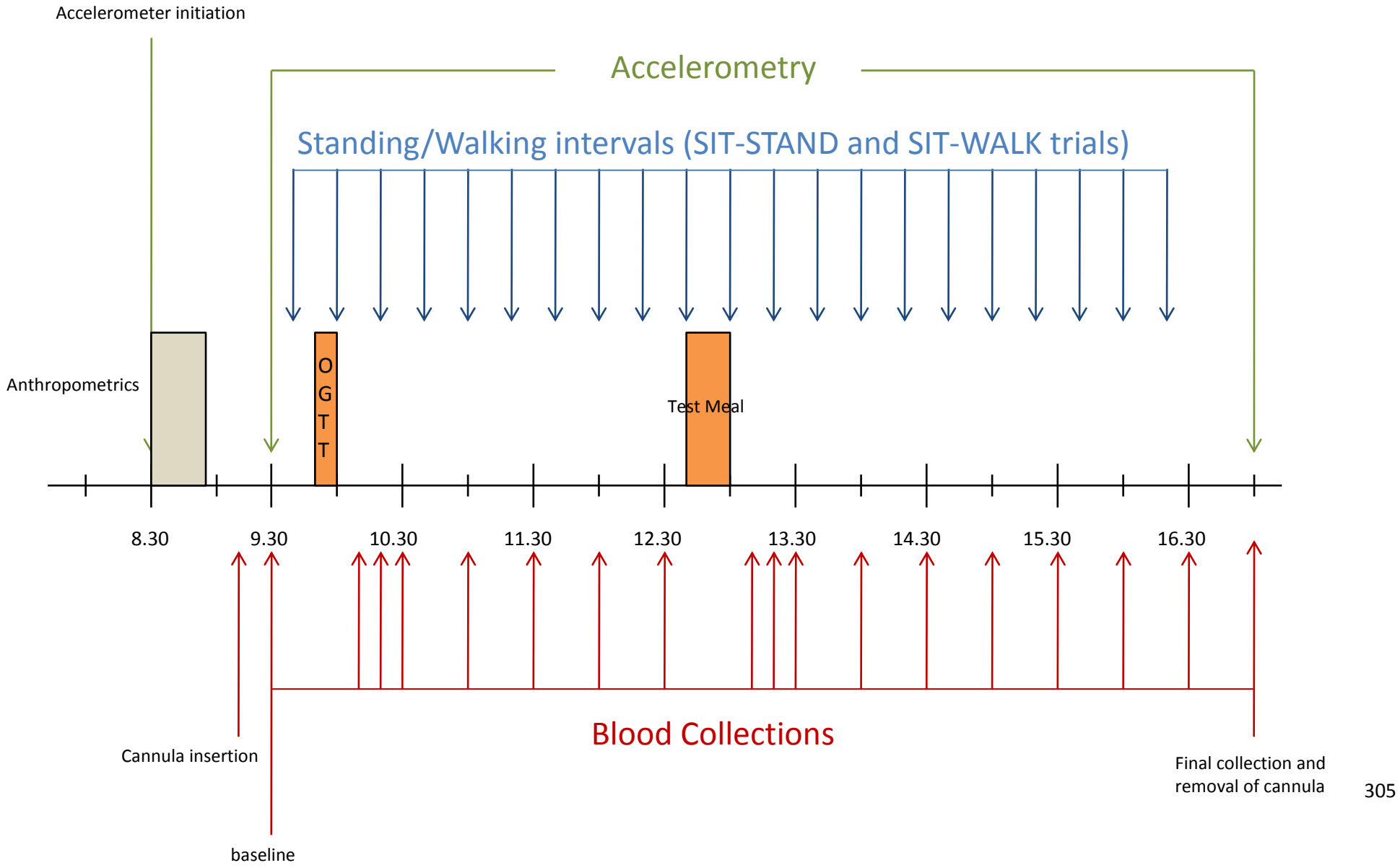
10.2.5.3. Trials 2 and 3: SIT-STAND and SIT-WALK

Participants, again attended the laboratory at 8.30am having followed identical procedures prior described for Trial 1 above.

The protocol for the OGTT, administration of the test meal and the timing of blood samples was identical to trial 1. In trials 2 and 3 time spent seated was

punctuated by 2 minute intervals of either standing (trial 2) or walking (trial 3) every 20 minutes commencing at 10.00am in order to achieve 3 breaks per hour. Trials 2 and 3 will from this point be referred to as SIT-STAND and SIT-WALK respectively. The exact timings of these intervals can be seen in figure 10.1. This pattern has been used previously to examine interrupted versus uninterrupted sitting with activity breaks (not standing).[273] During SIT-STAND, participants were required to stand from their seated position and remain standing by the desk for 2 minutes. They were discouraged from expending energy resulting from any movement other than standing. In SIT-WALK, walking intervals were performed at a speed of 2 miles per hr (3.2km/hr) which is equivalent to an energy expenditure of 2-2.9 METs [359] and reflects light intensity activity. Walking intervals were conducted on a walking platform (FitWork [TM] Walkstation, Details, New York) immediately next to the desk so that transit from sitting to walking was minimal. All intervals were observed and recorded to ensure they were completed properly and were precisely 2 minutes in duration. Following each standing or walking interval participants resumed their seated position immediately. Standing and walking intervals were performed at 10.00am and then on the hour, and at 20 and 40 minutes past the hour for the duration of the trial. A total of 19 intervals were performed in total. Mean steady state energy expenditure values for sitting, standing and walking, recorded during preliminary testing are detailed in the results section.

Figure 10.1. Diagram of protocol for SIT-ONLY, SIT-STAND and SIT-WALK trials



10.2.5.4. Oral glucose tolerance test and test meal

The oral glucose tolerance test consisted of 435ml of a standardised glucose drink (Lucozade Sport) containing 75g glucose. Participants were instructed to consume the test drink as quickly as possible (within 2 minutes) and the exact time was recorded and replicated across trials. The mixed test meal was a nutritionally complete meal replacement shake (Fortisip, Nutricia , UK) providing 6.0 grams of protein, 5.8 grams of fat, 18.4 grams of carbohydrate and 150 kilocalories per 100ml. This was prescribed to participants so as to provide 0.35g fat, 1.17 g carbohydrate, 0.29g protein and 39kJ (9.08kcal) per kilogram body mass. This ensured that approximately 33% of the total energy intake from this meal was from fat, 50% from carbohydrate and 17% from protein. This test meal was chosen as its composition mirrors that used in test meals in previous studies in adult males [260] [262] [264] [265] and because the values closely represent the average diet composition of the UK adult population (35% fat, 48% carbohydrate and 17% protein). [379]

10.2.5.5. Accelerometer data

Upon arrival on each trial day participants returned the GENEA accelerometer worn on the previous 2 days. The data of 48 hrs activity was uploaded using the GENEActiv software. Time spent in sedentary behaviour, light, moderate and vigorous activity were derived using published cut-points.[144] The resulting values were used to assess participants' adherence to pre-trial instructions (to avoid any exercise other than that required for day to day activities) and any between trial differences in physical activity.

10.2.5.6. Blood sampling and biochemistry

All blood samples were collected while participants were seated at the desk. Patency of the cannula was maintained by flushing with a small amount of non-heparinized saline (0.9% wt/vol sodium chloride, Baxter Healthcare, Norfolk, UK) after each collection. The saline waste remaining in the connecter tube was drawn off using a 2ml syringe immediately before the subsequent blood sample was collected. Blood samples were collected into 6ml fluoride oxalate and lithium heparin separator tubes. Samples were centrifuged at 4000 rpm for 10 minutes and plasma stored at -80C for later analyses of plasma glucose and insulin. Plasma samples were thawed and vortexed prior to analyses. Plasma insulin concentrations were determined using a commercially available immunoenzymetric assay (Insulin ELISA, ILB International, Hamburg, Germany). Plasma glucose concentrations were determined using an enzyme based colorimetric assay (Cayman Chemical Co., Ann Arbor, MI, USA). Plasma samples from each time point were analysed in duplicate with absorbance plotted against known standards using a microplate reader (Enspire 3100 Plate Reader, Perkin Elmer, MA, USA). Samples from each participant analysed in the same assays to avoid interassay variability where possible.

10.2.6. Outcome measures

The outcome measures for the current study were Matsuda Insulin Sensitivity Index, and incremental area under the curve for glucose and insulin for the whole 7 hr trial, and both the post-OGTT (3 hrs) and post-test meal (4 hrs) parts of the day. Insulin sensitivity index for the 3 hrs following the glucose

tolerance test was calculated using the following formula as described by Matsuda et al.[171]

Matsuda Insulin Sensitivity Index (M-ISI):

$$\frac{10000}{(\sqrt{[\text{fasting glucose} \times \text{fasting insulin}] \times [\text{mean glucose} \times \text{mean insulin during OGTT}]})}$$

The higher the index value the better a person's insulin sensitivity. An index less than or equal to 2.5 represents whole body insulin resistance. This method has been demonstrated to provide a good approximation of whole body insulin sensitivity following a glucose tolerance test and has been validated against the euglycemic-hyperinsulinemic clamp (EHC) method. [171]

Both total (tAUC) and positive incremental (iAUC) area under the concentration versus time curves for glucose and insulin after the mixed test meal were calculated using the trapezoidal method. This method approximates the AUC by considering the areas between time points to be trapezoidal in shape; the areas of individual trapezoids are then summed to provide the total AUC. The following equations were used:

Total (tAUC) and (iAUC) incremental area under the curve:

$$tAUC = \Sigma [(n_k + n_{k+1})/2 \times t]$$

$$iAUC = \Sigma [(n_k + n_{k+1})/2 \times t] - 17nb$$

Where *n* represents plasma glucose or insulin at time point *k, t* is the absolute difference in time (hrs) between *k* and k_{+1} and *nb* is the baseline value. This method has been used extensively to quantify area under concentration versus time curves.[380-383] In order to assess the independent effect of the interventions on plasma insulin and glucose responses during the 3hr period following the OGTT, the positive incremental area under the curve was computed for this period (from this point to be referred to as post OGTT iAUC). This is achieved by subtracting the baseline area for this 3 hr period. The separate positive incremental area under the curve was then computed for plasma glucose and insulin for the 4 hr postprandial period following the mixed test meal (from this point to be referred to as post meal iAUC).

10.2.7. Statistical analyses

In the absence of published data on glucose and insulin during interrupted and uninterrupted sitting at the time of study design, data from a previous study examining glucose and insulin responses to an oral glucose tolerance test in sedentary adults was used to determine the required sample size for the current study. Short et al[384] observed a mean (±SD) insulin sensitivity index (ISI) value (as calculated using the Matsuda formula) of 9.27 ±

1.17 and a test-retest correlation of 0.78 for repeated measurements with a coefficient of variation of 20%. Based on these values it was calculated that a sample of at least 19 participants would be required for 90% power to detect a 5% change in Matsuda ISI between trials at the 5% significance level.

Generalised estimating equation models were used to examine the differential effects of the three trials on the outcome measures. This approach is effective in examining overall between trial differences in repeated measures designs[385] and has been used previously in a study examining differences in glucose and insulin across different sitting protocols. [273] This method has been shown to have a number of advantages over traditional methods such as one-way repeated measures ANOVA including its ability to specify the desired correlation structure. In the current analysis an exchangeable working correlation model was used to account for dependancy in the data (for repeated measures). Pairwise comparisons between interventions were only carried out when the overall intervention effect was significant. In such cases postestimation pairwise contrasts with Bonferroni correction for multiple comparisons were used to examine differences between pairs of interventions. Initial univariate models were repeated following adjustment for pre challenge values (pre OGTT values for tAUC and post OGTT iAUC, and pre meal values for post meal iAUC), and then additonally for weight, and pre-intervention moderate to vigorous (of an intensity above 3 METs) physical activity as these have been previously associated with differences in postprandial responses.[386] Due to the minimum 7day washout period between interventions, carryover effects from previous interventions were not formally tested.

Significance was set at the 0.05 level and all analyses were carried out using STATA SE version 13 (StataCorp, College Station, US). Data are presented as mean ± SEM unless described otherwise. In figures 10.3 to 10.7 fully adjusted means are presented.

10.3. Results

The Consolidated Standards of Reporting Trials (CONSORT) participant flow diagram is shown in figure 10.2. Of the 27 participants who completed the preliminary testing, 25 completed all three experimental conditions and were included in the analysis. Characteristics of the final sample are detailed in table 10.1.

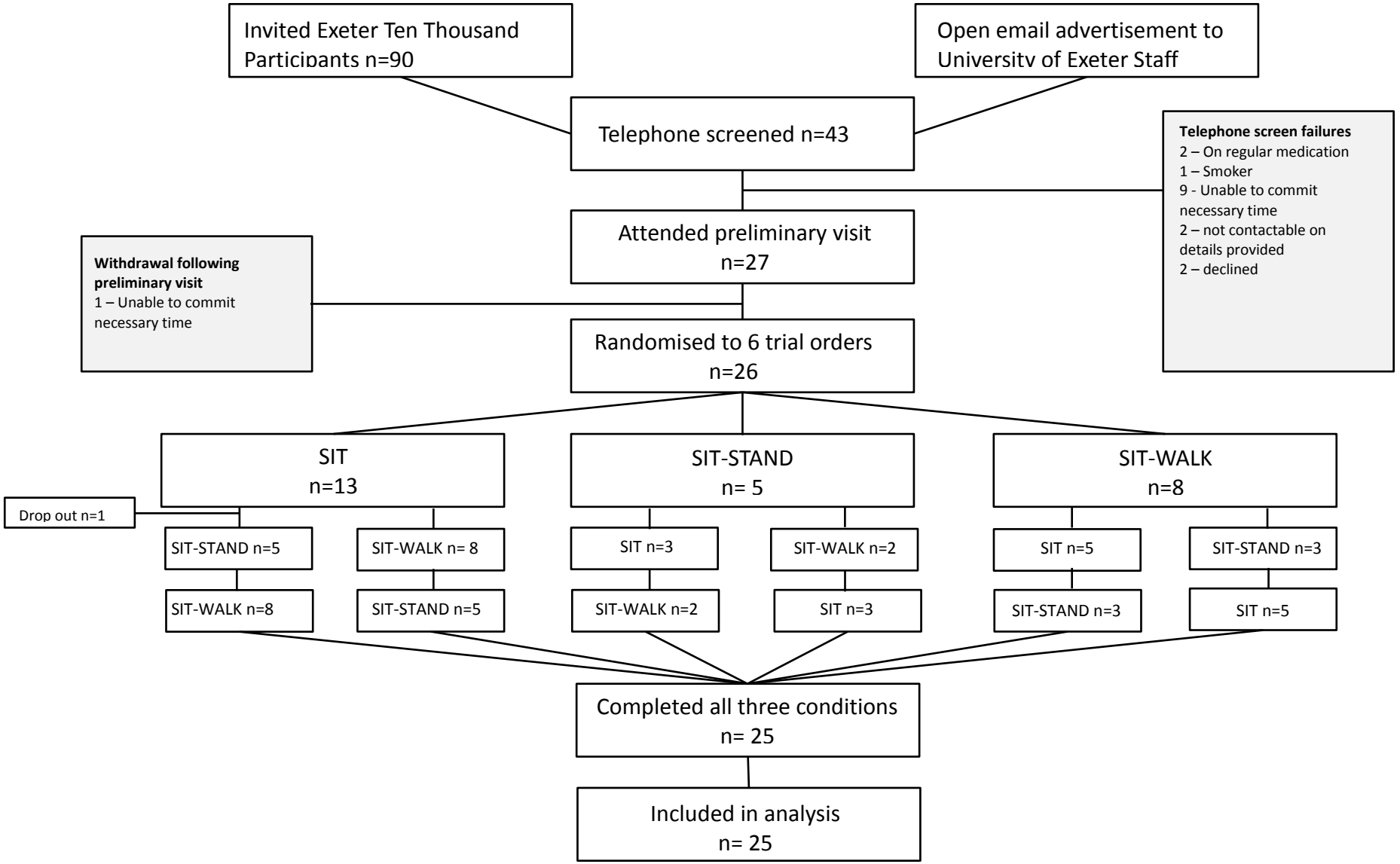


Figure 10.2. CONSORT diagram for participant flow through the study from recruitment to data analysis

Table 10.1. Participants characteristics. N=25. Data are mean ± SD

Characteristic		
Age	(yrs)	40.21 ± 12.19
Height	(cm)	177.33 ± 5.52
Weight	(kg)	82.40 ± 17.16
BMI	(kg/m^2)	26.12 ± 4.14
Waist Circumference	(cm)	87.26 ± 9.42
Body fat	(%)	26.56 ± 5.99
Blood pressure		
Systolic	(mmHg)	122.60 ± 6.82
Diastolic	(mmHg)	79.88 ± 3.56
Fasting Blood Analysis		
Glucose	(mmol/L)	4.34 ± 0.83
Insulin	(pmol/L)	66.61 ± 33.48
HOMA-IR		1.4 ± 0.63
Triglyceride	(mmol/L)	0.88 ± 0.46
Cholesterol	(mmol/L)	4.94 ± 0.69
HDL	(mmol/L)	1.55 ± 0.32
LDL	(mmol/L)	2.99 ± 0.75
Urea	(mmol/L)	5.58 ± 1.39
Creatinine	(umol/L)	86.88 ± 13.10
ALT	(u/L)	27.4 ± 12.82
ALP	(u/L)	58.88 ± 10.57

Steady state energy expenditure for walking at 2mph (2.94 ± 0.53, range 2.04-3.42 METs,) measured at the preliminary visit was significantly higher than for standing (1.17 ± 0.66, range 0.42-1.45 METs, $p<0.001$) and for sitting (0.94 ± 0.22 range 0.41-1.23 METs, $p<0.001$). Steady state energy expenditure for standing and sitting was not significantly different ($p=0.113$).

Mean accelerometer defined MVPA measured during the 48 hours prior to each was slightly higher prior to SIT-STAND (136.21 ± 18.71 minutes) than SIT-WALK (117.00 ± 13.85 minutes, $P=0.05$) but did not differ significantly from SIT-ONLY (124.90 ± 12.80 minutes). Prior MVPA did not differ significantly between SIT-WALK and SIT-ONLY.

All participants consumed the OGTT test drink within 2 minutes and finished their mixed test meal within 8 minutes. The average volume of the mixed test meal consumed by participants during the main trial days was 499.97 ± 101.13 ml, consisting of 29.99 ± 6.25g protein, 27.78 ± 3.05g fat, and 91.88 ± 19.14g carbohydrate.

10.3.2. 7hr plasma glucose and insulin

Mean plasma glucose and insulin concentrations during the three trials are illustrated in figures 10.3 and 10.4. There were significant between trial differences in glucose and insulin responses across the 7hr observation period for glucose (P<0.001) and insulin (p<0.001). In unadjusted GEE models tAUC for glucose for the whole trial day was significantly lower in both the SIT-WALK and SIT-STAND trials compared to SIT-ONLY. Following adjustment for body weight, baseline glucose and pretrial MVPA, tAUC for glucose remained 10% lower in SIT-WALK (3.94 ± 0.16 mmol/l/hr, P<0.001) and 8% lower in SIT-STAND (4.05 ± 0.18 mmol/l/hr, P<0.001) compared to the SIT-ONLY intervention (4.36 ± 0.23 mmol/l/hr). In unadjusted GEE models tAUC for insulin for the whole trial day was significantly lower in the SIT-WALK than in the SIT-STAND or SIT-ONLY trials. Following adjustment for covariates tAUC for insulin remained 20% lower in the SIT-WALK intervention (223.26 ± 45.84 pmol/l/hr) than in SIT–ONLY (292.5 ± 62.64 pmol/l/hr, P<0.001). There was no significant difference in tAUC for insulin between SIT-STAND and SIT-ONLY interventions (P=0.50).

10.3.3. Post OGTT period. 0-3hrs

Individual time point analysis showed that following adjustment for body weight, pre-trial MVPA and pre-OGTT glucose, plasma glucose was significantly lower in the SIT-WALK trial than the SIT-ONLY intervention at 30 minutes (peak), 60, 90, 120 minutes (P<0.05 for all). Following adjustment for covariates plasma insulin was significantly lower in the SIT-WALK than in the SIT-ONLY trial at 30 minutes (peak), 60, and 90 minutes. Significant between trial differences were observed in Matsuda ISI (P=0.006). In unadjusted GEE models Matsuda ISI was significantly greater during the SIT-WALK trial than during SIT-ONLY. As illustrated in figure 10.5 following adjustment for covariates, Matsuda ISI during the SIT-WALK trial (6.33 ± 0.53,) remained 12% higher than SIT-ONLY (5.62 ± 0.43, P=0.005). No significant differences were observed between the SIT-STAND and SIT-ONLY trials (P=0.9).

Significant between trial differences were also observed in post-OGTT iAUC for glucose (P=0.001), and insulin (P<0.001). In unadjusted GEE models positive incremental area under the curve for both glucose and insulin for the 3 hr period after the OGTT was significantly lower in the SIT-WALK trial than during the SIT-ONLY trial. As shown in figure 10.6, following adjustment for pre-OGTT plasma glucose and pre-trial MVPA, post OGTT iAUC for glucose during the SIT-WALK trial (0.56 ± 0.09 mmol/l/hr) was 27% lower than in the SIT-ONLY trial (0.73 ± 0.13 mmol/l/hr, p=0.001). No significant differences were observed between SIT-STAND and SIT-ONLY interventions (P=0.99).

As shown in figure 10.7 following adjustment for covariates post OGTT iAUC for insulin during the SIT-WALK trial (193.20 ± 18.3 pmol/l/hr) was 22 % lower than in the SIT-ONLY trial (239.04 ± 20.16 pmol/l/hr, *P*=0.001). No significant differences were observed between SIT-STAND and SIT-ONLY interventions (*P*=0.99).

10.3.4. Post meal period. 3-7hrs

Individual time point analysis showed that following adjustment for covariates there was a significant reduction in both plasma glucose and insulin concentrations at 240 minutes (1 hr post prandial) in SIT-WALK compared to SIT-ONLY (figure 10.6).Significant between trial differences were observed in post meal iAUC for glucose (*P*=0.01) and insulin (*P*<0.001). In unadjusted GEE models iAUC for glucose was significantly lower in both SIT-WALK and SIT-STAND compared to SIT-ONLY. Incremental AUC for post meal insulin was significantly reduced in SIT-WALK compared SIT-ONLY trials.

Following adjustment for covariates the reductions in post prandial iAUC for glucose in the SIT-WALK trial (0.55 ± 0.08 mmol.l.hr) and SIT-STAND trial (0.52 ± 0.06 mmol.l.hr) compared to SIT-ONLY (0.60 ± 0.06 mmol.l.hr) were attenuated to null (*P*>0.05).

Following adjustment for covariates post prandial iAUC for insulin during the SIT-WALK trial (91.92 ± 9.6 pmol/l/hr) was 19% 26% lower than in SIT-

ONLY (116.52 ± 13.08 pmol/l/hr, *P*=0.001). No significant differences were observed between SIT-STAND and SIT-ONLY trials (p=0.53). Fully adjusted means for post meal iAUC for glucose and insulin are shown in figures 6 and 7.

10.4. Discussion

Periods of prolonged sitting have been consistently associated with increased risk for metabolic diseases, but the underlying biological mechanisms are poorly understood. Observational and experimental studies to date have reported adverse associations between sitting time and health outcomes but are unable to conclude with any certainty that the risk is associated with sitting itself or with low energy expenditure. This study aimed to establish whether glucose metabolism would differ during a 7hr day of sustained sitting compared to 7hr days when sitting was interrupted without increased energy expenditure (standing only) and with bouts of physical activity, in a sample of males practising little habitual physical activity. This is the first study to examine the effect of these differing patterns of sitting on glucose and insulin following both an oral glucose tolerance test and a mixed test meal, and the first to examine the effects of intermittent standing as well as light intensity walking. It was observed that over a 7hr day, regularly interrupting sitting with short bouts of light intensity walking significantly improved insulin sensitivity, as defined by Matsuda, and reduced glucose and insulin responses during the post OGTT and insulin during the post meal observation periods compared to a day when sitting was sustained.

The present findings are consistent with those of Dunstan et al[273] and Peddie et al[275] who observed that when compared to periods of sustained sitting, interrupting sitting with regular bouts of walking reduced postprandial glucose and insulin. In the current study there was an 11% improvement in insulin sensitivity for the 3 hr post OGTT period during the SIT-WALK intervention compared to the SIT-ONLY trial. During this period iAUC for both glucose and insulin were significantly reduced during the SIT-WALK trial. During the post prandial period iAUC for insulin was also significantly lower in SIT-WALK compared to SIT-ONLY. These findings are also consistent with a number of previous studies which have observed a beneficial effect of acute light intensity walking on glucose and insulin after glucose ingestion.[387-389] Manohar et al[387] observed that very light intensity walking (at 1.9km.hr for bouts of around half an hour) during the postprandial period (following ingestion of mixed test meal containing 50g of carbohydrate) significantly reduced iAUC for glucose compared to inactivity in a sample of healthy (54% reduction) and diabetic (60% reduction) middle aged males over a 3hr observation period.

The magnitude of the differences in both post-OGTT glucose and insulin iAUC between SIT-WALK and SIT-ONLY trials (25% and 22% respectively) are more modest than those observed by Dunstan et al [273] (who reported a lowering of 30% for glucose and 23% for insulin iAUC) and Peddie et al [275] (who reported a lowering of 39% for glucose and 26% respectively for insulin iAUC). Both the current study and that by Dunstan et al examined middle-aged adults who did not exercise regularly, although the sample in the current study were far leaner (mean BMI 26.21 ± 4.14kg.m^2 compared to 31.2 ± 4.1kgm^2). As adiposity will

influence both fasting glucose and insulin sensitivity and is associated with insulin resistance [390-392] it is conceivable that this may explain the differences in effect size between the two studies to some degree. However, the studies by Peddie et al and Stephens et al report similar observations in younger and leaner samples than that employed in the current study(25.9 ± 5.3 yrs, BMI 23.6 4.0 $kg.m^2$, and 26.1 ± 4.5 yrs, BMI 23.6 ± 3.0 $kg.m^2$,respectively). In addition, while participants in the current study and that of Dunstan et al did not engage in regular physical activity, participants in the studies by Peddie et al and Stephens et al were described as recreationally active. These findings collectively suggest that differences in patterns of sitting and light intensity activity may be able to significantly influence metabolic parameters across age groups, BMI classifications, and habitual physical activity levels.

It is also possible that the difference between the present findings and those of Dunstan et al are attributable to differences in the carbohydrate quality and content in the test drink employed. Dunstan et al used a 200ml test drink consisting of 75g of glucose (as in the present study) and importantly, 50g of fat. The authors state that the inclusion of the fat content was in order firstly to simulate a mixed meal, and secondly to slow gastrointestinal emptying and spread the glucose and insulin responses over a longer period.[273] By slowing the rate of glucose absorption and the peak in blood glucose the incremental area under the concentration time curves may have been inflated relative to those in the present study.[393]

As discussed previously a fundamental question in determining the independent effect of sitting behaviour on health risk is whether the posture of sitting per se is detrimental or whether time spent sitting is a proxy for low daily energy expenditure which in turn represents the risk behaviour. To conclude that the posture of sitting exerts an independent detrimental effect on health, differences in energy expenditure between experimental groups need to be ruled out. The current findings, in agreement with previous studies,[273] [274] suggest that interrupting sustained periods of sitting with bouts of increased energy expenditure, in the form of light intensity walking, benefits glucose metabolism and thus metabolic health. Stephens et al [274] reported that differences in energy balance may account for a proportion of the observed differences in insulin action between a day of sustained sitting and a day of minimal sitting but not all, and concluded that factors other than energy expenditure are involved in the detrimental impact of sitting. The inclusion of the SIT-STAND trial was a novel aspect of this study and was designed to examine whether a change in posture (from sitting to standing) in the absence of a change in energy expenditure (steady state energy expenditure values did not differ between sitting and standing in the present sample) would also benefit glucose metabolism relative to sitting only. Evidence from animal studies suggests that it might be beneficial to metabolic health to interrupt the inactivity of postural muscles that is evident during prolonged sitting.[23] [24] Matsuda ISI during the SIT-STAND intervention did not differ significantly from the SIT-ONLY intervention and iAUC for glucose and insulin during this period was also not significantly different between SIT-STAND and SIT –ONLY trials. Post meal insulin did not differ significantly between SIT-STAND and SIT-ONLY and following adjustment for covariates the slight reduction in postprandial glucose

iAUC during both the SIT-WALK and SIT-STAND intervention did not reach statistical significance. If it is true that simply altering posture has no significant effect this suggests that interruptions to sitting must be of a certain energy expenditure in order to elicit a beneficial effect. This would support the findings of Stephens et al[274] who observed that when the reduction in energy expenditure during sitting was matched with a reduction in energy intake so as to prevent any energy surplus, the difference in insulin action between a day of sustained sitting and one of light intensity activity was attenuated.

10.4.2. Possible mechanisms

As discussed, potential mechanisms to explain the differential effects of sitting patterns on glucose and insulin regulation may be related to energy expenditure, to the specific actions of sitting, or both.[274] The lowering of both glucose and insulin during the post OGTT period by repeated bouts of low intensity walking suggests both increased insulin sensitivity and improved action of insulin, requiring less insulin secretion to compensate for the glucose excursion and regulate glucose metabolism. This is evidenced by the difference in the Matsuda index. There were no between trial differences in glucose iAUC during the post meal period although the fact that plasma insulin iAUC was significantly lower in SIT-WALK than in the SIT-STAND or SIT-ONLY interventions again suggests that intermittent low intensity walking might reduce the volume of insulin required to clear a given volume of glucose from circulation (i.e. improved insulin sensitivity).

A possible mechanism for this effect may relate to between trial differences in the rate of contraction of muscles involved in ambulation. During the SIT-ONLY trial where participants did not stand or walk and could rely on the chair back for postural support, the rate of contraction would be very low. This would increase, particularly in postural muscles, during the SIT-STAND intervention but would be far higher in the SIT-WALK intervention. It has been established that acute muscle contraction increases insulin stimulated glucose disposal in both healthy and insulin resistant skeletal muscles.[394 395] Muscular contraction and insulin robustly activate glucose transport from blood plasma by independently activating the translocation of GLUT-4 transporter molecules from an intracellular location to the plasma membrane. In insulin sensitive muscle, muscular contraction and insulin action have an additive effect on the rate of glucose clearance from the circulation into the muscle tissue.[396] The presence of muscular contraction would therefore necessitate, as apparent in the current findings, a smaller volume of insulin to regulate a given volume of glucose. After the acute effects of muscular contraction and GLUT-4 translocation are gone, insulin sensitivity remains elevated.[378 397] It has been suggested that frequent short bouts of activity may maintain an increased permeability of muscle cells to glucose, and maintain Glut-4 in a position within a cell where it can be readily recruited to the cell surface in response to further activity.[276]

Energy surplus, established over a number of days, has also been shown to adversely affect insulin sensitivity[344 345 398 399] and this may potentially contribute to the effects of a more chronic exposure to sustained sitting on

health. While an energy surplus may have contributed to higher insulin concentrations during the SIT-ONLY intervention it is more likely that this is due to the absence of the glucose clearing effect of muscular contraction evident in the SIT-WALK intervention, necessitating a higher volume of insulin to regulate plasma glucose concentrations. In any case, the absence of direct calorimetry in the present study, means that it is impossible to state: 1) that the OGTT and the test meal were sufficiently calorific to create an energy surplus, and 2), that the energy expenditure of the walking bouts during the SIT-WALK intervention (particularly in the early part of the observation period where the first between trial differences were observed) was sufficient to redress this energy surplus.

Acute muscle contractions that occur before or during stimulation of insulin secretion by glucose, can increase insulin sensitivity in both healthy and insulin resistant individuals, [400] and this has promise as an explanatory mechanism for the present findings. This has wider implications for research into sedentary behaviour as it suggests that low levels of movement or energy expenditure, rather than sitting itself, may be the underlying factor in the observed associations between high volumes of sitting and disease outcomes. In this way, it would seem that the influences of sitting and physical activity on health are not truly independent as postulated previously. This idea is supported by recent observational evidence. Maher and coworkers[375] observed significant (if small in magnitude) associations between accelerometer defined sedentary time and 11 cardiometabolic biomarkers (including fasting glucose and insulin, 2hr post-challenge plasma glucose and Homeostasis Model Assessment steady state Beta cell function and insulin sensitivity [HOMA %β and HOMA %S])

following adjustment for covariates including minutes of daily MVPA. However when MVPA was replaced in the analytical model by total physical activity accelerometer counts (including light intensity activity) all associations were attenuated with nine out of the eleven attenuated to null (including all markers of glucose and insulin regulation) and the other two only demonstrating minute effects. This suggests that residual confounding due to incomplete adjustment for physical activity may contribute to observed associations between sitting and metabolic risk,[375] and that differences in physical activity behaviour, including light intensity activity which makes up the majority of adults waking hours, might be more important.

However the exact underlying biological pathways remain unclear.[396] It also must be considered that if the beneficial effects of light intensity walking breaks on insulin sensitivity are attributable solely to the contraction of the large muscle groups it is not inconceivable that repeated transitions from sitting to standing or standing for very prolonged periods may also influence insulin sensitivity. This is evidenced in part by the study by Thorp et al[377] who observed that alternating 30 minute bouts of sitting and standing had a modest beneficial effect on circulating glucose levels. However, as discussed, the authors state that light ambulatory activity was permitted during these standing periods which means it is impossible to attribute this benefit to standing only.

10.4.3. Clinical significance

Diabetes is an established independent risk factor for cardiovascular disease.[336] [337] However there is a growing body of evidence that insulin resistance and hyperglycemia in the absence of diabetes are associated with endothelial dysfunction[401] [402] and therefore the atherosclerotic process may begin earlier in the spectrum of insulin resistance.[403] The magnitude of the excursion in plasma glucose from baseline during a postprandial period provides an effective marker of CVD risk.[404] [405] Postprandial hyperglycemia is associated with endothelial dysfunction, increased intima-media thickness (IMT) and as well as a higher prevalence of atherosclerotic plaques of the common carotid arteries, suggesting that mild to moderate postprandial hyperglycemia is involved in the development of early atherosclerosis.[406-408] There is evidence that the pathogenic molecular mechanism that underlies glucotoxicity involves the generation of oxidative stress which not only causes microvascular damage[409] but also platelet activation and the generation of thrombin which contribute to the progression of atherosclerosis. Intervention studies have demonstrated that the blunting of postprandial spikes has a direct beneficial effect on inflammation and endothelial function [410] and IMT.[410] [411]

In the present study both peak and 2 hr glucose values were significantly lower in the SIT-WALK than the SIT-ONLY trial, as was the post-OGTT iAUC for glucose and for insulin which suggests that interrupting sustained sitting with physical activity of at least light intensity may already impact and reduce CVD risk. Examination of data from 3370 participants from the Framingham Offspring Study suggested that reductions in 2 hr glucose of 2.1 mmol/l were associated

with reduction in 4 yr risk for CVD events of up to 42% (HR 1.42, 95% CI 1.17, 1.72).[412] While the between trial differences in glucose responses were smaller than this in magnitude (mean difference in plasma glucose at 2hrs was approximately 1mmol/l, SIT-ONLY vs SIT-WALK), and also smaller than those observed by Dunstan et al,[273] it is reasonable to suggest that this difference could contribute to a clinically significant reduction in cardiovascular risk. Similar small differentials in postprandial glucose seen in response to pharmaceutical interventions have been linked to reductions in oxidative stress, circulating adhesion molecules and improved endothelial function in non-diabetic subjects[413] [414] all of which are important clinical markers of cardiovascular disease risk.[415] In addition while the reductions in post meal glucose observed in the SIT-WALK trial compared to SIT-ONLY, did not reach statistical significance there was a significant reduction in insulin iAUC in the SIT-WALK intervention indicating that a lesser volume of insulin was required to clear a given volume of glucose. These findings therefore suggest that interrupting sitting with light intensity walking improves insulin sensitivity following both a high glucose load (OGTT) and a mixed test meal.

The present findings are significant as they suggest that small modifications in behaviour i.e. walking at a light intensity three times per hour can be of benefit to individuals who engage in prolonged periods of sustained sitting. Given the ever increasing prevalence of sitting in modern society and the volumes of daily sitting undertaken by the English population on a day to day basis (9.3) these findings are of direct relevance and could provide an early

template for interventions to reduce the adverse health consequences of sustained sitting or very low levels of physical activity.

Previous experimental studies have suggested that altering the posture of sitting by any means can offset the detrimental effects of sitting. In this study it would appear that muscular contraction and an increase in energy expenditure is required to obtain beneficial changes in glucose and insulin rather than simply a change in posture. The findings of the current study suggest that the underlying mechanisms relate to muscular contraction and energy expenditure and that a change in posture in the absence of an increase in energy expenditure is not sufficient to improve markers of metabolic health. Future studies involving similar protocols completed in direct calorimeters (although perhaps lacking in ethological validity) would be hugely beneficial. In this way it would be possible to directly examine the contribution of total energy expenditure to the observed effects of different interruptions in sustained sitting. The observed beneficial effect of repeated light intensity activity is encouraging, and further experimental studies are needed involving manipulation of the frequency, duration and intensity of light intensity activity bouts in order to establish a dose response association and to identify a pattern which might be most beneficial.

10.4.4. Strengths and limitations

The present study utilised participants with a broad range of ages (30-65 yrs). Participants were included who did not perform regular volitional moderate

to vigorous exercise in order to eliminate the potential confounding effect of detraining which has been observed to reduce insulin sensitivity. In addition participants were asked to refrain from any activity and to be as inactive as possible for 48 hrs prior to each trial day and any residual confounding effects of prior physical activity were minimised by adjusting for accelerometer determined pre-trial activity in the GEE models.

This is the first study to compare the effects of different sitting patterns on insulin sensitivity measured during a standard glucose tolerance test, and during a postprandial period. The examination of both fasting and postprandial glucose and insulin responses using OGTT and a mixed test meal is a significant strength of this study. A number of previous studies which have examined the differential effects of exercise and physical activity patterns on insulin sensitivity have measured skeletal muscle insulin sensitivity using the euglycemic-hyperinsulinemic clamp (EHC) technique. This involves infusing insulin at a constant dose to maintain insulin levels while modifying glucose infusion rates to maintain euglycaemia. A higher glucose infusion rate to maintain euglycaemia is indicative of greater skeletal muscle insulin sensitivity. This method, despite being regarded as a gold standard method for measuring insulin sensitivity, does not reflect postprandial responses that humans encounter day to day. Both glucose and insulin peak and fall during the postprandial period which is very different to the steady state glucose and insulin infusion during the EHC.[400] In this way the EHC technique excludes the contribution of pancreatic β-cell function. Conversely, postprandial changes in circulating glucose and insulin are determined by a range of factors including

skeletal muscle and hepatic insulin sensitivity, β-cell function, gastric filling and emptying, and intestinal absorption.[416] The study was designed to examine the effect of different sitting patterns on circulating glucose and insulin during the kind of working day and office environment experienced by many members of the UK population. The assessment of natural postprandial responses is also central to the study's ethological validity.

This design of the sitting interruptions is also a strength of this study. The walking pace was selected to be of light intensity (the mean steady state energy expenditure for this sample when walking at 3.2 km/hr was 2.7 METs). This allowed the examination of the effect of intermittent activity which would not contribute towards adherence to current physical activity recommendations[13] which state that activity (30 minutes) of at least moderate intensity (3METs and above) should be accumulated. This is also the first study of its type to examine the effect of intermittent standing. As discussed this allowed the separate examination of a change in posture and changes in energy expenditure on glucose and insulin.

The current study is not without limitation. Firstly it examined the acute effects of prolonged versus interrupted sitting over a 7hr observational period and therefore caution must be taken when extrapolating the findings to longer term exposures. A logical next step would be to extend these studies to examine the differential effects of exposure to different patterns of sitting, standing and walking over longer periods.

This study employed regular and consistent activity interruptions during days of sustained sitting. A pattern this regimented would clearly not reflect the irregular sporadic nature of transitions between sitting, standing and ambulation for an adult in a free-living situation. However while this pattern may not accurately represent free-living behaviour its employment does allow valuable insight into the potential benefits of such brief regular activity breaks. In addition interrupting sitting time in this way could be feasible in workplace settings where adults sit for prolonged periods [273 417 418] and could therefore form the basis for future interventions to improve employee well-being. A liquid test meal was used to ensure accurate standardisation of macronutrient delivery to each participant according to their body mass. This of course would not reflect participant's normal eating habits. While there is no reason to think that the response to liquid meals would be different, ideally postprandial responses would be assessed following consumption of foods more regularly consumed by the target population.

In order to isolate the differential effects of the three trials on insulin sensitivity every effort was made to ensure pre-trial diet and physical activity patterns did not differ between the three experimental conditions. Participants were instructed to refrain from any volitional physical activity or exercise behaviour other than essential day to day tasks and to try and ensure they remained as inactive as possible for the preceding 48 hrs. Suggested measures included using motorised transport were possible and using lifts rather than stairs etc. While participants wore accelerometers as instructed and there was very little non-wear time, there was of course some variation in pre- intervention

physical activity. This was adjusted for in the multivariate GEE models. However as it was not possible to undertake full dietary analysis on food and drink consumed before the trial we were reliant on participants replicating their intake across all three trial days. While this method has been used previously in a similar study, [275] and no participants reported any problems with this requirement, the absence of an objective measure means we cannot rule out some variation in pre-trial consumption. However, in order for this to bias the present findings this variation would need to be systematically different between trials and this seems unlikely. As participants were not aware which trial they would be undertaking until they arrived (with the obvious exception of the final trial) it is more likely that this variation would have been random which would simply have attenuated any true effect towards null.

10.5. Conclusions

The present findings suggest that interrupting sustained sitting with brief light intensity walking bouts significantly benefits insulin sensitivity in middle aged males. These findings lend support to experimental studies which have observed beneficial effects of interrupting sitting time with bouts of walking on a number of metabolic parameters. Encouragingly, these findings suggest that fairly minor behavioural changes (three 2 minute interruptions per hour) may benefit individuals who spend large proportions of their day sitting. As regular standing breaks did not elicit the same benefit it seems likely that the underlying mechanism relates to the increase in muscular contraction involved in ambulation. The prevalence of sitting behaviour in modern society makes these findings all the more significant and continued research is required to enhance

our understanding of the acute and chronic metabolic consequences of sustained sitting (or low levels of light intensity physical activity). Further experimental work is required to examine the differential associations between patterns of sitting and light intensity activity with other metabolic parameters in both healthy and clinical populations over a range of age groups. Further research is also necessary to conclusively determine whether frequent changes in posture (transitions from sitting to standing) are sufficient to elicit any effects or whether the metabolic benefits are linked to the acute cumulative energy expenditure of sitting interruptions.

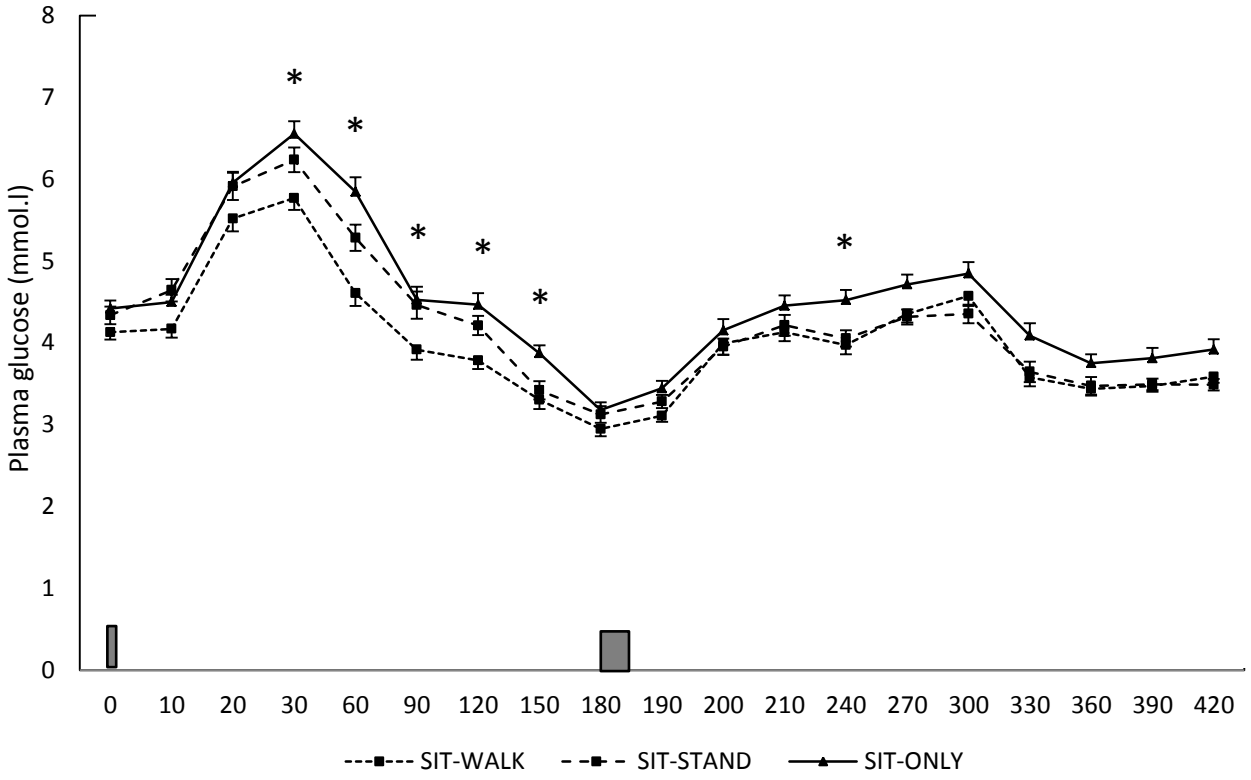


Figure 10.3. The effect of three trial conditions (SIT-WALK, SIT-STAND, and SIT-ONLY trials) on 7hr plasma glucose concentrations (mmol.l). Data represent mean ± SEM. Significant between trial differences at each time point were examined using GEE models adjusted for pre-trial MVPA and baseline values.
▯ = OGTT and mixed test meal. * = significant difference ($p<0.05$) between SIT-WALK and SIT-ONLY trial, † = significant difference ($p<0.05$) between SIT-STAND and SIT-ONLY trials

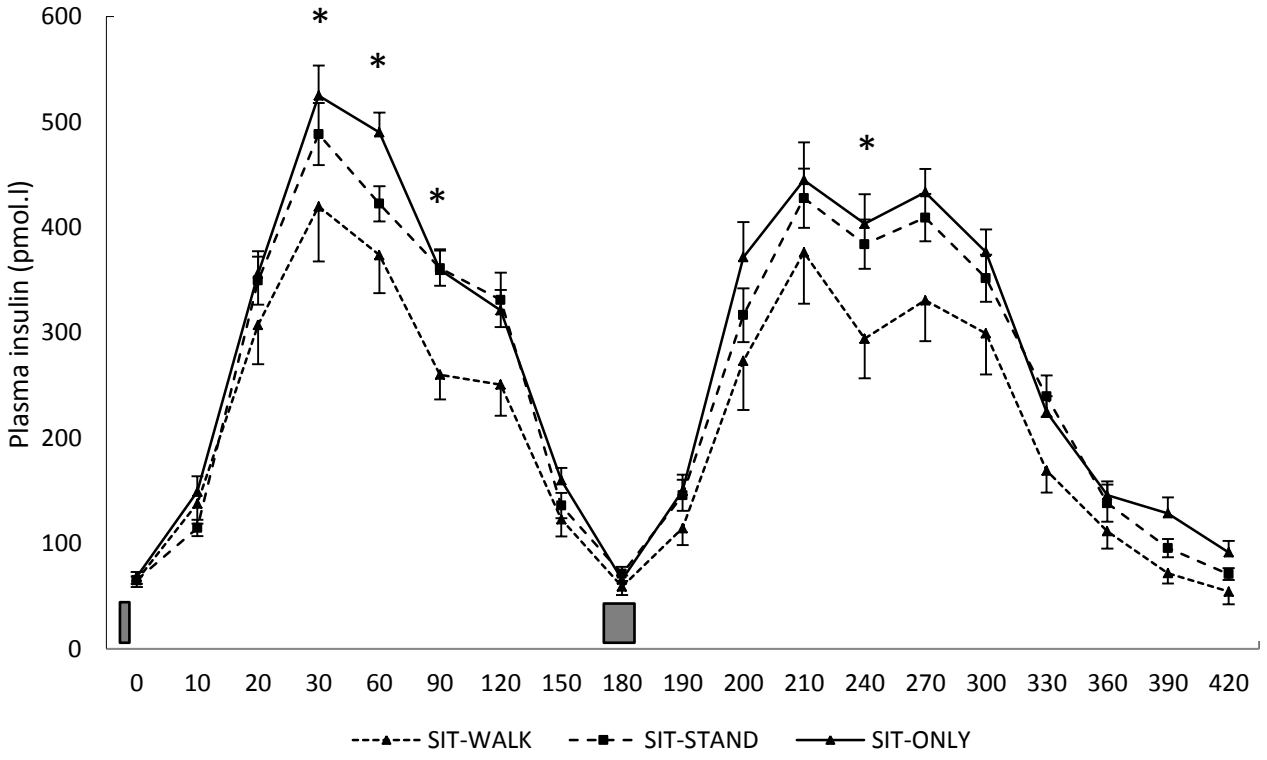


Figure 10.4. The effect of three trial conditions (SIT-WALK, SIT-STAND, and SIT –ONLY trials) on 7hr plasma insulin concentrations (pmol.l). Data represent mean ± SEM. Significant between trial differences at each time point were examined using GEE models adjusted pre-trial MVPA and baseline values.

▮= OGTT and mixed test meal. * = significant difference ($p<0.05$) between SIT-WALK and SIT –ONLY trial, † = significant difference ($p<0.05$) between SIT-STAND and SIT-ONLY trials

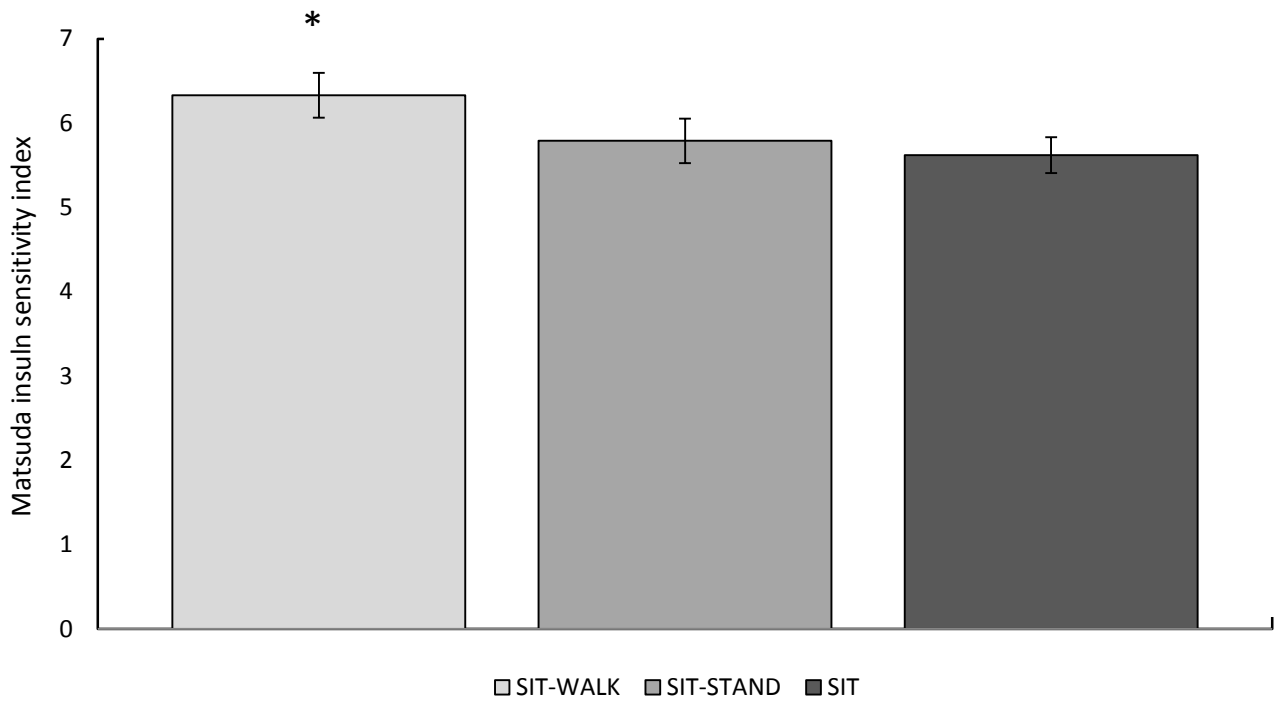


Figure 10.5. Matsuda insulin sensitivity index (M-ISI) for three trial conditions (SIT-WALK, SIT-STAND, and SIT-ONLY). Data represent adjusted means ± SEM. Significant between trial differences were examined using GEE models adjusted for pre-trial MVPA.
* = significant difference ($p<0.05$) between SIT-WALK and SIT-ONLY trials, † = significant difference ($p<0.05$) between SIT-STAND and SIT-ONLY trials

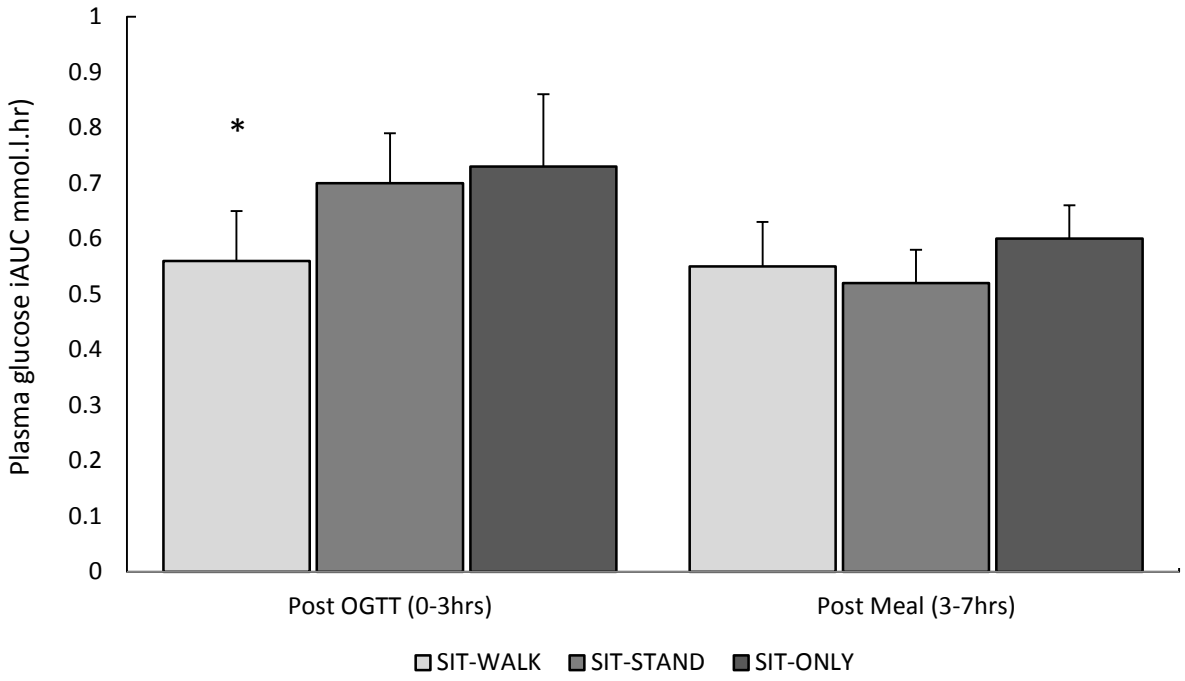


Figure 10.6. Plasma glucose iAUC (mmol/l/hr) for three trial conditions (SIT-WALK, SIT-STAND, and SIT-ONLY) for post OGTT (0-3hrs) and postprandial (3-7hrs) periods. Data represent adjusted means ± SEM. Significant between trial differences were examined using GEE models adjusted for pre-trial MVPA. * = significant difference ($p<0.05$) between SIT-WALK and SIT-ONLY trial, † = significant difference ($p<0.05$) between SIT-STAND and SIT-ONLY trials

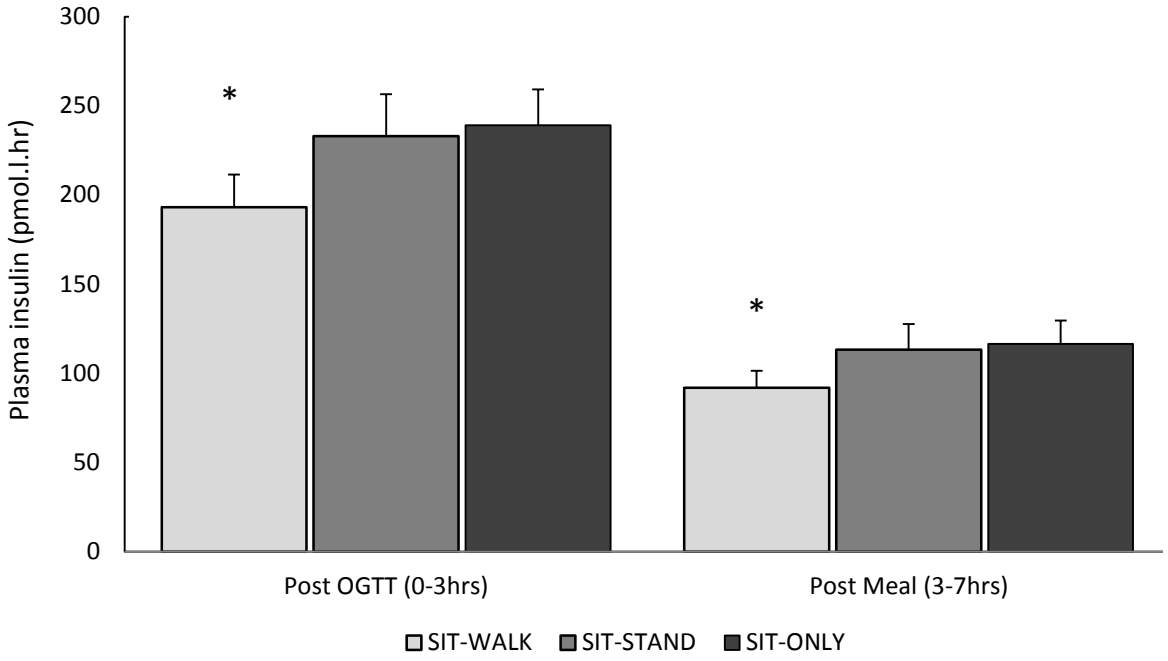


Figure 10.7. Plasma insulin iAUC (pmol.l.hr) for three trial conditions (SIT-WALK, SIT-STAND, and SIT-ONLY) for post OGTT (0-3hrs) and postprandial (3-7hrs) periods. Data represent adjusted marginal means ± SEM. Significant between trial differences were examined using GEE models adjusted for pre-trial MVPA. * = significant difference ($p<0.05$) between SIT-WALK and SIT-ONLY trial, † = significant difference ($p<0.05$) between SIT-STAND and SIT-ONLY trials, ‡ = significant difference ($p<0.05$) between SIT-WALK and SIT-STAND trials

Chapter 11

General discussion

11.1. Primary aims and statement of principle findings

This thesis aimed to address three main research questions: What is the health risk associated with sitting? Who might be most at risk? and what biological mechanisms underpin the risk associated with prolonged periods of sitting? In order to address these questions six investigations were undertaken using a variety of study designs including cross-sectional and prospective observational studies and laboratory based experiments that featured a range of analytical techniques. The main findings of this thesis suggest that sitting itself does not pose a risk to health (specifically, mortality, cardiovascular disease, diabetes and obesity) that is truly independent of physical activity. Previous observational studies have reported associations between high volumes of sitting and a number of health outcomes, although there are important issues regarding the accurate measurement of sitting behaviour in observational studies which are currently unresolved. These studies might also have been influenced by the confounding effects of total daily energy expenditure or prior obesity. The observational findings presented in this thesis (chapters 5-8) are supported by experimental evidence (chapter 10) which demonstrates that interrupting periods of sitting, (suggested by previous observational studies to elicit benefits to metabolism) only benefitted glucose and insulin regulation when the interruptions featured a meaningful change in energy expenditure.

These findings are potentially very significant in the context of the developing field of sedentary behaviour research. It had been previously postulated that sitting represents a risk to health that is independent of, and in addition to, only achieving low levels of physical activity. If this were true it would represent a very significant public health problem given the increasing opportunities for sitting in almost all aspects of 21st century society. The present findings suggest low levels of light intensity activity might be the true risk and that high reported levels of sitting may simply be indicative of this. However, much work is required to improve our understanding of the complex relationship between sitting, physical activity (particularly that of light intensity) and adiposity which requires improvements in the accuracy of the assessment of both sitting and physical activity in population based research. Also, further experimental studies that manipulate patterns of sitting and light intensity activity are required to assess the underlying metabolic changes associated with different patterns of each behaviour and which might contribute to differences in disease risk.

11.2. What is the risk? Associations of sitting and health

The first aim of this thesis was to examine the risk to health associated with high volumes of sitting. This aim was addressed in chapters five to eight. Chapters five, six and seven examined the prospective associations between sitting and mortality (from all causes and separately from CVD and CHD), incident cardiovascular disease (including first non-fatal MI and first angina episode) and incident type II diabetes. Chapter eight examined the cross-sectional and prospective associations between sitting time and prevalent and

incident obesity and also took the novel approach of directly examining the association between prior obesity and subsequent sitting time.

As described in chapter 3 there are a number of cross-sectional and prospective studies which have examined associations between indicators of sitting time and health outcomes. Previous prospective studies have observed positive associations between all-cause mortality and TV viewing,[53 55 70] travelling by car[153] and total daily sitting time,[149 152 153 305 306] as well as associations of CHD and CVD mortality with sitting time.[55] The prospective associations between sitting and type II diabetes is also fairly consistent in the existing literature. TV viewing has been repeatedly observed to predict incident diabetes[56 81 190-192] while positive associations have also been observed with occupational sitting time.[191] The existing evidence for associations between sitting and cardiovascular disease is more mixed, although the range of different cardiovascular outcome measures examined does limit comparability between studies. Nevertheless prospective studies have observed an increase in risk of cardiovascular events with increased TV viewing [65 67 164] and sitting time.[165-167] There is a wealth of cross-sectional evidence linking indicators of sitting time with markers of obesity and adiposity[206 289] although prospective evidence is mixed. While a number of studies have demonstrated prospective associations between sitting and obesity or increases in bodyweight and adiposity[66 191 217] others have found that while sitting does not predict the development of obesity, prior obesity does predict sitting time.[83 250]

The analyses described in chapters five to eight enhances the current evidence base by taking the novel approach of examining the associations between these four well researched health outcomes with five sitting indicators, including both total and domain specific sitting time, in the same population. The five sitting indicators employed in these analyses were: Sitting at work, TV viewing, non-TV leisure time sitting, total leisure time sitting, and total sitting from both work and leisure. This is an important methodological development for a number of reasons. Firstly, existing observational evidence suggests that the pattern of sitting (in addition to the overall volume of sitting) may be an important determinant of the magnitude of the associations with health outcomes.[109] Logically different sitting behaviours that occur in different contexts will vary in their frequency duration and pattern (the number of interruptions in a given period of sitting), have different correlates and determinants and may be influenced by different sources of confounding. They should therefore be examined separately in terms of their associations with health outcomes, although very few studies examine more than one specific sitting behaviour.

In chapter 5 mortality risk did not differ significantly across categories of TV viewing, sitting at work, non-TV leisure time sitting, total leisure time sitting and total sitting from both work and leisure time over fifteen years of follow-up. Similarly, in chapter 6 risk of incident cardiovascular disease (cardiovascular events including first non-fatal MI, and first angina episode) did not differ significantly across categories of the five sitting indicators over 10 years of follow-up. In chapter 7, TV viewing time and total sitting time were associated

with an increased risk of diabetes following adjustment for covariates including daily MVPA. However, following further adjustment for BMI the associations with TV viewing time and total daily sitting time were attenuated to null. No associations were observed with sitting at work, non-TV leisure time sitting or total leisure time sitting. In chapter eight there were no observed cross-sectional or prospective associations between any of the five sitting indicators with obesity. However, when occasions of obesity prior to baseline were modelled as an exposure variable with sitting at baseline as an outcome, prior obesity did predict both TV viewing and leisure time sitting. The differential associations observed between sitting indicators with incident diabetes (prior to final adjustment for BMI) and obesity (the association between antecedent obesity and TV viewing time only) is testament to the importance of examining individual sitting behaviours that occur in different contexts separately. These associations would have been missed if this novel methodology had not been considered and instead a single sitting indicator or a measure of total sitting only was employed.

The absence of prospective associations between sitting indicators and health outcomes in the fully adjusted models is inconsistent with a number of previous prospective studies which have demonstrated positive associations between sitting indicators and disease risk. There are however a number of potential explanations for these findings which relate to differences between cohorts and important methodological considerations.

11.2.2. Differences in reported volume of sitting time between cohorts

It is possible that the absence of associations between sitting and health outcomes in this thesis is due in part to the relatively low levels of daily sitting reported by the Whitehall II cohort. As discussed previously, 73% of the sample in the analysis of sitting and mortality risk in chapter 5 would have fallen into the lowest tertile for TV viewing described in analysis of data from the EPIC-Norfolk study by Wijndaele and co-workers,[55] and only 7% in the top tertile. Other studies of mortality risk have also reported far higher sitting values than those observed in the Whitehall II data.[150] The total sitting time values reported in the analysis of sitting and CVD risk in chapter 6 were lower than those reported in two previous prospective studies where significant associations were observed with CVD risk, but almost identical to another prospective study where no association was observed. The analysis in chapter seven is the first to look at prospective associations between total sitting and obesity. Previous prospective studies have focussed on associations with TV viewing and only one reported similar volumes of TV viewing to those reported in the Whitehall II cohort.[56] TV viewing is far higher in three cohort studies from the US[190-192] including the study by Krishnan which observed a higher risk of development of diabetes in participants (well over half of the study sample) who reported watching more than 5 hrs of television per day (>35 hrs per week). Of the Whitehall II participants examined in chapter seven around 72% reported watching less than 16 hrs of television per week. It is therefore possible that sitting behaviour within the Whitehall II cohort is insufficient to see associations with disease outcomes. However it must be acknowledged that significant differences in mortality risk have been observed for as little as 1 hr differences in daily sitting[53 55] even at low sitting volumes, suggesting that any associations

between sitting and disease risk in the present analyses should be evident even though mean daily sitting is relatively low.

11.2.3. The protective effect of walking

Another possible explanation for the absence of prospective associations between sitting and any of the health outcomes in the present analyses is the high volumes of walking reported in the Whitehall II cohort. As discussed previously this may reflect the commuting habits of London based employees. The public transport infrastructure in London is such that those working in the Whitehall offices of the British Civil Service are more likely to walk or stand (on buses or trains) than people residing in other areas of the country who may be more accustomed to commuting by car.[313] The mean (SD) daily walking time in the analysis groups from chapters five, six, seven and eight were 42.43 (±22.66), 46.70 (± 30.06), 42.73 (± 22.59) and 40.71 (± 20.83) mins/day which is considerably higher than the population average reported in the 2005 UK Time Use Survey (17 mins/ day).[314] A number of prospective studies have reported significant inverse associations between daily walking and risk for mortality (from all-causes[317] and from cardiovascular disease),[318] cardiovascular disease,[331] diabetes[191] and obesity.[191] Habitual active transport has been shown to reduce risk for mortality[315] and CVD[419] and active commuting has also been reported to moderate the association between TV viewing time and body mass index.[199 360] The pattern in which walking bouts are accumulated might also be important when considering a possible protective effect of walking within the Whitehall II cohort. The frequency and distribution of short walking bouts was not measured in the Whitehall II questionnaire and would be difficult to capture

accurately using self-report measures of walking. However given the experimental evidence detailed in chapter 10 of this thesis (and elsewhere)[273] [275] suggesting that repeated light intensity walking bouts may benefit metabolic health it is important to acknowledge the potential protective contribution of accumulating walking in this way. If Whitehall II participants not only undertake high volumes of walking but also walk intermittently, this could offer a degree of protection from the metabolic consequences of inactivity.

The volume of MVPA reported in the Whitehall II cohort is also high in comparison with previous cohort studies and it has previously been reported that London civil servants report higher levels of physical activity than the age-matched wider population.[319] It is therefore possible that the absence of prospective associations between sitting indicators and health risk in the current analysis is due to the protective effect of higher than average total daily energy expenditure within the study population. Statistical adjustment for the confounding effects of walking and MVPA is not helpful if the level of walking and activity is high for all levels of sitting. This protective effect of physical activity has been observed previously. Van der Ploeg and co-workers[153] observed that in people who were healthy at baseline only those who undertake no daily physical activity at all experienced an increase in mortality risk with higher levels of daily sitting. A number of other studies have also reported associations between sitting and health risk that are significantly attenuated in those who are physically active.[63 70 420]

11.2.4. The possible effects of residual confounding

Previous studies have concluded that sitting represents a risk to health that is unique and unrelated to physical activity. However it is possible that some of these observed associations are due to residual confounding. Possible sources of residual confounding in the current literature include differences in diet and snacking behaviour, incomplete adjustment for physical activity and failure to adjust for BMI or adiposity.

11.2.4.2. The confounding effect of snacking behaviour on the association between TV viewing and health

TV viewing, as a prevalent sedentary leisure time activity, is the most commonly researched sitting behaviour and has been repeatedly linked with disease risk.[53 65 191] In chapter seven, prior to adjustment for BMI there was a significant positive association between TV viewing and diabetes risk which was not evident in either non-TV leisure time sitting or sitting at work. As discussed previously it is possible that an association is more likely to be observed with TV viewing than with non-TV leisure time sitting because it can be recalled with more precision than other leisure time sitting activities which may happen more sporadically or for shorter periods. However TV viewing is also associated with snacking behaviour and particularly the consumption of energy dense foods and beverages,[74] possibly due to the influence of television food advertising. It has been reported that adults consume more food following exposure to food advertising regardless of how hungry they are.[74] Adjusting analyses of the association between TV viewing and waist circumference for food and beverage consumption during viewing has also been shown to significantly attenuate the

observed positive association.[321] The measurement of diet in observational studies is complicated and is often subject to substantial measurement error (both systematic and random)[421] which can affect the interpretation of nutritional information in epidemiologic studies.[422-424] This issue is further complicated by the need to examine the precise context surrounding food consumption. A randomised controlled trial of TV viewing in children observed that TV related snacking behaviour ceases when TV viewing stops.[425] This suggests that even adjusting analyses for overall snacking behaviour may miss the important co-occurrence of TV viewing with snacking. The absence of an accurate and reliable assessment of food intake means that it is impossible to rule out the contribution of snacking behaviour to the observed associations between sitting while watching TV and risk to health.

11.2.4.3. The confounding effects of energy expenditure

A key assertion from previous observational research examining either self-reported sitting or accelerometer defined sedentary time is that the detrimental effect of sitting is separate from and independent of the effect of physical activity. The persistent relationship between sedentary behaviour and disease outcomes or cardiometabolic deficits even when adjusted for physical activity has been cited as evidence of sedentary behaviour's unique health effect.[375] However the epidemiological analyses on which these assertions are based have tended to adjust for limited measures of physical activity such as duration of MVPA[53 190 191] or even subcomponents of MVPA such as leisure time physical activity.[62 152] There are a number of problems with this. Firstly, MVPA is not a homogenous entity. Moderate and vigorous activity have distinct

physiologic effects[426] and the proportions of moderate and vigorous activity that make up total MVPA would dictate the total energy expenditure for this period. Two people could therefore have the same recorded daily minutes of MVPA but might have vastly different activity profiles and total daily energy expenditures. Secondly, by adjusting for MVPA only, light intensity activity, which is also associated with health benefits[7] and which constitutes a far larger proportion of an individual's waking hours than MVPA, is ignored. When sedentary behaviour is defined by accelerometers (as time spent below a threshold movement value) it is not possible to adjust for time spent in MVPA and light intensity activity as collinearity would occur given that time spent in sedentary, light and moderate to vigorous activities would add up to 100% of wear time. However in the only paper to examine this methodological limitation, Maher and co-workers[375] observed that although accelerometer defined sedentary time was detrimentally associated with a number of metabolic markers following adjustment for covariates including daily minutes of MVPA, when MVPA was replaced in the analytical model with a measure of total daily physical activity (total accelerometer counts minus those accrued during sedentary behaviour) all associations were attenuated to null. This suggests that the observed associations between sitting and health outcomes may be due at least in part to differences in total daily energy expenditure or light intensity physical activity rather than sitting itself.

As discussed above, a number of studies have also presented results which also suggest that sitting behaviour and physical activity are not totally independent in their associations with health outcomes. Matthews et al[70]

observed that the association between sitting and mortality risk was strongest in those reporting low levels of moderate to vigorous physical activity while Pavey and co-workers[63] reported a significant interaction between sitting time and adherence to government physical activity recommendations in the association with all-cause mortality risk. In addition Chu and co-workers[420] observed an attenuated association of sitting time with metabolic syndrome, abdominal obesity, hypertriglyceridemia and hyperglycaemia in active compared to inactive participants (according to adherence to public health physical activity guidelines). Moreover associations with BMI and hypertension while significant in inactive participants were not significantly associated in active participants.

11.2.4.4. The confounding effects of adiposity

A number of epidemiological investigations into sitting behaviour and health have also failed to adjust for BMI or differences in adiposity. In chapter seven we reported that following adjustment for covariates including walking and MVPA there was a significant association between both TV viewing and total sitting time with risk for incident type II diabetes over 15 years of follow-up in Whitehall II participants. When analyses were additionally adjusted for BMI these associations were attenuated to null. Of the existing studies examining the prospective associations between sitting and diabetes risk only three included a marker of adiposity as a covariate. In all these studies the positive associations were significantly attenuated following adjustment for baseline BMI and in one study the association was attenuated to null. As described previously it has also been reported that markers of adiposity explained between 27.3% and 95.9% of the association between sitting time and a range of metabolic risk

markers.[252] These findings suggest that differences in health risk associated with sitting time might also be attributable in part to differences in adiposity.

It has been argued that obesity is solely on the causal path between sitting and increases in disease risk[54] and should therefore not be treated as a covariate. However analysis of the association between sitting and obesity in chapter eight not only showed that sitting was not predictive of future obesity but also that prior obesity was associated with higher levels of TV viewing and total leisure time sitting. A number of other prospective analyses have also observed reverse causality in the association between sitting and obesity[83 250] suggesting that obesity might be both a cause and a consequence of obesity. This is logical when it is considered that while spending large proportions of the day sitting displaces activities which require a higher energy expenditure and could therefore contribute to a positive energy balance and obesity, it is also very plausible that people who are overweight or obese may select leisure time activities or even occupations which require more sitting and less activity. This complex and potentially cyclical association between sitting and adiposity may confound associations between sitting and health outcomes and requires further research attention in order to understand how obesity influences sitting behaviour and how this might affect the relationship between sitting and disease risk.

11.2.5. The effects of exposure misclassification

Studies examining associations between sitting and health outcomes have defined their exposures in different ways and have employed a range of measurement tools to quantify them. Self-report questionnaires typically assessing total or domain specific sitting, objective measures of movement (where sedentary time is defined as time spent below a pre-determined threshold in total body movement) and physiological estimates of energy expenditure from heart rate data (where sedentary time is estimated from time spent below a heart rate threshold) have all been used in studies that have observed positive associations between 'sitting' and health risk. This heterogeneity not only limits comparability between studies but also limits understanding of the true nature of the exposure i.e. is it sitting itself, or low movement/heart rate that is the risk behaviour? In addition the use of any of these measures will introduce varying degrees of exposure misclassification and this is an important consideration when comparing studies and their findings.

The use of self-report measures of sitting is an important strength of the analyses presented in chapters five to eight as it allows the collection of contextual information which is not available from objective measures such as accelerometers or heart rate monitors. In this way it permits the necessary examination of both total and domain specific sitting time. Nevertheless self-reporting lifestyle and health behaviours is problematic and this is especially true for complex behaviours such as sitting which can occur in short periods sporadically throughout the day, and in a wide variety of contexts.

Misclassification of sitting, if non-differential, would lead to the attenuation of any true association with health outcomes towards the null. It is therefore possible that non-differential misclassification of sitting may have contributed to the absence of significant associations between sitting and mortality, cardiovascular disease, type II diabetes and obesity in the present analyses.

Conversely the potential effects of differential misclassification of sitting must also be considered when examining the present findings alongside the existing evidence base. It is likely that sitting behaviour is often underreported for reasons of social desirability due to the publicised health detriments associated with being inactive. It is also likely that there are systematic differences in the under-reporting of sitting behaviours between population subgroups which may influence observed associations with health outcomes. For example, people who are more active, health conscious (and therefore perhaps healthier) might be more likely to under-report behaviours such as TV viewing than those people who are less active or health conscious, or healthy. In this way systematic difference in underreporting might artificially inflate the associations between self-reported sitting and disease risk. Differences in patterns of under-reporting between study populations may also have contributed to the inconsistency between the findings described in chapter five to eight and those observed in previous cohort studies.

11.2.6. The potential for publication bias

While the findings from chapters five to eight are inconsistent with a number of previous observational studies linking sitting time with disease risk the possibility of publication bias within the current literature must also be considered. As discussed previously a recent meta-analysis[27] examining associations between sedentary time and health outcomes reported evidence of publication bias in the literature examining associations between sitting and diabetes. While no such analysis was reported for other health outcomes due to the relatively low number of published prospective studies it is logical to consider that other unpublished null findings exist.

Within the existing published literature, inconsistencies in the definition of sitting exposures in observational studies, the potential for significant exposure misclassification and the possible effects of residual confounding reinforce the need to establish the precise nature of the exposure and to begin to examine potential causal mechanisms which might explain the observed negative associations with health risk. This was another primary aim of this thesis.

11.3. What causes the risk? Differential effects of sustained versus interrupted sitting

In light of the uncertainty about the nature of the reported risk posed by sitting to health, chapter ten of this thesis aimed to address another primary aim of this thesis by examining a potential biological mechanism which might underpin a detrimental effect of sitting. In order to do this a laboratory based

experimental study with a three trial repeated measures cross-over design was undertaken.

It was observed that plasma glucose and insulin responses to a standard oral glucose tolerance test, plasma insulin response to a mixed test meal and insulin sensitivity (as defined by Matsuda)[171] were all significantly improved when a seven hour day of sitting at a desk was interrupted every 20 minutes with two minute bouts of light intensity walking compared to a control trial of sustained sitting. Conversely repeated two minute bouts of standing did not significantly improve any of the outcome measures relative to the control trial. The likely mechanism for these findings relates to the additive effect of muscular contraction on muscle cell glucose uptake and insulin sensitivity. These findings are consistent with two other experimental studies which have also shown beneficial effects of repeated short bouts of walking.[273 275] Results from this study are encouraging as they suggest that fairly minor behavioural modifications (the addition of three short walking breaks per hour) may be of significant benefit to individuals who spend extended periods of the day sitting down.

Importantly, this study is the first to examine the effect of repeated short bouts of standing, a necessary step in clarifying the risk associated with sitting. As discussed previously a fundamental question regarding the reported independent effects of sitting is whether the posture of sitting itself is detrimental or whether sitting is simply a proxy for low energy expenditure or levels of light intensity activity.[375] The finding that repeated changes in posture (from sitting to

standing), in the absence of a meaningful increase in energy expenditure, did not significantly improve markers of glucose regulation suggests that the observed risk associated with high volumes of sitting may actually be attributable to low levels or an absence of light intensity activity rather than sitting per se.

This conclusion is consistent with observational evidence (described above) that associations between sedentary time and biological risk markers (including markers of glucose and insulin regulation) were attenuated when analyses were adjusted for total physical activity (including light intensity activity) rather than just duration of MVPA.[375]

11.4. Overall summary

This thesis has provided a novel and detailed examination of sitting behaviour and its association with health using both observational and experimental methodologies and a range of analytical techniques. Analyses of observational data from the Whitehall II study (presented in chapters five to eight) revealed no significant associations between total or domain specific sitting time with risk for mortality, cardiovascular disease, diabetes or obesity in fully adjusted analyses. Findings from these analyses are largely inconsistent with existing prospective studies which have reported significant positive associations between sitting and disease risk. However the range of measures used and hence the variety of definitions of the exposure employed by these studies makes comparisons between studies difficult and also leaves

uncertainty as to the nature of the risk behaviour. The possibility of the contribution of residual confounding (due to incomplete or imprecise adjustment for dietary factors, adiposity and physical activity) in existing prospective studies adds to this uncertainty. It is argued that associations between sitting and health outcomes that are persistent following adjustment for time spent in moderate to vigorous physical activity is evidence for a link between sitting time and health that is unique and independent of physical activity. It would follow that the true exposure is related to the posture of sitting itself. However, by only adjusting for moderate to vigorous physical activity it is impossible to say with any certainty that observed associations are not simply reflective of differences in light intensity activity. A number of studies have also reported associations between sitting and mortality risk and metabolic health that are far weaker[63 70 420] or even non-significant[153] in those who are physically active, again suggesting that the associations of sitting and physical activity with health are not entirely independent.

The experimental study presented in chapter 10 builds on existing experimental evidence by examining whether standing (i.e. not sitting but not moving) has the same benefits to glucose metabolism as light intensity ambulation. The absence of an effect of repeated bouts of standing again suggests that movement and energy expenditure are the important variables rather than the posture of sitting itself. The experimental investigation of patterns of sitting and light intensity activity is in its infancy and developments in this area are key to a better understanding of the previously observed associations between sitting and health and the biological mechanisms which

underpin them. The present findings while not consistent with a detrimental effect of sitting per se are encouraging as they suggest that small increases in light intensity activity could improve the health of people who spend large and sustained periods of their day sitting down. This is particularly significant given the increasing opportunities for sitting in all areas of daily life.

11.5. Strengths and limitations of thesis

A significant strength of this thesis is the use of both observational and experimental study designs to examine the relationship between sitting and health. The use of a range of sitting exposures including both total and domain specific sitting indicators is a novel approach and one that provides further insight into the potentially differential associations between specific sitting behaviours and health outcomes. As different sitting behaviours may be associated with different durations or patterns of sitting or with the co-occurrence of other health behaviours (for example TV viewing and snacking behaviour) this can allow important insight into to the possible mechanisms for observed associations.

While the use of rich population level data allows the examination of the prevalence of sitting and the associations with objectively defined health outcomes, the examination of experimental manipulation of sitting, standing and walking takes this one step further by directly assessing resultant changes in metabolic parameters which might underpin these associations. In this way it has been possible to begin to address the fundamental questions in this field,

relating to the true nature of the exposure (i.e. does sitting itself effect health or is it a proxy for low levels of movement/energy expenditure).

This thesis is not without limitation. Both the Whitehall II and HSE datasets were not designed to examine sitting behaviours in detail, and therefore the questionnaire items relating to sitting limited the research questions that could be addressed. It was not possible to examine the duration or frequency of individual bouts of sitting, only the overall duration of sitting (or specific sitting behaviours) in a given period. Given existing observational and experimental evidence relating to interrupting sustained periods of sitting, by focussing on overall average daily sitting values important associations between health outcomes and different durations of sitting and physical activity may have been masked. As these cohort studies were not designed to examine the associations between sitting and health they also did not collect data on potentially important confounders that are specific to individual sitting behaviours such as snacking during TV viewing. In addition, although prospective data from the Whitehall II study allowed the examination of disease incidence, the absence of multiple measures of sitting over a number of time points prevented the examination of how changes in sitting might be reflected in changes in disease risk.

It was also not possible to separately examine sitting while in transport. This was combined with the measure of sitting at work in the Whitehall II questionnaire (participants were asked ‘on average how many hours per week do you spend sitting at work, including driving or commuting’) and was not

featured in the HSE 2008 questionnaire. An increasing proportion of workers in affluent societies are employed in white collar office based occupations[320] in which sitting predominates. Therefore commuting to and from work remains a potentially important contributor to differences in daily sitting and physical activity behaviours.[427] Active commuting is associated with both higher total daily physical activity[427] and important positive health effects.[428-430] It has also been observed that habitual active transport may moderate the observed association between TV viewing and obesity.[199 360] The inability to distinguish between work related sitting and sitting during commuting in the analyses within this thesis may mean that important associations were masked. Failure to adjust for important differences in sitting and physical activity during commuting may have confounded analysis of the association between work sitting and disease risk.

The generalisability of the current findings must also be considered. Although the Whitehall II study sample provides high quality data on participants from a broad range of socioeconomic backgrounds, it is an occupational cohort study of employees from one industry sector, in a single area of the country, who at the study's inception were all healthy enough to be in active employment. For this reason caution must be taken when using these findings to make inferences to populations from other geographic areas, industry sectors or to the population as a whole. Also, as discussed previously due to the specific inclusion criteria imposed for the purposes of the analyses of trends in sitting and accelerometer defined sedentary time, the study sample taken from the HSE 2008 dataset may not be representative of the population of England.

The laboratory based intervention study detailed in chapter 10 featured a sample of 25 healthy but inactive males preventing direct inferences being made to other population groups. However the findings of this study and others[273-275] suggest that light intensity activity breaks in a given period of sitting can benefit glucose metabolism in both male and female participants of a range of ages and body mass index classifications.

11.6. Future directions for research

The findings and discussion within this thesis has highlighted two main directions for further research which would significantly advance our understanding of sedentary behaviour and its link with health. These are the fundamental questions of what is the precise nature of the exposure, and how should it be measured?

11.6.2. Defining the exposure.

In order to better understand the reported link between daily sitting and disease risk it is necessary to definitively establish the nature of the exposure behaviour i.e. whether, as previously hypothesised, sitting represents a unique and independent risk to health or whether, as suggested by the evidence presented in this thesis and elsewhere, sitting is a proxy for low levels of movement or energy expenditure.

The implications of the uncertainty as to the true nature of the exposure are wide ranging. Sitting is a ubiquitous behaviour and as such offers a wide range of opportunities for intervention. Specific common sitting behaviours such as TV viewing could be targeted by interventions, and durations or patterns of sitting could be changed in schools or in the work place in efforts to reduce the apparent risk. However, by assuming the risk comes from sitting itself as a discrete behaviour (the implication being that simply not sitting leads to a reduction in risk) clinicians or policy makers might incorrectly recommend counter measures involving standing. This may not be of any benefit if the true exposure relates to low levels of energy expenditure rather than posture. Standing in the absence of an increase in energy expenditure may still constitute the same risk behaviour and as such these potentially costly and disruptive interventions may be ineffective. Recently, Peeters and co-workers[431] used data from the Australian Longitudinal Study on Women's Health to examine differences in annual per capita health care costs according to average daily sitting time and habitual physical activity. It was observed that physical inactivity but not sitting time was associated with higher annual health related costs. When the interaction between the two measures was examined, sitting time did not add to the higher costs associated with inactivity. These findings highlight the risk of focussing on the wrong exposure as it appears that measures to reduce sitting would not affect the burden of disease while continued efforts to increase physical activity would reduce healthcare costs.

Further experimental studies examining the precise mechanisms that underpin the previously observed detrimental associations between sitting and

health are central to establishing the true nature of the exposure. It is vital that any future experimental studies should aim to differentiate between the effect of posture only (sitting versus standing) and the effect of an increase in movement or energy expenditure. This could be accomplished in a number of ways. In chapter 10 the inclusion of an experimental condition in which a sustained period of sitting was interrupted with standing was an important and novel aspect of this study as it begins to address the question of whether simply not sitting is of benefit or whether some kind of activity needs to be undertaken. This methodology certainly holds promise for future intervention studies. Studies examining different patterns of sitting, standing and light intensity activity could also include direct calorimetry which would allow the precise determination of the contribution of differences in energy expenditure to any observed metabolic effects.

Of the small number of existing experimental studies examining the acute effects of patterns of sitting (including the study detailed in chapter 10) most have focussed on glucose and insulin regulation[273-275 377] although one additionally examined plasma triglyceride concentrations[275] and a further study examined associations with appetite regulatory hormones.[432] There are number of metabolic parameters which may have been previously associated with sitting time in observational studies (including markers of inflammation, endothelial function and fat metabolism) which contribute to disease risk and which therefore require closer examination in controlled experimental conditions.

11.6.3. Improving measurement precision to clarify the associations between sitting and health in observational studies.

As discussed previously imprecise measurement of sitting in observation studies may influence the observed associations with health outcomes. The importance of examining sitting behaviour in different contexts is highlighted in this thesis by the differential associations observed between different sitting behaviours with diabetes risk in chapter seven and the association between prior obesity and TV viewing only in chapter eight. This contextual information can be easily provided by self-report measures of sitting. However, as discussed above, estimates of sitting based on self-report measures may be undermined by issues of exposure misclassification. Bias due to both recall error and social desirability are both possible. Conversely objective measures do not measure sitting behaviour itself, just the absence of movement, which can also lead to misclassification and increases the uncertainty as to whether sitting itself or low levels of movement is the risk behaviour.

The importance of establishing the true nature of the exposure and measuring it accurately is evident when the potential consequences of this uncertainty are considered. Chapter nine addresses the other primary aim of this thesis by describing the prevalence of self-reported leisure time sitting behaviours and accelerometer defined sedentary time in England. It was observed that men and women in England sit and watch TV for over two hours per day during the week and almost three hours per day at weekends, and sit for almost four and five hours per day during their leisure time on weekdays and weekend days respectively. When it is considered that all participants included

in this sample were in full time employment and that these sitting estimates represent leisure time sitting behaviour only, then this in itself suggests that if sitting behaviour does represent a risk to health then the scale of the exposure is significant. However as discussed previously, day to day lifestyle behaviours such as sitting are difficult to recall as they can occur sporadically and often for very short periods. Behaviours which are considered socially undesirable such as TV viewing are also likely to be underreported. The use of these self-report estimates may therefore lead to a significant underrepresentation of the true prevalence of sitting and therefore an underestimate of the population level of the exposure.

Conversely estimates of accelerometer defined sedentary time (defined as time spent below a movement threshold of 200 counts per minute) suggest that that both men and women spend almost 10 hrs per day engaged in sedentary behaviour. However as standing and some slow ambulation may also be classified as sedentary behaviour according to this movement threshold,[121] without additional contextual information about sitting behaviours it is possible that such measures may overestimate the population prevalence of sedentary behaviour. If policy makers were deciding how much funding to allocate to tackling the health burden associated with sitting based on the population prevalence of the risk behaviour then the measurement tool chosen to measure the risk behaviour could significantly affect the resources allocated.

Although sitting behaviour might be under-reported across the whole population, the degree of underreporting might also differ between population

subgroups which might in turn lead to incorrect conclusions regarding who might be most at risk or who might benefit most from interventions to reduce the risk behaviour. In chapter nine leisure time TV viewing on weekdays was observed to be significantly higher in men than in women, higher in the older age groups compared to younger age groups and higher in those of lower socioeconomic position as indicated by either employment grade or area deprivation score. Based on these findings it might be considered prudent to target a reduction in TV viewing in older men of low socioeconomic status. There is no way of knowing for certain whether this association reflects a difference in risk or simply a difference in the recall or reporting bias of TV viewing between genders, age groups or between socioeconomic classifications. It is therefore possible that research time and money and public funding might be misspent targeting a group within the population who are actually at no greater risk than anyone else. Conversely it must also be considered that by using an objective measure of sedentary behaviour such as accelerometers important differential associations by type of sitting might be lost.

As discussed previously there is a need for objective measures which are able to differentiate accurately between sitting, standing and walking. The development of pattern recognition approaches (2.3.5) to the use of raw accelerometer data hold considerable promise. Being able to accurately define both total volume of sitting and durations of individual bouts of sitting and walking without the problems associated with recall error or bias would allow clarification of the associations between sitting, light intensity activity and health

outcomes. The addition of new technology such as wearable cameras could also allow the objective collection of contextual information necessary to examine context specific sitting which in turn would allow identification and consideration of behaviour specific determinants and confounders.

11.7. Practical implications of findings

Sedentary behaviour research remains in its infancy and as described above, a number of research questions need to be addressed to further advance our understanding of the associations between sitting time, light intensity activity and health. Nevertheless the results of the investigations presented within this thesis have a number of practical implications for researchers, policy makers and clinicians.

11.7.2. Implications for researchers

Researchers examining population level data on sitting and light intensity activity should measure domain specific sitting as well as total sitting time. The distinction between work related sitting and sitting while commuting would also be an important addition to the literature. The correlates and determinants of separate sitting behaviours are likely to be different, and an examination of individual behaviours is crucial in fully understanding their differential associations with health outcomes.

A further implication of the findings and discussion from this thesis is that observational studies should clearly define the exposure they are measuring

(total/domain specific sitting vs low movement) and select the best possible measurement tool available for that exposure (self-report or accelerometer). The inherent limitations of these methods in measuring sitting or sedentary time should be acknowledged. Great lengths should also be taken to ensure the accurate measurement of potential confounding factors including diet, adiposity and physical activity and the possibility of residual confounding, and the implications of this for the findings of observational analyses should be discussed. Where possible, studies examining associations between sitting and health outcomes should adjust their analyses for a measure of total physical activity energy expenditure (including light intensity activity) rather than time spent in MVPA. While it must be considered that precise adjustment for total physical activity energy expenditure would be more problematic in studies employing self-report measures of physical activity due to difficulties in recalling and reporting light intensity activity with any accuracy, estimates of common light intensity activities such as walking may be used (as employed in chapters five to eight). Studies employing accelerometer measures of sedentary time should adjust for total accelerometer counts (excluding counts accumulated below the sedentary threshold value).

Where self-report measures of sitting are analysed in multivariate models, sensitivity analysis should be undertaken to examine the possibility that selection bias may influence estimates of sitting within the study population. Similarly, where accelerometers are used to measure sedentary time sensitivity analysis should be performed to address the possibility that estimates of prevalence or associations with health outcomes were influenced by;

misclassification due to choice of the cut-point used to determine sedentary time, or selection bias due to wear time criteria or the definition of non-wear.

As discussed the fundamental question facing this field relates to whether the observed risk to health is a result of sitting itself or of low levels of energy expenditure. Experimental studies examining possible underlying mechanisms for these associations remain the best way to address this question. Researchers should separately examine the effects of posture and movement in order to better understand the risk behaviour. This could be achieved by either examining the effect of a change in posture (from sitting to standing), and a change in energy expenditure in separate trial arms or by directly and accurately measuring energy expenditure in order to establish the contribution of differences in energy expenditure to observed effects. Ideally a range of metabolic parameters should be examined as there are many underlying factors in the development of disease which could potentially be implicated in disease risk.

The effect of different patterns of sitting, standing and walking should also be considered in order to clarify the effect of total energy expenditure per se versus repeated acute last bout effects of muscular contraction. This will offer further insight into the relationship between sitting, light intensity activity and metabolism.

11.7.3. Implications for policy makers

The findings presented in this thesis raise important issues which must be considered by policy makers. The findings suggest that sitting does not, as postulated previously, represent a risk to health that is independent of, and in addition to achieving only low levels of habitual physical activity. Experimental work examining the associations of sitting and light intensity activity with health and the mechanisms which might underpin these associations is still in it's infancy. Observational evidence linking sitting and disease outcomes is undermined by the significant issues of exposure misclassification from both self-report and current objective measures of sitting/sedentary time and residual confounding from failure to properly adjust for total daily energy expenditure or BMI. It is therefore impossible to say with any confidence that sitting is not simply a proxy for low levels of energy expenditure. The possibility that sitting poses an independent risk to health cannot be ruled out but the considerable gaps in our current understanding make it premature to produce guidelines for how populations should alter their behaviour. Establishing the prevalence of sitting is also problematic due to imprecision in the techniques currently available to classify total or domain specific sitting at a population level. Continuing efforts to define and accurately measure sedentary and light intensity activity behaviours and to establish the mechanisms that may underpin the observed associations with disease outcomes in the wider literature are essential before intervention design and guideline development.

11.7.4. Implications for clinicians

The results of the investigations within this thesis suggest that clinicians should be cautious about warning of the risks of sitting behaviour that are additional to and separate from the risks of low levels of physical activity. As discussed previously it is not possible to rule out the possibility that reported relationships between sitting time and health outcomes are due to low daily energy expenditure, the best solution to which is to increase daily physical activity even at light intensities. The health benefits of physical activity are well established,[304] and even sporadic light intensity activity, such as that employed in the experimental studies examining patterns of sitting time (both in chapter 10 of this thesis and elsewhere)[273 275] have been shown to improve a number of metabolic parameters. Habitual physical activity is still only undertaken by a minority despite these accepted health benefits and therefore until more robust epidemiological and mechanistic evidence exists about the specific risks of prolonged sitting the promotion of a physically active lifestyle should still be a priority for clinicians.

11.8. Conclusion

This thesis aimed to enhance understanding of the association between sitting time and health by examining fundamental questions relating to the true nature of the exposure, the health risk associated with sitting and the potential biological mechanisms which underpin this health risk. This thesis has enhanced the existing evidence base by highlighting the importance of separately examining specific sitting behaviours in the varying contexts in which they occur. Such behaviours are associated with different patterns of sitting (in

terms of frequency, duration and total volume), and as evidenced by the analyses in this thesis are differentially associated with sociodemographic correlates and health outcomes.

Overall, findings from this thesis suggest that the previously reported prospective associations between sitting time and health risk may in fact be due to differences in light intensity physical activity. It has been postulated that sitting represents a risk to health that is independent of and in addition to the effects of physical activity. However previous studies have failed to adequately adjust for the effect of physical activity and therefore the observed associations may be due to residual confounding caused by differences in light intensity physical activity. This conclusion is supported by experimental manipulation of patterns of sitting, standing and walking, the findings from which suggest that interrupting the posture of sitting elicits no significant beneficial effect unless energy expenditure is increased by undertaking light intensity activity. If standing rather than sitting is not beneficial then the true exposure must relate to the absence, or low levels of light intensity activity rather than anything related to the sitting posture. This study is the first to directly address the fundamental question regarding the true nature of the exposure by testing the potential beneficial effect of changes in posture only versus changes in energy expenditure. In this way this thesis has made an important and novel contribution to the literature.

This thesis has also highlighted the complex bidirectional nature of the association between sitting behaviour and adiposity which requires further

investigation as a potential confounder for the previously observed associations between sitting and disease risk.

By addressing fundamental questions regarding the previously observed associations between sitting time and health, and in doing so identifying important methodological limitations in the existing evidence, this thesis has made a significant contribution to the sedentary behaviour research. In recent years, public health messages have increasingly encouraged people to reduce sitting behaviour (and often replace it with stationary standing). The findings from this thesis suggest that a better message would be to encourage movement at a low intensity.

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Appendix

Appendix 1.1. Summary of studies: sedentary behaviour and mortality

Author	Sample	Study design	Outcome (no. cases, % of sample if reported)	Sedentary measure	Covariates	Association
Chau et al 2013	50817 Norwegian men & women	Prospective, 3.3 yr f/u	Cardiometabolic disease mortality (388, 0.76%) All-cause mortality (2.1%)	Self-reported total sitting, TV viewing and occupational sitting	Age, gender, education, alcohol consumption, smoking status, BMI, diabetes, CHD, minutes of daily MVPA.	Positive
Dunstan et al 2010	8800 Australian men & women	Prospective, 6.6 yr f/u	Cardiovascular mortality (87, 1%) All-cause mortality (284, 3.2%)	TV viewing time	Age, sex smoking, education, diet	Positive
Inoue et al 2008	83034 Japanese men & women	Prospective, 8.7 yr f/u	All-cause mortality (4564, 5.5%)	Self-reported total sitting	Age, area, occupation, smoking, alcohol, BMI, diet, exercise, sedentary activity, walking or standing hrs, leisure time PA	Positive
Katzmarzyk et al 2009	17013 Canadian mean & women	Prospective, 12 yr f/u	Cardiovascular mortality (759, 4.5%) All-cause mortality (1832, 10.8%)	Self-reported sitting time	Age, smoking, alcohol, leisure-time PA	Positive
Koster et al 2012	1906 American men & women	Prospective, 2.8 yr f/u	All-cause mortality (145, 7.6%)	Accelerometer defined sedentary time	Age, gender, ethnicity, education, alcohol consumption, smoking status, BMI, diabetes, CHD, mobility limitations, minutes of daily MVPA.	Positive
Leon-Munoz et al 2013	2635 Spanish men & women	Prospective, 8yr f/u	All-cause mortality (846, 32%)	Self-reported total sitting time	Age, gender, ethnicity, education, alcohol consumption, smoking	Positive

					status, BMI, METhr/wk of leisure time PA	
Matthews et al 2012	240819 American men & women	Prospective, 8.5 yr f/u	Cardiovascular mortality (4684, 2%) All-cause mortality (17044, 7%)	TV viewing	Age, sex, race, education, smoking, diet, leisure time physical activity	Positive
Patel et al 2012	123216 American men & women	Prospective, 14 yr f/u	Cardiovascular mortality (6369, 5.2%) All-cause mortality (19230, 15.6%)	Self-reported sitting time	Age, marital status, education, smoking, BMI, alcohol, caloric intake, co morbidities score, physical activity	Positive
Stamatakis et al 2011	4512 Scottish men & women	Prospective, 4.3 yr f/u	Cardiovascular mortality (215, 4.8%) All-cause mortality (325, 7.2%)	TV and screen-time	Age and sex	Positive
van der Ploeg et al 2012	222947 Australian men & women	Prospective, 2.8 yr f/u	All-cause mortality (5405, 2.4%)	Self-reported sitting	Age, gender, education, urban/rural residence, alcohol consumption, smoking status, BMI, self-rated health, MVPA	Positive
Warren et al 2010	7744 American men & women	Prospective, 21 yr f/u	Cardiovascular mortality (377, 4.9%)	TV viewing and car use	Age, gender, education, alcohol consumption, smoking status, BMI, family history of CVD, diet, self-rated physical activity level	Positive
Weller & Corey 1998	6620 Canadian women	Prospective, 7 yr f/u	All-cause (449, 6.8%) Cardiovascular mortality (159, 2.4%)	Self-reported sitting,	Unadjusted	Positive

Wijndaele et al 2011	13197 British men & women	Prospective, 9.5 yr f/u	Cardiovascular mortality (373, 2.8%) All-cause mortality (1270, 9.6)	TV & video viewing	Age, gender, education, alcohol consumption, smoking status, BMI, family history of CVD, diet, minutes of daily MVPA	Positive

Appendix 1.2. Summary of studies: sedentary behaviour and CVD

Author	Sample size, gender	Study design	Outcome (no. cases, % of sample if reported)	Sedentary measure	Covariates	Association
Chomistek et al 2013	71018 American women	Prospective, 12.2 yr f/u	Cardiovascular disease (4235, 5.9%)	Self-reported daily sitting	Age, ethnicity, family income, education, marital status, smoking, family history of MI, depression, alcohol intake, diet, leisure time physical activity	Positive
Hawkes et al 2011	1966 Australian men and women	Prospective, 3 yr f/u	Cardiovascular disease (32, 1.6%)	TV viewing	Sex, age, education, marital status	Positive
Herber-Gast et al 2013	6154 Australian women	Prospective, 9.9 yr f/u	Cardiovascular disease (177, 2.8%)	Self-reported total sitting	Age, education, smoking, alcohol consumption, physical activity and BMI	Null
Manson et al 2002	73743 American women	Prospective, 3.2 yr f/u	Cardiovascular disease (1551, 2.1%)	Self-reported sitting/lying/sleeping	Age, leisure time physical activity energy expenditure	Positive
Stamatakis et al 2011	4512 Scottish men & women	Prospective, 4.3 yr f/u	Cardiovascular disease (422, 9.3%)	TV and screen-time	Age, sex, ethnicity, BMI, smoking, social class, long-standing illness, marital status, diabetes, hypertension, physical activity	Positive
Wijndaele et al 2011	12608 British men and women	Prospective, 6.9 yrs f/u	Cardiovascular disease	TV viewing	Age, gender, education, smoking status, alcohol consumption, relevant medications, family history, sleep duration, leisure time, physical activity energy expenditure.	Positive

Allinson et al 2011	1543 American men and women	Cross-sectional	Atherosclerosis associated inflammation	Self-reported total sitting	Age, gender, ethnicity, education, BMI, smoking status, alcohol consumption, waist circumference, longstanding illness	Positive
de Heer et al 2012	11268 Mexican men and women	Cross-sectional	CVD risk score	Self-reported total sitting	Employment status and leisure time physical activity	Positive
George et al 2013	63048 Australian men	Cross-sectional	Cardiovascular disease	Self-reported daily sitting	Age, educational status, household income, smoking status, functional limitation, BMI, daily MVPA	Null
Hamer et al 2012	446 British men & women	Cross-sectional	Pericardial fat	Accelerometer defined sedentary time	Age, sex, BMI, HDL-cholesterol, blood pressure, HBA1c, smoking status, statin use, employment grade. Total accelerometer wear time, physical activity	Null
Hamer et al 2012	443 British men & women	Cross-sectional	Coronary artery calcification	Accelerometer defined sedentary time	Age, sex, BMI, total and HDL-cholesterol, blood pressure, HBA1c, smoking status, statin use, employment grade. Total accelerometer wear time, physical activity	Null
Sidney et al 1996	4280 American men and women	Cross-sectional	CVD risk score	TV viewing	Age, education, smoking, alcohol consumption, test centre, physical activity score	Positive

Appendix 1.3. Summary of studies: sedentary behaviour and metabolic disease

Author	Sample size, gender,	Study design	Outcome (no. cases, % -of sample if reported)	Sedentary measure	Covariates	Association
Ekelund et al 2009	191 British men and women	Prospective, 1 yr f/u	Insulin sensitivity (HOMA-IS)	Accelerometer defined sedentary time and TV viewing	Age, sex, waist circumference, smoking status, minutes of daily MVPA	Null
Cooper et al 2011	528 British men and women	Prospective, 6 months f/u	Insulin resistance (HOMA-IR)	Accelerometer defined sedentary time	Age, sex, waist circumference, smoking status, area deprivation score, family history of diabetes, minutes of daily MVPA	Positive
Ford et al 2010	23855 German men & women	Prospective, 7.8 yr f/u	Diabetes (927, 3.9%)	TV viewing <1r vs >4hrs.d	Age, sex education, occupational activity, smoking, alcohol, PA, diet, systolic BP	Positive
Hawkes et al 2011	1966 Australian men and women	Prospective, 3 yr f/u	Diabetes (247, 12.6%)	TV viewing <2 vs >4hrs.d	Age, sex, education, marital status	Positive
Helmerhorst 2009	376 British men and women	Prospective 5.5 yr f/u	Fasting insulin	Heart rate defined sedentary time	Age, sex, fat mass, fasting insulin, smoking status, minutes of MVPA	Positive
Hu et al 2001	37918 American men	Prospective, 10 yr f/u	Diabetes (767, 2%)	TV viewing >40 vs <1hrs.wk	Age, duration of smoking, diabetes mellitus, family history, physical activity	Positive
Hu et al 2003	68497 American women	Prospective, 6yr f/u	Diabetes (1515, 2.2%)	TV viewing >40 vs <1hrs.wk	Age, hormone use, alcohol, smoking, family history, diabetes mellitus, physical activity, diet	Positive
Krishnan et al 2009	45668, Black	Prospective, 10 yr	Diabetes (2928,	TV viewing >5 vs	Age, family history, diabetes	Positive

	American women	f/u	6.4%)	<1hr.d	mellitus, education, family income, marital status, cigarette use, alcohol, energy intake, coffee consumption, vigorous physical activity, walking	
Matthews et al 2008	240817, Amercan men & women	Prospective, 8.5 yr f/u	Diabetes (15942, 6.6%)	TV viewing <1 vs ≥7hrs.d	Age, sex race, education, smoking, diet, physical activity	Positive
Stamatakis et al 2001	4512 Scottish men and women	Prospective, 4.3 yr f/u	Diabetes (279, 6%)	TV and screen time <2 vs ≥ 4hrs.d	unadjusted	Positive
Wijndaele et al 2011	12608 British men & women	Prospective, 6.9 yr f/u	Diabetes (341, 2.7%)	TV and video viewing <2.5 vs >3.6hrs.d	unadjusted	Positive
Bankoski et al 2011	1367 American men & women	Cross-sectional	Metabolic syndrome (ATP)	Accelerometer defined sedentary time	Age, sex, ethnicity, education, alcohol consumption, smoking status, BMI, minutes of MVPA	Positive
Bertrais et al 2005	3834 French men and women	Cross-sectional	Metabolic syndrome (NCEP)	Screen-time	Age, sex, education, smoking status, adherence to PA recommendations	Positive
Chang et al 2008	2353 Taiwanese men and women	Cross-sectional	Metabolic syndrome	TV viewing	Age, sex, education, household income, smoking status, alcohol intake, leisure time physical activity	Positive
Chen et al 2009	1460 Chinese men and women	Cross-sectional	Metabolic syndrome	TV viewing	Age, sex, smoking status, alcohol consumption, total calories, carbohydrate, fat and fibre intake	Positive
Cooper et al 2011	528 British men and women	Cross-sectional	Insulin resistance (HOMA-IR)	Accelerometer defined sedentary time	Age, sex, waist circumference, smoking status, area deprivation score, family	Null

					history of diabetes, minutes of daily MVPA	
de Heer et al	11268 Mexican men and women	Cross-sectional	Diabetes	Self-reported daily sitting time	Age, sex, employment status, educational attainment, family history of diabetes, hypertension, cholesterol level, and leisure time physical activity.	Positive
Dunstan et al 2005	6162 Australian Men and women	Cross-sectional	Metabolic syndrome (WHO)	TV viewing	Age, sex, education, marital status, family history of diabetes, dietary intake, leisure time MVPA	Positive
Dunstan et al 2004	8299 Australian men and women	Cross-sectional	Impaired glucose tolerance	TV viewing	Age, sex, education, marital status, family history of diabetes, leisure time MVPA	Positive
Ekelund et al 2009	192 British men and women	Cross-sectional	Insulin resistance (HOMA-IS)	Accelerometer defined sedentary time and TV viewing	Age, sex, waist circumference, smoking status, minutes of daily MVPA	Positive for TV viewing
Ford 2005	1626 American men and women	Cross-sectional	Metabolic syndrome (NCEP)	TV viewing	Age, sex, education, ethnicity, smoking status, alcohol, daily MVPA	Positive
Gardiner 2011	1958 Australian men and women	Cross-sectional	Metabolic syndrome (IDF)	TV viewing	Age, education, self-rated health, employment level smoking status, alcohol consumption, diet, daily MVPA	Positive
George et al 2013	63048 Australian men	Cross-sectional	Diabetes	Self-reported daily sitting	Age, educational status, household income, smoking status, functional limitation, BMI, daily MVPA	Positive
Gao et al 2007	455 Puerto Rican and Dominican men	Cross-sectional	Metabolic syndrome	TV viewing	Age, sex, ethnicity, education, BMI, smoking status, alcohol,	Positive

	and women				fat intake, activities of daily living score, leisure time MVPA	
Healy et al 2011	4757 American men and women	Cross-sectional	Insulin action and sensitivity (HOMA-IS and HOMA-β)	Accelerometer defined sedentary time	Age, sex, educational attainment, ethnicity, income, smoking status, alcohol consumption, diet, medical history	Positive
Healy et al 2008	168 Australian men and women	Cross-sectional	Glucose metabolism	Accelerometer defined sedentary time	Age, sex, educational attainment, ethnicity, income, smoking status, alcohol consumption, diet, medical history, and daily MVPA	Positive
Healy et al 2008	169 Australian men and women	Cross-sectional	Metabolic syndrome risk	Accelerometer defined sedentary time	Age, sex, educational attainment, ethnicity, income, smoking status, alcohol consumption, diet, medical history, and daily MVPA	Positive
Healy et al 2008	4064 Australian men and women	Cross-sectional	Metabolic risk score	TV viewing	Age, sex, educational attainment, ethnicity, income, smoking status, alcohol consumption, diet, medical history, and daily MVPA	Positive
Kim et al	483 Japanese men and women	Cross-sectional	Metabolic syndrome	Accelerometer defined sedentary time	Age, sex, smoking status, calorie intake, accelerometer wear time, minutes of daily MVPA	Positive
Li et al	358 Chinese men and women	Cross-sectional	Metabolic syndrome	TV viewing	Age, sex, BMI	Positive
Mabry et al 2012	1335 Omani men and women	Cross-sectional	Metabolic syndrome (WHO)	Self-reported daily sitting	Age, sex, marital status, employment status, fruit and vegetable intake, family history	None

					and MET-min/wk from MVPA	
Sisson et al 2009	3556 American men and women	Cross-sectional	Metabolic syndrome (AHA)	TV viewing and computer usage	Age, sex, smoking, education, ethnicity, percentage fat in diet, adherence to physical activity recommendations	Positive for men only
Scheers et al	370 Flemish men & women	Cross-sectional	Metabolic syndrome	Accelerometer defined sedentary time	Age, sex, education, smoking status, alcohol consumption, minutes of MVPA	Null
Stamatakis et al 2012	2765 British men and women	Cross-sectional	Diabetes	Self-reported leisure time sitting and accelerometer defined sedentary time	Age sex, employment status, smoking status, education, depression, alcohol consumption, fruit and vegetable intake, accelerometer wear time and minutes of daily MVPA	Positive
Tonstad et al 2009	60903 American men and women	Cross-sectional	Diabetes	Self-reported TV viewing	Age, sex, ethnicity, education, income, alcohol use, sleep habits, daily MVPA, and BMI	Positive
Vancampfort 2012	114 Belgian men and women	Cross-sectional	Insulin resistance	Self-reported total sitting	Age, sex, smoking, BMI and minutes of weekly MVPA	Positive
Wijndaele et al 2009	992 Flemish men and women	Cross-sectional	Metabolic syndrome risk score	TV viewing/computer use	Age education level, smoking status, dietary intake and leisure time physical activity	Positive
Yateset al 2012	505 British men and women	Cross-sectional	Insulin resistance	Self-reported total sitting	Age, sex, ethnicity, social deprivation, smoking status, daily MVPA, and BMI	Null

Appendix 1.4. Summary of studies: sedentary behaviour and obesity

Author	Sample	Study design	Outcome (no. cases, % of sample if reported)	Sedentary measure	Covariates	Association
Ball et al 2002	8726 Australian women	Prospective, 4yr, f/u	BMI maintenance	Self-reported total sitting time	Age, employment level, smoking, alcohol consumption, marital status, selected eating behaviours	Positive
Blanck et al 2007	18583 American men and women	Prospective, 7 yr f/u	Weight gain	Self-reported leisure time sedentary behaviour	Age, education, BMI, HRT, smoking, daily energy intake	Positive
Ching et al 1996	17795 American men	Prospective, 2yr f/u	Obesity	TV viewing	Age, smoking status, leisure time physical activity	Positive
Crawford et al 1999	881 American men and women	Prospective, 3yr f/u	BMI	TV viewing	Age, education smoking, diet	Null
Coakley et al 1998	19478 American men	Prospective, 4yr f/u	Weight change	TV viewing	Age, hypertension and hypercholesterolaemia	Positive
De Cocker et al 2010	5562 Australian women	Prospective, 6 yr f/u	Weight gain	Self-reported total sitting	Age, area of residence, education, employment grade, marital status, number of children, smoking status, alcohol consumption, leisure time physical activity	Null
Ekelund et al 2008	393 British men and women	Prospective, 5.6 yr f/u	BMI, fat mass, waist circumference	Heart rate defined sedentary time	Age, sex, physical activity energy expenditure	None. Reverse causality observed
Hu et al 2003	50277 American women	Prospective, 6yr f/u	Obesity (3757, 7.5%)	TV viewing >40 vs <1hrs.wk	Age, hormone use, alcohol, smoking, family history,	Positive

					diabetes mellitus, physical activity, diet	
Mortensen et al 2006	4945 American men	Prospective, 13 yr f/u	BMI	Self-reported sitting	Age, sex, smoking, physical activity	Null. Reverse causality observed
Oken et al 2007	902 American women	Prospective, 6 month f/u	Post-partum weight retention	TV viewing	Maternal education, gestational weight gain, prepregnancy BMI, smoking status	Positive
Parsons et al 2007	11301 British men and women	Prospective, 30 yr f/u	BMI	TV viewing frequency	Maternal BMI, social class, alcohol consumption, smoking, fruit and vegetable consumption	Positive
Pinto Pereira et al 2012	6562 British men and women	Prospective, 5yr f/u	BMI and BMI change	TV viewing	Age, frequency of MVPA, smoking status, fathers occupational class, education, longstanding illness, birth weight, diet, BMI and alcohol consumption,	Null
Raynor et al 2006	1422, American men and women	Prospective, 1yr f/u	Weight regain	TV viewing	Age, sex, ethnicity, education, employment status, marital status, physical activity	Positive
Saunders et al 2013	276 Canadian men and women	Prospective, 6yr f/u	Visceral fat accumulation	Self-reported total sitting time	Age, sex, baseline BMI, total physical activity, energy intake, smoking, education, income,	Positive
Stamatakis et al 2012	2972 British men and women	Prospective 21 yr f/u	Waist circumference	TV viewing frequency	Sex, smoking, alcohol, medication, social class, baseline exercise and MVPA	Positive

					at follow-up	
van Uffelen et al 2010	8233 Australian women	Prospective,	Body weight gain	Self-reported total sitting	Age, education, marital status, depression, physical activity smoking status, alcohol intake, area of residence, energy intake	Positive
Wijndaele et al 2009	1867, Australian mean and women	Prospective, 3yr f/u	Weight gain	TV viewing	Age, sex, baseline BMI, education, marital status, smoking	Positive
Wijndaele et al 2010	3846 Australian men and women	Prospective, 5yr f/u	Waist circumference	TV viewing	Age, education, employment status, household income, smoking, alcohol intake, parental history of diabetes	Positive
Aadahl et al 2007	1693 Danish men and women	Cross-sectional	BMI, waist circumference	TV viewing and leisure time sedentary behaviour	Age, sex, diet, alcohol, smoking status,	Positive
Banks et al 2011	74981 Thai men and women	Cross-sectional	BMI	TV viewing	Age, sex income and education	Positive
Bertrais et al 2005	3834 French men and women	Cross-sectional	BMI	Screen-time	Age, sex, education, smoking status, adherence to PA recommendations	Positive
Bowman et al 2006	9157 American men and women	Cross-sectional	Overweight	TV viewing	Age, sex, ethnicity, household income, exercise frequency, snacking frequency	Positive
Brown et al 2003	714 Australian men and women	Cross-sectional	Overweight or obesity	Self-reported sitting	Age, sex, number of children, working pattern, leisure time physical activity	Positive
Chang et al 2008	2353	Cross-sectional	BMI and waist	TV viewing	Age, sex, education,	Positive

	Taiwanese men and women		circumference		household income, smoking status, alcohol intake, leisure time physical activity	
Charreire et al 2010	4682 French men and women	Cross-sectional	Overweight	TV viewing	Age, education level, smoking status, place of residence	Positive
Chau et al 2012	10785 Australian men and women	Cross-sectional	Obesity	Leisure time sitting	Age, sex, education	Positive
Ching et al 1996	17795 American men	Cross-sectional	Obesity	TV viewing	Age, smoking status, leisure time physical activity	Positive
Cleland et al 2008	2001 Australian men and women	Cross-sectional	Waist circumference	TV viewing	Age, sex, occupation, education, smoking status, number of children, leisure time physical activity	Positive
Choi et al 2010	2019 American men and women	Cross-sectional	Obesity	Occupational sitting	Age, sex, marital status, number of children, household income, depression, longstanding illness, smoking, alcohol consumption, Leisure time MVPA	Positive
de Heer et al	11268 Mexican men and women	Cross-sectional	Obesity	Self-reported daily sitting time	Age, sex, employment status, educational attainment, family history of diabetes, hypertension, cholesterol level, and leisure time physical activity.	Positive
Dickerson 2011	2840 American men and women	Cross-sectional	BMI	TV viewing	Age, sex, ethnicity, education, area of residence, weekly MVPA	Positive
Du et al 2013	466605 Chinese	Cross-sectional	BMI, waist	Self-reported leisure	Age, sex area of residence,	Positive

	men and women		circumference and body fat percentage	time sitting	leisure time physical activity energy expenditure	
Dunstan et al 2005	6162 Australian Men and women	Cross-sectional	Obesity	TV viewing	Age, sex, education, marital status, family history of diabetes, dietary intake, leisure time MVPA	Positive
Dunton et al 2009	10984 American men and women	Cross-sectional	BMI	Leisure time sedentary behaviours and sedentary transport	Age, sex, education, ethnicity, MVPA	Positive
Ekelund et al 2008	393 British men and women	Cross-sectional	BMI, fat mass, waist circumference	Heart rate defined sedentary time	Age, sex, physical activity energy expenditure	Positive
Fitzgerald et al 1997	2453 Male and female Pima Indians	Cross-sectional	BMI	TV viewing	Age and physical activity	Positive
Fotheringham et al 2000	697 Australian adults	Cross-sectional	BMI	Computer use	Age, sex, physical activity	Null
Frank et al 2004	10878 American men and women	Cross-sectional	Obesity	Sitting in a car	Age, sex, ethnicity, education, household income, transport related physical activity	Positive
Fung et al 2000	468 American men	Cross-sectional	BMI	TV viewing	Age, alcohol consumption, fibre and fat intake, smoking status	Positive
Gao et al 2007	455 Puerto Rican and Dominican men and women	Cross-sectional	Waist-hip ratio	TV viewing	Age, sex, ethnicity, education, BMI, smoking status, alcohol, fat intake, activities of daily living score, leisure time MVPA	Positive
Giles-Corti et al 2003	1803 Australian men and women	Cross-sectional	Overweight and obesity	TV viewing	Age, sex, area socioeconomic status,	Positive

					leisure time physical activity	
Granner et al 2010	189 American women	Cross-sectional	BMI	TV viewing	Age, education, employment status, physical activity	Positive
Healy et al 2008	168 Australian men and women	Cross-sectional	Waist circumference and BMI	Accelerometer defined sedentary time	Age, sex, educational attainment, ethnicity, income, smoking status, alcohol consumption, diet, medical history, and daily MVPA	Positive
Healy et al 2008	169 Australian men and women	Cross-sectional	Waist circumference	Accelerometer defined sedentary time	Age, sex, educational attainment, ethnicity, income, smoking status, alcohol consumption, diet, medical history, and daily MVPA	Positive
Healy et al 2011	4757 American men and women	Cross-sectional	Waist circumference	Accelerometer defined sedentary time	Age, sex , educational attainment, ethnicity, income, smoking status, alcohol consumption, diet, medical history	Positive
Heinonen et al 2013	1993 Finish men and women	Cross-sectional	BMI and waist circumference	Self-reported leisure time sitting	Age, sex, socioeconomic status, smoking status, alcohol consumption, diet, genetic variants associated with body mass, occupational physical activity	Positive
Helmink et al 2011	221 Dutch adults	Cross-sectional	BMI	Self-reported total sitting	Age, sex, education, occupation, country of birth, total leisure time physical	Positive

					activity	
Ishizaki et al 2004	6676 Japanese men and women	Cross-sectional	BMI and waist-hip ratio	Occupational sitting	Age, sex, smoking status, alcohol consumption, education, marital status, habitual exercise	Positive
Jakes et al 2003	15515 British men and women	Cross-sectional	BMI	TV viewing	Age, alcohol consumption, smoking, status, vigorous and total physical activity	Positive
Johnson et al 2006	1555 American women	Cross-sectional	Obesity	TV viewing	Age, socioeconomic status, smoking status, depression and physical activity	Positive
Komal et al 2010	4187 Indian men and women	Cross-sectional	Obesity	TV viewing	Age, sex, leisure time physical activity	Null
Kronenberg et al 2000	1778 American men and women	Cross-sectional	BMI	TV viewing	Age, study centre, smoking status, alcohol consumption, education, income and leisure time physical activity	Positive
Leite and Nicolosi 2006	1415 Italian men and women	Cross-sectional	Waist circumference	TV viewing	Age, sex, employment status, education, smoking status, alcohol consumption, diet, occupational physical activity, leisure time physical activity	Positive
Lynch et al 2010	111 American women	Cross-sectional	BMI	Accelerometer defined sedentary time	Age, ethnicity, education, marital status, energy intake, MVPA	Positive
Lynch et al 2011	103 American men	Cross-sectional	Waist circumference	TV viewing	Age, ethnicity, education, marital status, energy intake, MVPA	Null

Maher et al 2013	4618 American men and women	Cross-sectional	Waist circumference	Accelerometer defined sedentary time	Age, sex, ethnicity, education, household income, medical history, smoking status, alocohol consumption, total energy and fat intake, total physical activity counts	Null
Martinez-Gonzalez et al 1999	15239 European men and women	Cross-sectional	BMI and obesity	Self-reported total sitting time	Age, sex, country of residence, physical activity	Positive
McGuire et al 2011	126 Canadian men and women	Cross-sectional	Abdominal obesity	Accelerometer defined sedentary time	Age and sex	Null
Mummery et al 2005	1579 Australian men and women	Cross-sectional	BMI	Occupational sitting time	Age, occupation, leisure time physical activity	Positive
Oppert et al 2006	5478 French men and women	Cross-sectional	BMI, waist circumference, body fat	Occupational sitting	Age, educational level	Positive for waist circumference
Parsons et al 2005	11109 British men and women	Cross-sectional	BMI	TV viewing	Age, parental BMI, Social class, smoking, alcohol intake, Diet, physical activity	Positive
Proper et al 2007	1048 Australian men and women	Cross-sectional	Overweight and obesity	Leisure time sitting	Age, sex, socioeconomic status, education, working hours, physical activity	Positive
Richmond et al 2010	6049, American women	Cross-sectional	BMI	TV viewing	Age, ethnicity, maternal education, parental obesity, household income	Positive in black women only
Salmon et al 2000	3392 Australian men and women	Cross-sectional	BMI	TV viewing	Age, sex, ethnicity, socioeconomic status, household income	Positive
Santos et al 2010	4091 Azorean men	Cross-sectional	BMI	Self-reported total sitting	Age, meal frequency, smoking, alcohol	Positive

					consumption	
Schaller et al 2005	893 German men and women	Cross-sectional	Obesity	TV and computer use	Age, sex, energy intake, smoking, socioeconomic status and physical activity	Positive
Shields et al 2008	42612 Canadian men and women	Cross-sectional	Obesity	TV viewing, computer use, reading	Age, sex, marital status, household income, area or residence, immigrant status, leisure time physical activity	Positive for TV and computer use
Shuval et al 2013	452 American adults	Cross-sectional	BMI and waist circumference	Self-reported total sitting, sitting in transport and computer use	Age, sex, ethnicity, marital status, health status, physical activity, health insurance coverage	Positive
Sidney et al 1996	4280 American men and women	Cross-sectional	Obesity	TV viewing	Age, education, smoking, alcohol consumption, test centre, physical activity score	Positive
Stamatakis et al 2012	5948 British men and women	Cross-sectional	Waist circumference and BMI	TV viewing other leisure time sitting and accelerometer defined sedentary time	Age, sex , social class, employment status, alcohol consumption, unhealthy eating index, psychological a distress, medication, occupational physical activity, accelerometer defined MVPA	Positive
Stamatakis et al 2012	2765 British men and women	Cross-sectional	BMI and waist circumference	Self-reported sitting and accelerometer defined sedentary time	Age, sex, occupational status, smoking, education, depression, alcohol consumption, medication, diet, accelerometer wear time (where appropriate), diet.	Positive

Stamatakis et al 2009	6215 Scottish men and women	Cross-sectional	BMI and waist circumference defined obesity	TV viewing/screen based entertainment	Age, sex, occupational class, frequency of snacking, adherence to physical activity guidelines	Positive
Sugiyama et al 2010	1408 Australian men and women	Cross-sectional	BMI	TV viewing time	Age, sex, ethnicity, socioeconomic status, active transport	Positive
Sugiyama et al 2008	2210 Australian men and women	Cross-sectional	Obesity	Leisure time sedentary behaviour	Age, sex, educational attainment, employment status, household income, physical activity	Positive
Swartz et al 2012	232 American men and women	Cross-sectional	Body fat	Accelerometer defined sedentary time	Age, sex, lifestyle moderate, walking moderate and vigorous intensity physical activities	Positive
Thomson et al 2008	613 Canadian men and women	Cross-sectional	Overweight and obesity	TV viewing	Age, sex, snacking behaviour	Positive
Thorp et al 2010	4164 Australian men and women	Cross-sectional	BMI and waist circumference	Self-reported sitting and TV viewing	Age, sex, education, family history of diabetes, employment status, smoking status, alcohol intake, diet quality, total leisure time physical activity time	Positive
Tudor-Locke et al 2009	158 Australian women	Cross-sectional	BMI	Occupational sitting	unadjusted	Positive
Vandelanotte et al 2009	2650 Australian men and women	Cross-sectional	Overweight and obesity	Internet and computer use	Age, sex, employment status, education, physical activity	Positive
van Uffelen et al 2010	8233 Australian women	Cross-sectional	Body weight	Self-reported total sitting	Age, education, marital status, depression, physical	Positive

					activity smoking status, alcohol intake, area of residence, energy intake	
Vioque et al 2000	1772 Spanish men and women	Cross-sectional	Obesity	TV viewing	Age, sex, educational level, smoking, marital status. Physical activity	Positive
Yates et al 2012	505 British men and women	Cross-sectional	BMI and waist circumference	Self-reported total sitting	Age, sex, ethnicity, social deprivation, smoking status, daily MVPA, and BMI	Null

Appendix 2.1. Ethics approval for intervention study (chapter 10)

College of Life and Environmental Sciences
SPORT AND HEALTH SCIENCES

St. Luke's Campus
University of Exeter
Heavitree Road
Exeter
EX1 2LU
United Kingdom

Certificate of Ethical Approval

Proposal: 2013/410

Title: The effect of prolonged continuous versus interrupted sitting on metabolic health

Applicants: Associate Professor Melvyn Hillsdon with Richard Pulsford and Dr Katarina Kos

The proposal was reviewed by the Ethics Committee and was approved from November 2012 to May 2013

Signature: 

Name/Title of Ethics Committee Administrator: Alison Hume, Student Services Manager

Your attention is drawn to the attached paper which reminds the researcher of information that needs to be observed when Ethics Committee approval is given.

Appendix 2.2. Participant information (chapter 10)

SPORT AND HEALTH SCIENCES
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EX1 2LU
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Fax: +44 (0)1392 724726
Email: sshs-school-office@exeter.ac.uk

February 2013

Does prolonged sitting affect markers of metabolic health?

Participant information sheet

Investigators: Richard Pulsford, Dr Katarina Kos, Associate Professor Melvyn Hillsdon

We would like to invite you to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information and to discuss it with other people, including the researchers, your friends, relatives and your healthcare team if you wish. Ask if there is anything that is not clear or if you would like more information or the opportunity to discuss the study further. Take time to decide whether you wish to take part in this study.

Thank you for taking the time to read this information.

What is the purpose of this study?

It is widely acknowledged that physical activity is associated with many positive health benefits such as a reduced risk of obesity, diabetes, heart disease, high blood pressure and cholesterol. However in the last 10 years, considerable attention has been directed at possible harmful effects of prolonged periods of sitting, either at work or at home. Sitting down for extended periods may increase the risk of diseases such as obesity, diabetes and heart disease and may increase the amount of fats and sugar in the blood. It has also been observed that interrupting long periods of sitting may lessen these risks. However, little is known about the relationship between different patterns of sitting and health. The aim of this study is to examine the changes that occur in the levels of sugars (glucose) and hormones that control appetite in the blood during a whole day of sitting compared to days when sitting time is broken up by short bouts of standing or walking. The results will help us better understand the risks of prolonged sitting and the potential benefits of breaking up prolonged periods of sitting.

Why have I been invited?

We have invited you to take part because we are looking for male participants who meet a range of entrance criteria for this study.

Who is organising the study?

The organisers of this study are Richard Pulsford and Associate Professor Melvyn Hillsdon from the University of Exeter and Dr Katarina Kos of the University of Exeter Medical School.

What would I have to do?

You will be asked to attend a laboratory at the University of Exeter's St. Luke's campus on four separate occasions.

Preliminary testing visit (visit 1)

This will take no more than 90 minutes. This visit will initially provide you with an opportunity to discuss with the investigators any questions you may have regarding any aspect of the study's objectives, procedures or results. You will then be asked to sign a consent form stating that you are happy to take part.

If you agree to take part the rest of this first visit will involve some preliminary measurements including, height, weight, body fat percentage (using an electronic scale) and blood pressure (using an automatic blood pressure monitor). You will then be fitted with a portable gas analyser consisting of a rubber face mask attached to a small box which you will wear for a total of 35 minutes and which will collect and analyse all the air you breathe out. You will be seated for the first 20 minutes before being asked to stand for five minutes. You will then sit down for another 5 minutes before being asked to walk on a small motorised treadmill for 5 minutes. This will provide us with an idea of how much energy you use while sitting, standing and walking.

Before you leave you will be given an instruction pack for the remainder of the study. You will be required to;

1. wear an accelerometer (a small activity monitor which looks like a wrist watch) for 1 day prior to each subsequent visit. You will hand this in upon arrival for the main trial days
2. record your food intake on the day prior to the first main trial and then repeat the same food intake as far as possible on the day prior to subsequent trial days
3. refrain from any moderate or vigorous intensity physical activity (other than day to day tasks) for 48 hrs and from consuming alcohol for 24 hrs prior to attendance at the main trials
4. to refrain from eating or drinking anything apart from water for 10 hrs prior to the main trials

Trials 1-3 (visits 2-4)

Each trial day will last from 8.30am to 5.30pm. Upon arrival a cannula (small rubber tube) will be placed in a vein in your arm using a small needle to allow us to obtain blood samples. You will also be fitted with another accelerometer for your wrist and a similar activity monitor that attaches to your thigh using adhesive strips to monitor your activity during the day. During trial 1 you will be asked to sit at a desk from 9.00am to 5.00pm. You will be provided with a computer with internet access and a selection of newspapers. You are also free to bring any work, DVDs or books from home. Trials 2 and 3 are exactly the same but the day will be broken up by 2 minute periods of standing (trial 2) and slow walking on a small walking platform (trial 3) every 20 minutes. You will be given a test drink (Lucosade) during the morning and a meal replacement drink at lunch time. The meal replacement drink is a bit like a milkshake and is designed to provide all the nutrients required from a normal meal. You will also be free to drink as much water as you like during the trial days. Over the course of the day a total of 19 small blood samples

will be taken from the cannula while you are seated to examine the levels of glucose and insulin circulating in your blood.

At 5.00pm on each trial day, following the final blood collection, the cannula will be removed and you may help yourself to a selection of food.

Do I have to take part?

Please remember that participation in this study is entirely voluntary. It is up to you to decide whether you would like to take part or not and if you decide to take part you are free to leave the study at any time without giving a reason as to why you wish to do so. If you do decide to participate in this study you will be asked to sign a consent form before you start. You will be given a copy of the consent form and this information sheet for your own records.

What are the potential risks of taking part?

Blood sampling and intravenous access can cause some temporary discomfort associated with insertion of a needle. There is also a small risk of localised bleeding/bruising, risk of blood clot formation (less than 1 in 100) or fainting. However these techniques are used extensively in physiological testing. The investigators are trained and experienced in all aspects of these procedures to ensure that they are performed safely and with the minimum possible discomfort.

Are my results confidential?

If you consent to take part in this study you have a right to privacy. Your name will be linked to an ID number on a password protected database and only these IDs will be used as labels during blood and data analysis.

What will happen to the results of this study?

The results will increase our understanding of the risks associated with prolonged sitting and the potential benefits of breaking up extended periods of sitting. We will aim to publish the findings in research journals and to present them at conferences in the UK or abroad. Your data will always remain anonymous and your name will not appear on any results.

Who has reviewed this study?

All research activity at the University of Exeter is examined and approved by an ethics committee to protect your interests. This study has been approved by the Ethics Committee of Sport and Health Sciences, College of Life and Environmental Sciences, University of Exeter.

Contacts for further information

If you would like more information or if you have any further questions about the study please contact the investigators using the details below:

Richard Pulsford	Associate Professor Melvyn Hillsdon
School of Sport and Health Sciences	School of Sport and Health Sciences
Richards Building	Richards Building
St. Lukes Campus	St. Lukes Campus
Exeter University	Exeter University
EX12LU	EX12LU
Tel: 07709 179 500	Tel: 01392 722868
Email: rmp210@exeter.ac.uk	Email: m.hillsdon@exeter.ac.uk

Appendix 2.3. Informed consent form

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St Luke's Campus
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EX1 2LU
United Kingdom

Tel: +44 (0)1392 722896/722884
Fax: +44 (0)1392 724726
Email: sshs-school-office@exeter.ac.uk

Informed consent form

Does prolonged sitting affect markers of metabolic health?

Participant identification number:
Investigator: Richard Pulsford **please *initial* each box**

1. I confirm that I have read and understand the information sheet dated January 2013 and have been given a copy to keep ☐
2. I have had the opportunity to ask questions about the study and have received satisfactory answers ☐
3. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason ☐
4. I agree that my details can be stored on a secure computer database ☐
5. I understand that my blood samples will be stored for analysis now and in the future in research related to this study and only by this research group ☐
6. I understand that if I am withdrawn from the study, data and samples already collected and anonymised may be used in conjunction with this study ☐
7. I understand that the study consists of three trial days which begin at 8.30AM and are anticipated to finish at around 5.00PM ☐
8. I agree to take part in the above study and know how to contact the research team ☐

When you have **initialled** all the boxes above, please sign and date below

Name of Participant	Date (DD/MM/YYYY)	Signature

Name of Person taking Consent (Investigator or other designated person)	Date (DD/MM/YYYY)	Signature

Name of the investigator 1 for participant; 1 for researcher	Date (DD/MM/YYYY)	Signature

Appendix 2.4. Physical activity readiness questionnaire (chapter 10)

Physical Activity Readiness
Questionnaire - PAR-Q
(revised 2002)

PAR-Q & YOU

(A Questionnaire for People Aged 15 to 69)

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly: check YES or NO.

YES	NO		
☐	☐	1.	**Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?**
☐	☐	2.	**Do you feel pain in your chest when you do physical activity?**
☐	☐	3.	**In the past month, have you had chest pain when you were not doing physical activity?**
☐	☐	4.	**Do you lose your balance because of dizziness or do you ever lose consciousness?**
☐	☐	5.	**Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?**
☐	☐	6.	**Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?**
☐	☐	7.	**Do you know of any other reason why you should not do physical activity?**

If you answered

YES to one or more questions

Talk with your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want — as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

NO to all questions

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- start becoming much more physically active – begin slowly and build up gradually. This is the safest and easiest way to go.
- take part in a fitness appraisal – this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively. It is also highly recommended that you have your blood pressure evaluated. If your reading is over 144/94, talk with your doctor before you start becoming much more physically active.

DELAY BECOMING MUCH MORE ACTIVE:

- if you are not feeling well because of a temporary illness such as a cold or a fever – wait until you feel better; or
- if you are or may be pregnant – talk to your doctor before you start becoming more active.

PLEASE NOTE: If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

Informed Use of the PAR-Q: The Canadian Society for Exercise Physiology, Health Canada, and their agents assume no liability for persons who undertake physical activity, and if in doubt after completing this questionnaire, consult your doctor prior to physical activity.

No changes permitted. You are encouraged to photocopy the PAR-Q but only if you use the entire form.

NOTE: If the PAR-Q is being given to a person before he or she participates in a physical activity program or a fitness appraisal, this section may be used for legal or administrative purposes.

"I have read, understood and completed this questionnaire. Any questions I had were answered to my full satisfaction."

NAME _____

SIGNATURE _____ DATE _____

SIGNATURE OF PARENT or GUARDIAN (for participants under the age of majority) _____ WITNESS _____

Note: This physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if your condition changes so that you would answer YES to any of the seven questions.

Supported by: Health Canada Santé Canada

continued on other side...

SIT Study

Appendix 2.5. Participant pre-trial instructions (chapter 10)

Pre-trial instruction sheet

Thank you very much for agreeing to take part in the SIT Study. We are very grateful for your help. It is very important that you adhere to the following do's and don'ts on **the day before each trial**:

1. **DO** – wear the physical activity monitor provided. This should be worn on your left wrist (like a wrist watch) **from 8.30AM** on the day before the trial day and taken off and given to one of the investigators when you arrive at the laboratory on the morning of your trial.

2. **DO** – accurately record **everything you eat and drink** on the day before each trial day on the food diary sheet provided. It is very important that you then use this sheet to follow the exact same diet on the day before the next trial days.

3. **DO NOT** – undertake any moderate or vigorous **exercise or physical activity** (e.g. going to the gym, playing sport, or going jogging) on the **two days** prior to each trial. Day to day activities such as walking, stair climbing and light house work are fine.

4. **DO NOT** – consume **any alcohol** on the day before the main trials.

5. **DO NOT** – eat or drink anything apart from water **after 10.00PM** on the day before the main trials. In order to accurately measure how your blood sugar is regulated it is very important that you attend the laboratory having fasted for 10 hours.

6. **DO** – attend the laboratory in **comfortable clothing** (loose fitting trousers – tracksuit trousers would be best) and footwear (training shoes). One of the activity monitors will be attached on your thigh so wearing shorts underneath your trousers would be a good idea.

Adherence to all these instructions is **vital to the measurements** we can make during the trials. We ask that you do your utmost to keep to these instructions. However, if you forget to adhere to any part of them please contact Richard as soon as possible and you trial can be rescheduled.

If you have any questions or problems regarding any part of these instructions please contact Richard immediately on 07709179500

Thanks again

Appendix 2.6. Food record diary (chapter 10)

SIT Study

Food Diary

We would like you to record everything you eat and drink on the day before your first main trial day. The quantity of each item can be described in weight (e.g. grams of rice), volume (e.g. a hand-full of pasta) or simply the number of items/portions (e.g. number of Weetabix/cups of fruit juice).

We would like you to repeat this exact diet on the day before the next two trial days.

	Food	
	Type	Quantity
Breakfast		
Morning (before lunch)		
Lunch		
Afternoon (between lunch and evening meal)		
Evening meal		

Evening		

Appendix 2.6. Timetable for main trial days

Real Time	Test Clock	Participant	Bloods	Intervals/meals
0830		8.30 – 8.45 arrival at lab		
0840				
0850		Weight taken		
0900		0900 Seated	Cannula inserted	
0910		0900-1000 Rest period		
0920				
0930				
0940				
0950				
1000	0.00	Main test protocol	Baseline sample[1]	OGTT[3] – Int1[4]
1010	0.10		Sample 2	
1020	0.20		Sample 3[1]	Int2[2]
1030	0.30		Sample 4	
1040	0.40			Int3
1050	0.50			
1100	1.00		Sample 5[1]	Int4[3]
1110	1.10			
1120	1.20			Int5
1130	1.30		Sample 6	
1140	1.40			Int6
1150	1.50			
1200	2.00		Sample 7[1]	Int7[3]
1210	2.10			
1220	2.20			Int8
1230	2.30		Sample 8	
1240	2.40			Int9
1250	2.50			
1300	3.00		Sample 9[1]	Test meal[3] Int10[4]
1310	3.10		Sample 10	
1320	3.20		Sample 11[1]	Int11[2]
1330	3.30		Sample 12	
1340	3.40			Int12
1350	3.50			
1400	4.00		Sample 13[1]	Int13[2]
1410	4.10			
1420	4.20			Int14
1430	4.30		Sample 14	
1440	4.40			Int15
1450	4.50			
1500	5.00		Sample 15[1]	Int16[3]
1510	5.10			
1520	5.20			Int17
1530	5.30		Sample 16	
1540	5.40			Int18
1550	5.50			

1600	6.00		Sample 17[(1)]	Int19[(3)]
1610	6.10			
1620	6.20			Int20
1630	6.30		Sample 18	
1640	6.40			Int21
1650	6.50			
1700	7.00	Food and drinks provided. Participants free to leave	Sample 19[(2)]	Int22[(1)]
1710	7.10		–cannula out	
1720	7.20			
1730	7.30			

Appendix 3.1 Gant chart for PhD studies

		Year 1												Year 2												Year 3											
		2010			2011												2012												2013									
		O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D
	PhD Upgrade																																						
Chapter 1	Writing																																						
Chapter 2	Writing																																						
Chapter 3	Lit searches																																						
	Writing																																						
Chapter 4	Whitehall II Study																																						
Chapter 5	Data analyses																																						
	Writing																																						
Chapter 6	Data analyses																																						
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Chapter 7	Data analyses																																						
	Writing																																						
Chapter 8	Data analyses																																						
	Writing																																						
Chapter 9	HSE analyses																																						
	Writing																																						
Chapter10	Planning																																						
	Recruitment																																						
	Data collection																																						
	Data analyses																																						
	Writing																																						
Chapter11	Writing																																						