Longitudinal patterns of physical activity from midlife to old age: predictors and consequences for cardiovascular disease morbidity and mortality risks

THESIS presented for the degree of DOCTOR OF PHILOSOPHY

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DECLARATION OF AUTHORSHIP

I, Daniel Aggio, confirm that the work presented in this thesis is a result of my own work. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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ABSTRACT

Background/aims

Physical activity is important for almost all aspects of healthy ageing, including cardiovascular disease (CVD) prevention. While an age-related decline in physical activity is clear from cross-sectional studies, there are few prospective cohort studies with sufficient follow up to identify the long-term patterns of physical activity across adulthood and into old age. Subsequently, the predictors and health consequences of long-term patterns of physical activity are unclear. The primary aim of this thesis is to identify the patterns of long-term physical activity from midlife to old age and examine the predictors of such patterns and consequences in relation to cardiovascular morbidity and mortality.

Methods

This thesis uses data from the British Regional Heart Study, a prospective cohort study of men recruited in 1978-80 when they were aged 40 to 59 years. Initially, this thesis uses data from baseline up to the 20-year follow up, when men were aged 60-79 years, to examine change and trajectories of total and specific types of physical activity. Subsequent analyses explore associations between trajectories of physical activity and CVD risk factors, major stroke and coronary heart disease events, CVD mortality and all-cause mortality up until June 2016.

Results

One of the key findings was that total physical activity levels in old age were largely predicted by midlife physical activity. Trajectories of physical activity varied according to type; walking and recreational activity were more variable over time than total physical activity and sport/exercise. Smoking, being overweight or obese and suffering from breathlessness were associated with increased odds of following unfavourable trajectories for total and specific types of physical activity. Sociodemographic, health and behavioural factors were also associated but the direction and magnitude of associations were specific to physical activity type. Compared to a low, decreasing trajectory, light stable and moderate, increasing trajectories were associated with more favourable levels of CVD risk factors and a lower risk of all-cause mortality, CVD mortality and major coronary heart disease. There was also a

dose-response relationship, suggesting that higher levels of physical activity across adulthood were more favourable.

Conclusions

Physical activity levels in midlife largely determine activity levels throughout adulthood and into old age. Sport and exercise appears to be the most stable physical activity type and the strongest predictor of subsequent activity levels, whereas walking and recreational activity are more variable. A range of sociodemographic, health and behavioural factors were associated with long-term patterns of physical activity and could be used to inform intervention strategies. Although sustaining/increasing moderate levels of physical activity from midlife to old age are optimal for minimising risks of CVD and mortality, maintaining a light level of physical activity across the adult life course can also provide significant survival benefits and could be achievable for the least active.

IMPACT STATEMENT

Most importantly this thesis demonstrated the importance of promoting engagement in physical activity from early life, with a particular emphasis on sport and exercise. This provides support for public health leaders and policymakers seeking to promote policies that encourage physical activity across the life course. Although this thesis emphasises the importance of early intervention, it also highlights opportunities for intervention during later life. First, public health practitioners should be aware of the various indicators in midlife that predict lifelong inactivity and support the public in making changes to physical activity at the earliest opportunity. Second, it highlights a range of life events and sociodemographic-, behavioural- and health-related factors that could be targeted by population-wide interventions to reduce barriers to physical activity.

This thesis also supports the argument that even modest levels of physical activity are beneficial in later life. If more research is conducted that supports these findings, it may contribute to the debate around the appropriateness of the current physical activity guidelines for older adults, which at present advocate for the same level of aerobic physical activity as the rest of the adult population.

The most important clinical implication for healthcare professionals is that current physical activity levels are the most important indicator of subsequent CVD and mortality risk. Past physical activity behaviour may help understand levels of CVD risk factors but is not essential for predicting CVD and mortality risk.

This thesis also has implications for future research. Hopefully, the findings of this thesis will pave the way for more research using group-based methods to identify physical activity trajectories across longer periods of the life course, in more diverse populations and using device-based measures of physical activity. Subsequent research could help further our understanding of the origins of lifelong physical activity and highlight new opportunities for intervention.

The results of this thesis have been disseminated via publications in scientific journals and conference presentations. Some of the work in this thesis has also received widespread media attention, featuring in news articles in the UK and abroad. Finally, the results have been shared with contacts at relevant stakeholders such as Sport England.

FREQUENTLY USED ABBREVIATIONS

BIC	Bayesian information criterion
BMI	Body Mass Index
BRHS	British Regional Heart Study
CHD	Coronary Heart Disease
CI	Confidence Interval
CRP	C-reactive protein
CVD	Cardiovascular disease
m	Metre
GBTM	Group-based trajectory modelling
HR	Hazards ratio
Hs-TnT	High-sensitivity cardiac troponin T
ICC	Intra-class correlation coefficient
ICD	International Classification of Diseases
IL-6	Interleukin-6
Kg	Kilograms
LCGA	Latent class growth analysis
MI	Myocardial infarction
mmHg	Millimetre of mercury
mmol/L	Millimoles per Litre
NT-proBNP	N-terminal pro-brain natriuretic peptide
OR	Odds ratio
RR	Risk ratio
tPA	tissue plasminogen activator antigen
UK	United Kingdom
vWF	von Willebrand factor
WHO	World Health Organisation

MEDIA

UK, national tabloid – Daily Mail

UK, national tabloid – Daily Express

USA, news magazine – Time Magazine

BMJ Open Blog – https://blogs.bmj.com/bmjopen/2017/09/20/physically-active-mid-lifers-more-likely-to-be-active-into-old-age/

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CHAPTER 1. INTRODUCTION

1.1 Introduction and rationale for thesis

1.1.1 Ageing and cardiovascular disease

Population projections estimate that there will be 21.9 million people aged 60 and over by the year 2039 in the UK, comprising nearly 30% of the population. This is a 7% increase in the proportion of over 60 year olds compared to 2014 when there were 14.9 million (1). As a result, many more adults will be making the transition from midlife to old age, a critical life stage when the absolute risks of many chronic diseases, including cardiovascular disease (CVD) rise steeply (2). In this ageing population, preventing the onset of chronic disease is the key to promoting healthy ageing.

CVD refers to diseases of the heart and circulatory system, including coronary heart disease (CHD) and stroke. Mortality rates from CVD have steadily declined in the last few decades but it is still ranked as the second most common cause of death in the UK, with 158,000 deaths in 2015 (3). One explanation for this decline is that survival rates following a myocardial infarction (MI) have continued to improve in the UK, reflecting the rise in the prescribing of evidence-based medications (4). Despite declines in CVD mortality, more people than ever are living with CVD, resulting in increased burden in terms of disability and economic cost, with an estimated spend of £26 billion in 2015 in the UK (5). As such, research on the prevention of CVD remains a high priority. It is generally well accepted that CVD can be largely prevented through healthy lifestyle behaviours (6). Physical activity is one such behaviour that has been the focus of prevention attempts; however, most studies on the predictors and benefits of physical activity focus on a fairly short timeframe. As such, the determinants of long-term physical activity and the related health benefits in old age remain uncertain.

1.1.2 Physical activity and cardiovascular disease

Physical activity is defined as any bodily movement produced by skeletal muscles requiring energy expenditure (7). Physical activity can be accumulated in a variety of ways, including voluntary activities such as sports and exercise, spontaneous activities that are required for daily living (e.g. washing) and obligatory activities that are required for survival (8). As discussed in detail in section 2.3.1, over the past five to six decades, environmental changes

and technological advances have resulted in large secular changes in physical activity participation (9, 10). There is also a suggestion, primarily from cross-sectional data, that there is an age-related decline in physical activity (11). These declines begin in childhood and then become more rapid between the fifth and ninth decades of life (11) and may be implicated in the onset of numerous chronic conditions as well as the increased risk of CVD as people age (2).

Most research suggests that optimal health benefits are achieved through moderate-to-vigorous intensity activity (12). Based on this evidence, the World Health Organisation (WHO) recommends adults should accumulate at least 150 minutes of moderate-to-vigorous physical activity per week or 75 minutes of vigorous intensity physical activity (7). Worldwide it is estimated that eliminating physical inactivity (i.e. not meeting physical activity guidelines) completely would avert 5.3 million deaths and 6% of the burden from CHD (13). In the UK, the proportion of CHD deaths attributable to physical inactivity is even higher, rising to 10.5% (13).

Despite the risks, a large proportion of older adults do not meet current physical activity guidelines (14). Indeed, a recent study showed that only 7.9% of older adults continuously meet these guidelines and only 4.9% started to take up this level of physical activity in old age (14). To date, most prospective studies exploring change in physical activity have focussed on fairly short time frames, and the long-term patterns of physical activity into old age have not been extensively studied. It is possible that certain subgroups are able to maintain, delay declines, or even increase physical activity into old age, but this is less known. Furthermore, the extent and timing of these age-related changes in physical activity are unclear. Thus, we have a limited understanding of the factors that initiate change and the subsequent impact of these changes on CVD morbidity and mortality.

1.1.3 Life course perspective on physical activity

Life course epidemiology is an approach used to investigate the long-term impact of physical and social factors during specific life stages on future health and disease risk (15). The life course approach accounts for the possibility that exposures can act cumulatively across the life course as well as there being critical periods whereby an exposure during a specific life stage has a particularly strong effect on the development of on an outcome but has little or no effect at other life stages (15).

Over recent years, this pioneering approach has been increasingly used to understand how physical activity tracks across the life course, to identify factors associated with change in physical activity and to investigate how physical activity at particular life stages is associated with future health risks. Understanding the tracking or stability of physical activity over time is important for identifying its modifiability and appropriate periods for intervention. As discussed in detail in Chapter 2.2, previous physical activity is one of the strongest predictors of current physical activity levels (16), highlighting some degree of tracking longitudinally. Importantly, however, physical activity during specific life stages may be crucial for establishing a lifelong habit for physical activity. For example, it has been recognised that adolescence may be an important period for establishing a habit for physical activity in later life (17). However, the transition from midlife to old age, a period that coincides with several major life events that could influence physical activity, has been less studied. Furthermore, at present, the majority of studies investigating patterns or change in physical activity during this period have been over relatively short time frames and have used fairly crude methods to describe change, with only a small number of repeated measures. Subsequently, these studies neglect to capture potentially important fluctuations in physical activity.

This thesis uses a life course approach to understand how and why physical activity changes from midlife to old age and the subsequent impact on CVD and mortality later on in life.

1.2 Objectives of thesis

The primary aim of this thesis is to understand the patterns of total and specific types of physical activity from midlife to old age and the subsequent risk of CVD and mortality in later life. The main research objectives of this thesis are:

I. To examine the tracking of total and specific types of physical activity (walking, recreational activity and sport/exercise) from midlife (aged 40-59 years) to old age (aged 60-79)
II. To identify the trajectories of total and specific types of physical activity from midlife to old age and examine their predictors
III. To investigate the association between trajectories of total physical activity from midlife to old age and CVD risk factors in old age
IV. To investigate the association between trajectories of total physical activity from midlife to old age and subsequent major CVD events, CVD mortality and all-cause mortality in old age

1.3 Overview of methodology

This thesis analyses data collected as part of the British Regional Heart Study (BRHS), a prospective cohort study which was initially designed to investigate regional variations in CVD across Britain. The BRHS involves a large representative sample of 7735 men recruited from one primary care centre in each of 24 towns across Great Britain. Men were initially examined in 1978-80 when aged 40 to 59 years. Men have since been followed up periodically until the present day via postal questionnaires, physical examinations, the National Health Service Central Register and reports from General Practitioners. A full description of the BRHS can be found in Chapter 3. This thesis uses data spanning 40 years including questionnaire data from baseline up to the 20-year follow up, with subsequent follow up for CVD events and mortality until 2016.

The BRHS is highly appropriate for addressing the objectives of this thesis as it provides repeated measures of self-reported physical activity over a long timeframe, including measures of different physical activity types. Further, the same physical activity questionnaire was administered at each wave allowing comparisons over time. In addition, the BRHS has regular objective measures of CHD events, CVD events and mortality, allowing the relationship between physical activity trajectories and these outcomes in later life to be investigated. The BRHS is comprised of a large and geographically representative sample of British men, but it does not include women or represent black and minority ethnic groups.

1.4 Structure of thesis

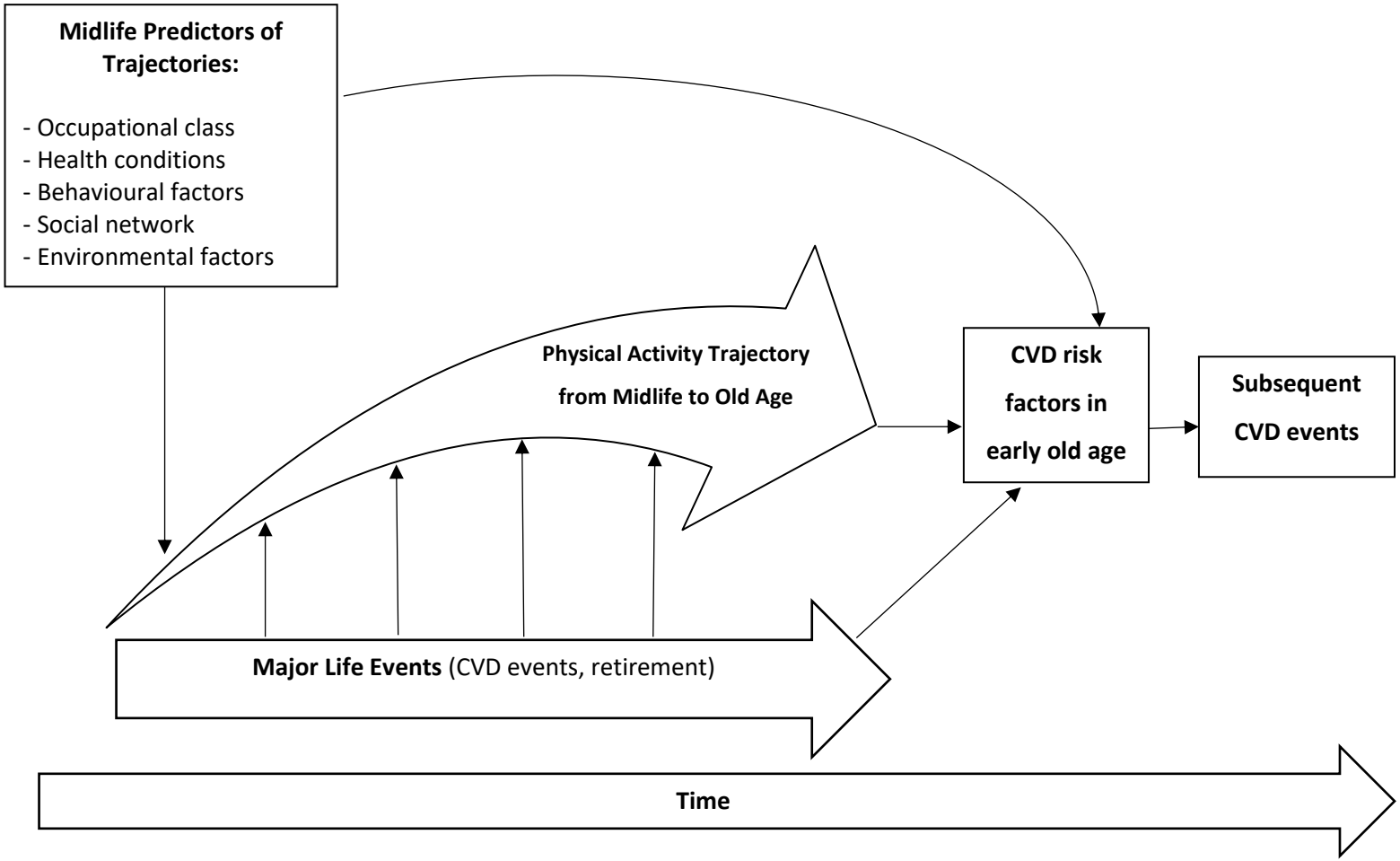
Following this introduction, Chapter 2 provides a review of the literature. This review includes an epidemiological and aetiological overview of CVD, a description of secular and life course physical activity trends and discusses the correlates and determinants of physical activity. It also describes the relationship between physical activity and CVD risk and mortality. Chapter 3 describes the BRHS design and methodology, the measurements and data used in this thesis, and the analytical techniques used to examine the data. Chapters 4 to 8 present the results of analyses performed to address the objectives of this thesis. Each of these chapters includes a literature review, rationale for the study, aims and hypotheses, followed by the methods, results, discussion and conclusion. Chapter 4 explores the stability and tracking of physical activity and specific types of physical activity from midlife (40-59 years) to old age (60-79 years) using data from baseline, 12-, 16- and 20-year follow ups. Chapter 5 identifies the 20-year trajectories of physical activity and physical activity types and the predictors of these trajectories using data from baseline up to the 20-year follow up. Chapter 6 develops on these findings by exploring how the identified trajectories are associated with CVD risk factors measured at the 20-year follow up physical examination when men were in old age. This leads to Chapter 7 which investigates the association between the 20-year physical activity trajectories and subsequent CVD incidence and mortality up to 2016. The conceptual framework of this thesis is shown in Figure 1.1. Arrows indicate the pathways linking midlife factors and major life events with physical activity trajectories and subsequent CVD risk and mortality. To conclude, the final chapter synthesises the findings from chapters 4-7 and discusses the public health implications and recommendations for future research.

1.5 Thesis publications

1. **Aggio D**, Papacosta O, Lennon L, Whincup P, Wannamethee SG, Jefferis BJ. Association between physical activity levels in mid-life with physical activity in old age: a 20-year tracking study in a prospective cohort. BMJ Open. 2017;7(8):e017378.
2. **Aggio D**, Papachristou E, Papacosta O, Lennon LT, Ash S, Whincup PH, Wannamethee SG, Jefferis BJ. Trajectories of self-reported physical activity and predictors during the transition to old age: a 20-year cohort study of British men. Int J Behav Nutr Phys Act. 2018;15(1):14.

3. **Aggio D**, Papachristou E, Papacosta O, Lennon LT, Ash S, Whincup PH, Wannamethee SG, Jefferis BJ. Association Between Twenty-Year Trajectories of Non-Occupational Physical Activity From Midlife to Old Age and Biomarkers of Cardiovascular Disease: A 20-Year Longitudinal Study of British Men. Am J Epidemiol. 2018;187(11):2315-2323.
4. **Aggio D**, Papacosta O, Lennon LT, Ash S, Whincup PH, Wannamethee SG, Jefferis BJ. Tracking of sport and exercise types from midlife to old age: a 20-year cohort study of British men. Eur Rev Aging Phys Act. 2018;15:16.
5. **Aggio D**, Papachristou E, Papacosta O, Lennon LT, Ash S, Whincup PH, Wannamethee SG, Jefferis BJ. Twenty-Year Trajectories of Physical Activity Types from Midlife to Old Age. Med Sci Sports Exerc. 2019;51(3):481-9.
6. **Aggio D**, Papachristou E, Papacosta O, Lennon LT, Ash S, Whincup PH, Wannamethee SG, Jefferis BJ. Trajectories of Physical Activity from Midlife to Old Age and Associations with Subsequent Cardiovascular Disease and All-Cause Mortality. J Epidemiology and Community Health. *In Press.*

Figure 1.1. Conceptual Model for Thesis



CHAPTER 2. LITERATURE REVIEW

In this review I provide an epidemiological and aetiological overview of CVD, including a discussion on established and novel risk factors for CVD. In addition, I summarise the literature on secular and temporal trends of physical activity and explore the evidence on the correlates and determinants of physical activity. Sections 2.4 and 2.5 examine the evidence on the association between physical activity patterns and the risk of CVD and mortality in older age. The final section summarises all the evidence discussed, highlighting the gaps in the literature and how this thesis addresses them.

2.1 Search strategy to identify literature

Various searches were conducted to identify relevant observational longitudinal studies examining physical activity stability, patterns/trajectories of physical activity and the impact of long-term physical activity habits on CVD and mortality in old age by entering keywords into Web of Science (Core Collection) and Pubmed as title searches. Searches were initially conducted in 2016 and updated in late 2018. Studies with an experimental design were not considered. No restrictions were made for date of publication or language. Separate searches were conducted for i) physical activity tracking/stability and ii) physical activity patterns/change and associations with subsequent CVD and mortality. Reference lists of identified papers were also checked for relevant papers. Keywords used for the searches can be found in Appendix 2A.

2.2 Overview of cardiovascular disease

2.2.1 Epidemiology and pathophysiology of CVD

Although death rates from CVD have been falling for almost five decades in the UK, it is still ranked as the second most common cause of death, accounting for 26% (n=158,155) of all deaths in the UK in 2015 (3). CHD and stroke are the most common types of CVD and were responsible for 44% and 25% of CVD deaths in the UK in 2015, respectively. The observed decline in death rates from CVD over recent decades is likely due to reductions in smoking and improvements in the treatment and management of the major risk factors (18, 19). As a result, more people than ever are living with CVD. Indeed, estimates suggest that more than

5 million people alive in the UK in 2015 had previously suffered a CVD event (5), contributing to considerable burden in terms of morbidity, disability and quality of life. In 2015, the estimated cost of CVD to the economy was €26 billion (5). Almost half of which (46%) was due to healthcare costs, 35% was due to production losses and 23% was down to informal care costs. With more people than ever living with CVD, prevention is still a high priority.

Atherosclerosis is the primary cause of the majority of CHD and a large proportion of cerebrovascular disease (20, 21). Atherogenesis refers to the gradual accumulation of atherosclerotic plaques, resulting in a thickening of the artery walls and a narrowing of the arterial lumen, ultimately leading to restricted blood flow to the myocardium. These plaques can also form in carotid arteries, resulting in a narrowing of the cerebral arteries (carotid atherosclerosis) and causing a large proportion of strokes (22). Chronic inflammation of the arterial walls and endothelium is central to the development of atherosclerotic plaques and is triggered by a variety of factors, including dyslipidemia and hypertension (23). Over time the arterial walls are weakened and under increasing mechanical stress can rupture forming a thrombus. The thrombus may subsequently obstruct blood flow to the brain or heart, eventually leading to stroke or MI.

The most severe outcomes of CHD include fatal and non-fatal MI and sudden ischaemic death (24). Other manifestations include angina pectoris, a condition caused by restricted blood flow to the heart, resulting in chest pain. Angina can be classified as stable if symptoms are predictable, such as after exertion (stable angina), or unstable if symptoms occur irregularly/even at rest.

Cerebrovascular disease outcomes include stroke and transient ischaemic attacks (TIA) (25). TIAs, often referred to as a ‘mini-stroke’, are caused by restricted cerebral blood flow characterised by a temporary loss of neurological function lasting less than 24 hours. Strokes, on the other hand, have longer lasting and irreversible symptoms (26).

2.2.2 Established risk factors for CVD

As described in the previous section, there are several factors that are involved in the atherosclerotic process leading to CVD. Many of these factors are modifiable and can be targeted to reduce CVD risk. Among the modifiable risk factors, there are eight established, or traditional, risk factors proposed by the WHO that are responsible for a large proportion of preventable deaths, including alcohol use, tobacco use, hypertension, high body mass index (BMI), physical inactivity, dyslipidaemia, hyperglycaemia and poor diet. Globally, these

factors are recognised as the leading risk factors for all-cause mortality and are responsible for a large proportion of MI and stroke deaths (27, 28).

2.2.2.1 Hypertension

Hypertension is ranked as the leading risk factor for mortality globally by the WHO and is attributed to 13% of deaths globally (28). The prevalence of hypertension and proportion of deaths attributed to hypertension has been on the rise over recent years. Between 1990 and 2015, the proportion of adults with hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) increased from 17% to 21% (29). In 2015, it was responsible for approximately 40% of all heart disease and stroke deaths, a 1.4-fold increase from 1990 (29).

Blood pressure is positively associated with the risk of both stroke and CHD. At ages 40-69 years, every 20 mmHg decrease in systolic blood pressure is associated with more than a twofold decrease in the risk of stroke and a twofold decrease in the risk of CHD (30). These associations persist but are less pronounced in the oldest old. The causes of hypertension are complex, but lifestyle factors, such as inactivity, unhealthy diet, harmful use of alcohol and tobacco use are all implicated (31).

2.2.2.2 Tobacco use

Tobacco use, primarily smoking, is ranked second among the leading global risk factors for mortality worldwide and is the most important lifestyle-related risk factor on this list. It is estimated to cause 35.7% of MIs (27) and 10% of CVD globally (28). Although smoking prevalence has been falling over recent years in many countries, the WHO estimated that 1.1 billion adults smoked tobacco worldwide in 2015 (32). The negative health consequences of smoking are widely documented, with recent meta-analyses estimating that smoking doubles the risk of all-cause and CVD mortality in older adults (33, 34). There is evidence that smoking cessation, but not reduction (35), can reverse the adverse effects of smoking, resulting in similar survival rates to those who have never smoked (33, 34, 36). Subsequently, promoting cessation has and will continue to be for many years a major public health target.

2.2.2.3 Hyperglycaemia

High blood glucose, or hyperglycaemia, is ranked as the third leading risk factor for mortality worldwide (28). The underlying cause of hyperglycaemia is insulin resistance or abnormal

insulin secretion, resulting in an elevated concentration of blood glucose. A fasting blood glucose of ≥ 7.0 mmol/L is defined as hyperglycaemia and concentrations greater than ≥ 11.1 mmol/L are classified as diabetic (37). Worldwide 11% of the population are diagnosed with this condition (28). Left untreated, hyperglycaemia can lead to a number of serious complications, including blindness, nerve damage, kidney failure and heart disease (37). A recent meta-analysis showed that a 1 mmol/L higher blood glucose is associated with a 40% increase in the risk of CVD mortality (38). Diet combined with physical activity can be effective in the prevention of diabetes in individuals who are at high risk (39).

2.2.2.4 Overweight/Obesity

Overweight and obesity is defined by the WHO as "abnormal or excessive fat accumulation that presents a risk to health". Obesity is one of the most commonly researched and hotly debated topics in public health today, largely owing to its importance for health and increasing prevalence worldwide. BMI is the most commonly used indicator of excess adiposity, calculated by dividing weight (kg) by height squared (m^2). A BMI of 25kg/m² to 29.9kg/m² is defined as overweight and a BMI of ≥ 30kg/m² is defined as obese. In 2016, more than 26% of UK adults were defined as obese (40). In England, the prevalence of obesity has almost doubled in the last two decades (41), largely due to nutritional transitions coupled with increasing sedentariness (42). Furthermore, the prevalence of overweight and obesity increases with age, peaking in early old age before tailing off in the oldest old (41). According to the WHO, an estimated 2.8 million people worldwide die as a result of being overweight or obese each year (28). Although obesity typically poses the greatest risk, being overweight also increases the risk of CVD mortality (43). Similar observations have been found using alternative measures of adiposity (44, 45); however, some evidence suggests that central obesity, measured via waist circumference, poses a greater risk than BMI-defined obesity (44). Excess adiposity often presents itself with many other CVD risk factors and is consistently associated with hypertension, dyslipidaemia and type 2 diabetes (46). This clustering of risk factors highlights the complex interrelationship between these CVD risk factors and suggests common underlying mechanisms.

2.2.2.5 Dyslipidaemia

Dyslipidaemia is defined as raised total or low-density lipoprotein (LDL), or low levels of high density lipoprotein (HDL) (47). Globally, it is estimated that 22% of the adult population has elevated cholesterol (total cholesterol ≥6mmol/L) (28), with concentrations typically

increasing with age (48). High cholesterol is responsible for 4.5% of deaths worldwide, equivalent to 2.6 million deaths per year, and is attributable for a third of CHD (28). A meta-analysis of 61 prospective studies showed that the risk of CHD mortality more than halved for every 1 mmol/L lower total cholesterol (49) although the benefits were less pronounced for stroke and in older adults. Diet, physical activity, adiposity and tobacco use are among the major modifiable determinants of cholesterol (50).

2.2.2.6 Alcohol

Several studies have demonstrated a U-shaped relationship between alcohol consumption and CVD mortality, with light and moderate consumption deemed optimal compared to abstainers and heavy drinkers (51, 52). A recent systematic review of 63 intervention studies highlighted more favourable changes in CVD risk factors in subjects exposed to a period of moderate alcohol consumption compared to controls (53). However, there is considerable debate over the reported protective effect of light to moderate consumption. Studies contesting this relationship have highlighted issues with the inclusion of former heavy drinkers in the 'abstainer' reference group, as they have a significantly higher risk of mortality than lifetime abstainers (54, 55). There is, however, consensus that heavy alcohol consumption poses a substantial risk to mortality from various causes, including CHD and stroke (51, 55, 56).

2.2.2.7 Poor diet

Various dietary components are known to contribute to the development of CVD, including high intake of saturated fat, salt, sugar and low intake of fruit and vegetables (57). Dietary fat plays an important role in determining plasma cholesterol levels. High dietary fat can lead to elevated cholesterol, which subsequently increases CHD risk (58). High intakes of salt and added sugar are associated with elevated blood pressure and insulin levels, respectively (59, 60). Meeting the recommended 5 portions of fruit and vegetables per day has also been shown to protect against CVD (61). It is hypothesised that the nutrients found in fruit and vegetables, such as antioxidants, folate and vitamins B6 and B12, are cardioprotective (62). However, only around a third of adults meet the 5-a day recommendation (57).

2.2.2.8 Physical inactivity

Physical inactivity is ranked as the fourth leading global risk factor for mortality (28). The wide-ranging health benefits of physical activity are well documented, yet many adults do

not meet current physical activity guidelines (14, 63). According to the Health Survey for England (2016), 34% of men and 42% of women do not meet current physical activity guidelines, which rises steeply to more than 60% in adults over 75 years (63). Early landmark studies from over half a century ago demonstrated a lower incidence of CVD in men from more active professions compared to men in more sedentary professions (64, 65). Since then, accumulating evidence has confirmed these findings in various settings (66) and shown that physical activity can also play a role in protection against stroke and in the secondary prevention of CHD (67). Sections 2.4 and 2.5 explore the evidence on the associations of physical activity with CVD risk factors and CVD incidence/mortality in detail.

2.2.3 Novel risk factors for CVD

Although these established risk factors explain a large proportion of CVD mortality (27, 28), a large amount of variability remains unexplained by these markers. Over recent years, a number of novel risk factors have been identified as playing a key role in the development of CVD. One such factor that has attracted considerable interest is the role of systemic low-level inflammation. It is now known that inflammation plays a key role in the development of atherosclerotic plaques (68). In particular, acute-phase proteins, such as C-reactive protein (CRP), have been implicated in several inflammatory processes leading to the development of atherosclerotic lesions (69). A meta-analysis including more than 160,000 individuals found that a one standard deviation increase in CRP was associated with approximately 1.3 times greater risk of CHD, stroke and cardiovascular mortality after adjustments for established risk factors (70). CRP also stimulates the production of the proinflammatory cytokine interleukin 6 (IL-6), which has pro-inflammatory properties that have a destabilising effect on atherosclerotic plaques (71). A meta-analysis of 29 prospective studies showed that a one standard deviation increase in IL-6 was associated with 1.3-fold increase in the risk of non-fatal and fatal CHD events after adjusting for a range of CVD risk factors (72). Another meta-analysis specifically in older adults found that compared to the lowest levels of IL-6, older adults with the highest levels of IL-6 were at a 1.5 and 1.7 times greater risk of all-cause and CVD mortality, respectively, after adjusting for established risk factors (73).

Disruptions in haemostasis can trigger clot formation, thereby inducing thrombosis (74). Similarly, elevated levels of haemostatic factors such as von Willebrand factor (vWF), a marker of endothelial dysfunction, markers of fibrinolytic activity (e.g. d-dimer and tissue plasminogen activator [tPA] antigen) and procoagulants (e.g. factor VIII) are all associated with an increased risk of CVD (75-79). A recent meta-analysis of 21 prospective studies (13

with tPA, 18 with d-dimer and 15 with vWF) in the general population explored associations between hemostatic factors and CHD. For every one standard deviation increase in tPA, d-dimer and vWF the risk of CHD was raised by 1.13, 1.23 and 1.16 times, respectively. Most included studies adjusted for traditional risk factors, including at least one lipid marker (80).

Furthermore, markers of cardiac injury, such as N-terminal pro-brain natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (Hs-TnT), have been associated with increased levels of other CVD risk factors and an increased risk of CVD (81, 82). A recent meta-analysis of 12 prospective studies in general populations showed that compared to individuals with the lowest NT-proBNP levels, those with the highest levels were at more than a two-fold increased risk of all-cause and CHD mortality and more than a three-fold increased risk of CVD mortality after adjusting for traditional risk factors, although the effects were slightly attenuated in men (83). A similar increased risk of all-cause and CVD mortality has also been observed in those with elevated levels of TnT (84).

2.3 Life course and secular trends in physical activity

2.3.1 Secular trends in physical activity

Participation in physical activity has changed considerably over the last century, but these secular trends are known to vary by physical activity types. As well as increases in food intake, secular declines in physical activity have also been implicated in the obesity epidemic. Several studies have shown notable declines in household-, occupational- and transport-related physical activity. In the National Health and Nutrition Examination Survey (NHANES), it was estimated that daily energy expenditure from occupational activity had declined by 142 calories in men from the 1960s to 2011 (9), presumably due to the environmental changes that have led to more sedentary jobs. Compared to 1950, approximately twice as many adults were employed in occupations classified as low active in 2000 (10). The rapid rise in motor vehicle ownership has also led to an increase in passive travel. There are now more vehicles per licensed drivers and more miles driven, with a 0.4 increase in daily mileage per year over the last 50 years (10). Similarly, work-related trips made by walking and public transport have gradually declined (10). In contrast, increases in other pursuits that are typically sedentary have been observed. For example, only 10% of households owned a TV in 1950, compared to 98% in the year 2000 (10). It was estimated that for every ten years, household TV viewing increased by 36 minutes per day from 1950 (10). Similarly, in Danish adults, increases in leisure and occupational sitting time were observed between 2007 and 2010 but there were

also increases in leisure-time moderate-to-vigorous physical activity. Increases in sitting time appeared to outweigh increases in moderate-to-vigorous physical activity, with an overall decrease in energy expenditure of 0.4 METs (metabolic equivalents) per day (85). One of the arguments against the role of rising inactivity on obesity trends is that several studies have shown that leisure-time physical activity has remained fairly constant over recent decades. For example, in the U.S. between 1990 and 2000 the proportion of men and women meeting physical activity recommendations remained fairly constant (10). Data from the Baltimore Longitudinal Study of Ageing (BLSA) also showed no significant changes in moderate intensity (4-5.9 METs) leisure-time physical activity between the 1960s and late 1990s. There were also increases in high intensity (≥6 METs) leisure-time physical activity over the same period (86). Similar findings were also reported in UK adults with regular sport and exercise participation remaining at ~40% between 1997 and 2006. In fact, in adults aged 45 and over, regular sport and exercise participation increased during this period (87). Specifically, notable increases were observed for cycling, swimming, running, racquet sports, and gym/fitness club attendance in this age group (87). This is in line with more recent trend data in Australian adults showing an increase in the proportion of adults with ≥150 minutes per week of leisure-time physical activity between 2002 and 2012 (88). While it is encouraging that the proportion of adults taking part in leisure-time physical activity seems to be stable or even increasing, this may not offset the declines observed in several other domains and a large proportion of the population still remain inactive.

2.3.2 Physical activity across the life course

The life course perspective considers the changeable nature of physical activity behaviour over time. Important age differences have been reported in cross-sectional studies, with older adults generally reported as being less active than younger adults and children (11). However, cross-sectional data do not capture within-person changes and therefore cannot be used to make inferences about the ageing process. Longitudinal studies following the same individuals over time have highlighted some important transitions during the life course where physical activity may be particularly important and susceptible to change (89, 90). However, very few studies have covered prolonged periods of the life course extending into old age and beyond.

2.3.2.1 Tracking of physical activity

Longitudinal studies making multiple measurements in the same individuals have given rise to the concept of "tracking" in epidemiological research. Fundamentally, tracking seeks to describe the stability of an outcome over time, but there are several concepts involved. One of the most commonly cited definitions describes tracking as the tendency of an individual to maintain relative rank among a group over time (90). Tracking can also refer to the stability or correlation between measurements from one time point to the next, typically estimated with a correlation coefficient (91). Another concept of tracking is the predictability of later values from previous values of the same measure (92). Each of these tracking concepts requires longitudinal assessment (i.e. at least two measures) of a measure in the same individuals. Tracking studies can help establish the origins of health behaviours and identify life periods when behaviours are most susceptible to change. Thus, these studies are crucial for informing the timing of interventions.

Three recent reviews have summarised the evidence on the tracking of physical activity during childhood and adulthood (17, 89, 93). They concluded that physical activity tracks moderately throughout childhood and adulthood, but tracking was lower during transitionary periods, such as from childhood to adolescence and from adolescence to adulthood. Tracking in older adults has been less studied and generally only examined over shorter time periods. In the limited number of existing studies, no obvious differences have been observed with other periods in adulthood (17, 90, 93). One Norwegian study tracked physical activity in men and women aged 20-54 years at baseline and found moderate correlation (Spearman correlation coefficient: 0.25-0.32) and agreement (weighted kappa: 0.24-0.29) over 28 years of follow up (94). Tracking coefficients were weaker in women compared to men and when the follow up period was longer, which is supported by findings in other studies (95, 96). This study also found that baseline physical activity levels strongly predicted the same physical activity level at later examinations, particularly in those who were highly active (Odds ratio [OR] 27.3 95% confidence interval [CI] 18.0, 41.3).

Few other tracking studies have extended from childhood or early adulthood into old age but they seem to be in agreement that physical activity is moderately stable during this period (95-97). There are more studies that have focussed on the later life period in isolation. For instance, Armstrong et al. examined physical activity over 8 years of follow up in adults aged 65 and over and found that tracking varied according to physical activity type (98). Tracking coefficients were lowest for shopping in males (r=0.17) and females (r=0.16) and highest for

outdoor activity in both males (r=0.50) and females (r=0.58). When absolute time spent in activities was considered, shopping, walking, strength and flexibility training were the most likely to increase during follow up. There is also evidence that specific types of activity earlier in life can promote physical activity maintenance during old age. In the Evergreen study, a cohort study in 642 Finnish older adults aged 65 and over, competitive sport participation retrospectively reported between the ages of 10 and 19 years was associated with increased odds of maintaining high levels of physical activity in old age (99). A retrospective study in 712 US older adults aged 70 years and over found that varsity sport participation in high school was the strongest predictor of current physical activity amongst a range of personal, behavioural and personality characteristics (100). Another study in Swedish older adults aged 76 years found that sport participation in childhood and adulthood was more strongly correlated with physical activity in old age than other types of activity, including transport, household and occupational activity (101). There is also evidence that sampling a greater diversity of sports in early life raises the odds of being active later in life (102, 103).

Risto Telama proposes four key theories in his review to explain this tracking phenomenon: 'carry-over value hypothesis', 'ability and readiness hypothesis', 'habit formation hypothesis', and 'self-selection hypothesis' (17). The 'carry-over hypothesis' is a concept closely linked to the Continuity Theory of Normal Ageing (104), suggesting that activities that are carried out in adulthood are likely to be those that were initiated and learned early on in life (104). This concept may be particularly important for lifelong sport participation, where sport-specific skills are likely to be acquired early on in life. For example, we know that participation in certain types of activities, such as soccer, swimming and gymnastics, is highly dependent on prior engagement (105, 106). In connection with this concept, the 'ability and readiness hypothesis' relates to early positive experiences and skill acquisition that lay the foundations for continued participation or uptake later in life. Plausibly, sampling a range of different activities early in life increases physical and psychological readiness to maintain or take up activities later on in life. In the habit formation hypothesis, habits are defined as repeated behaviours that individuals make more automatically, with less awareness and cognitive effort than planned activities (17, 99). They are formed through repetition of a behaviour in specific contexts, leading to an automatic behavioural response from situational cues (107). These cues could come from a variety of sources, such as geographical location, time of day or a previous action (108). Habits may be particularly influential on everyday activities that form our daily routine, such as our mode of transport, stair/escalator/lift use and housework etc. Although most behavioural theories, such as the theory of planned

behaviour (109) and social cognitive theory (110), suggest that intentions are the key drivers of behaviour, there is still a significant amount of variability in behaviour that remains unexplained. A recent study showed that habits contribute substantially to physical activity levels after controlling for intentions and behavioural control (111). The self-selection hypothesis suggests that those who are predisposed with higher levels of fitness and motor performance are more likely to maintain high physical activity levels across the lifespan than those who are not predisposed with the same traits. Although genetic research in physical activity is in its early stages, twin studies have shown that there is a heritable component to physical activity (112). It is also well established that genetics play important roles in fitness and obesity (113, 114), which may subsequently predispose physical activity levels. Social factors may also contribute to the theory of selection. For example, children born earlier in the academic year are more likely to be selected in school sports than those born later in the year (115). Maturational factors are likely to explain this association, particularly in sports where stature is advantageous. The nature of this phenomenon is likely due to the Matthew Effect, whereby individuals who are predisposed with desirable characteristics for sports competition are given more opportunities to continue participation than those who do not possess these characteristics (115).

2.3.2.2 Methodological considerations

As well as the demographic, biological, social and behavioural factors that can initiate change in physical activity, which are discussed in detail in section 2.4, there are a range of methodological factors that can influence the tracking of physical activity.

An important decision when designing physical activity research is the choice of instrument to measure physical activity. This choice is made difficult by the plethora of measurement tools available. In cohort studies, ideally the instrument needs to be consistent across waves to ensure comparability. Historically, physical activity has most frequently been measured using self-report measures. Indeed, most of what is known about physical activity has come from studies using self-report measures. They are cheap, easy to administer to a large sample and can capture participation in a variety of activities. Disadvantages include recall bias, whereby respondents inaccurately report past events, which may be particularly prevalent in older adults with age-related memory decline (116). In addition, several studies tracking physical activity over time do not report on the validity and reliability of their measure, so measurement error may be an issue. Differences in recall ability for specific types of activity

may also impact tracking studies. For example, organised activities such as sport may be easier to recall than spontaneous activities such as domestic- and transport-related activities.

Objective or device-based measures have been increasingly used over recent years to address the limitations of self-report. Device-measured physical activity is less prone to recall and social desirability bias and is consequently more stable than some self- or proxy-reported methods (17). Furthermore, device-based measures provide additional information on the amount and intensity of physical activity. Importantly, many of the device-based measures available today were not developed or were too expensive to use when many existing cohort studies began. Hence, many cohort studies have continued to use the self-report measures that have been used from study conception.

As described previously, the duration of study follow up can influence tracking estimates; tracking coefficients tend to be higher for shorter follow up periods. In addition, few tracking studies account for factors that can influence tracking, such as season, life events and health conditions (17, 90). Many of the traditional techniques used to study tracking are unable to account for these confounding factors. However, modern techniques are now available that can control for important covariates and handle additional repeated measurements, providing a more complete picture of physical activity patterns.

In summary, the finding that physical activity is somewhat stable over the life course could be interpreted positively or negatively as it means that activity as well as inactivity is likely to be maintained. It is encouraging that there may be life periods when physical activity is potentially modifiable where we may be able to intervene, but additional research using more advanced techniques, with life course follow up, is required to understand reasons for stability or instability and the impacts of major life events.

2.3.2.3 Trajectories of physical activity across the life course

Trajectories are defined as the path of change of an outcome over age or time (117). Generally, at least 3 repeated measures in the same individuals are required to describe a trajectory. Recent advances in statistical methods that can handle repeated measures and the increased availability of statistical programmes that can apply them has led to a growing body of research on the developmental trajectories of important disease risk factors and health outcomes.

Conventional approaches to describe trajectories of physical activity are often more subjective or theory driven. Typically, researchers will use clinically relevant cut offs to group

individuals into pre-determined categories, usually resulting in groups that are categorised as persistently active or inactive, increasing or decreasing physical activity levels and those who follow an inconsistent pattern (14, 118, 119). For example, in the English Longitudinal Study of Ageing (ELSA), a population-based cohort following 5022 older adults over a ten year period including six physical activity measurements, 49% of older adults were categorised as persistently active (i.e. moderate/vigorous physical activity at least once a week), 3.7% as persistently inactive and the remainder as inconsistent (118). This approach divides the sample into clinically meaningful groups but it does not utilise the full information available, restricting how much we understand about the course of activity over time and how different patterns lead to a particular outcome. Furthermore, this approach relies on the assumption that these trajectory groupings truly exist. It is possible that subjects making minor fluctuations in activity are misclassified into trajectory groups that could be perceived as making major changes in behaviour.

Random effects models, also known as multilevel models, are another commonly used approach as they account for clustering of repeated measures within the same individual and can therefore estimate within-person changes in physical activity across age or time (120). Several longitudinal studies with repeated measures have used this technique to identify average population-level growth trajectories (14, 121-123). These studies highlight that into old age there is on average a gradual age-related decline in physical activity (122, 123). However, there is already evidence to suggest that an average trajectory does not adequately describe groups of individuals who follow very different patterns of behaviour. In the BRHS, a prospective study of older British men (aged 70-90 years), subjects were divided into the classic trajectory groupings as seen in the majority of the literature (i.e. persistently active/inactive, increasing/decreasing and inconsistent) based on whether they met current physical activity guidelines at three time points over 2 years of follow up (14). Multilevel models were then performed in each group to determine the trajectories of seven different measures of objectively measured physical activity. Men who adopted the guidelines had an annual increase of 816 steps/day, whereas men who stopped meeting the guidelines demonstrated an annual decrease of 1229 steps/day (14). Although there was an initial subjective classification of physical activity patterns, these findings show that trajectories are not uniform.

More recently, data-driven approaches, such as growth mixture modelling and group-based trajectory modelling (GBTM), a form of latent class growth analysis (LCGA), have been applied to identify trajectories of physical activity. While there are some technical differences, which

will be discussed in further detail in Chapter 3 (Section 3.4.5), these approaches share the same goal of identifying groups of individuals that follow similar patterns of behaviour change over time (117). This approach is particularly useful when it is hypothesised that trajectories are not uniform and has been frequently used in studies of younger populations to identify physical activity trajectories (124-133) but less so in older adults (7, 134-138). Some of these studies have identified trajectories of physical activity that overlap in later life (134, 136), while others report more stable trajectories (7, 135, 139).

Although evidence on the patterns of total physical activity has been growing, very little research has been conducted to describe the trajectories of specific types of physical activity across the life course. Existing studies have only described change in physical activity types across two time points, focussing mainly on the retirement transition. For example, data from the European Prospective Investigation into Cancer and Nutrition (EPIC) Norfolk study, a prospective cohort study of adults aged 45-79 years, showed that physical activity changes during retirement were specific to type. Transport and occupational activity declined, whereas recreational activity (including sport/exercise, walking/cycling for pleasure, do-it-yourself and gardening) and household activities increased (140). Similar domain-specific changes were observed in 446 retiring Belgian adults but phase of retirement was also found to be important (141). Another study in 928 retiring older adults, also observed notable changes in time spent walking from pre to post retirement. Approximately 50% increased their time spent walking by 60 minutes or more per week, whereas 31% decreased their time spent walking by 60 minutes or more per week (142). To my knowledge, no previous studies have utilised additional repeated measurements or data-driven approaches to describe long-term trajectories of specific physical activity types in older adults.

Overall, irrespective of the approach used to describe long-terms changes in physical activity, there is fairly consistent evidence of an age-related decline, but these declines are not necessarily uniform. Another clear message from current research is that physical activity in old age seems to be substantially but not completely determined by activity levels earlier in life. However, few studies have utilised the full information available to precisely describe the patterns of activity, and the patterns of specific types of activity across the life course remain largely unexplored.

2.4 Correlates and determinants of physical activity from adulthood to old age

There are a number of theoretical models that have been developed to explain and promote engagement in health behaviours. Many of the classic theories, such as the Theory of Reasoned Action (143), place a great deal of weight on individual-level factors. Recent theoretical advances have highlighted additional wider influences on health behaviours. The ecological model of health behaviour acknowledges that health behaviours are influenced on multiple levels including 'intrapersonal (biological, psychological), interpersonal (social, cultural), organisational, community, physical environmental, and policy factors', as shown in figure 2.1 (144).

Consequently, the ecological model has provided the theoretical basis for a growing body of research to understand the broader influences of physical activity behaviour. Indeed, a recent review of systematic reviews published between 1999 and 2012 identified 36 separate correlates of physical activity in adults, 20 of which were also classified as determinants (112). Many of the original investigations included in these reviews employed a cross-sectional design and therefore can only identify factors with a statistical association with physical activity (i.e. correlates), while only a handful of studies had a longitudinal design for assessing causal relationships (i.e. determinants).

2.4.1 Demographic factors

2.4.1.1 Evidence from cross-sectional studies

Evidence from systematic reviews suggest that two of the most consistent correlates of physical activity are the non-modifiable factors age and gender (112). The inverse association between age and physical activity is fairly conclusive from cross-sectional studies (16, 112, 145). Physical activity is also consistently higher in men than in women (16, 112). Higher levels of education, income/socioeconomic status and a white ethnic background are also positively associated with physical activity (112, 146). A recent systematic review of 131 studies found a fairly conclusive social gradient for total leisure-time physical activity, with the most affluent having the highest physical activity and least affluent the lowest. However, associations were in the opposite direction for occupational physical activity, since the least affluent tend to be employed in more active professions (147). Associations between marital status and physical activity are less conclusive (112). Some studies have found higher levels

of physical activity among married older adults compared to single adults of the same age (16, 148). Plausibly, marriage may help maintain social networks in old age, preventing social isolation. Recent studies have shown that isolated older adults are less likely to engage in physical activity and other healthy behaviours than non-isolated older adults (149).

2.4.1.2 Evidence from prospective studies

A recent umbrella systematic review from the "Determinants of Diet and Physical Activity" (DEDIPAC) project, including 19 systematic reviews or meta-analyses, suggested there is probable evidence that younger age and being male are positive determinants of physical activity in adults (150). Studies using growth curve modelling techniques suggest there is a gradual age-related decline in physical activity during early old age followed by more rapid declines thereafter (123, 135). Steeper declines have also been observed in less educated older adults (122). However, longitudinal studies using more advanced growth curve modelling techniques, such as GBTM, suggest that these age-related changes are not necessarily uniform (134). Some adults' physical activity may decline more rapidly with age and others may even increase their physical activity (134, 136, 137). Distinct age-related changes may be explained by a range of factors, such as past behaviours, onset of health conditions, functional declines and major life events.

Another umbrella review from the DEDIPAC project found evidence that higher levels of education and socioeconomic status are correlates but not determinants of physical activity in adults (151, 152). However, there is some evidence to suggest that the negative impact of socio-economic disadvantage can accumulate across the life course. In a cohort of 2770 Scottish men and women aged 35–54, prolonged exposure to poor socio-economic circumstances throughout the life course was associated with the lowest levels of sport and exercise participation in adulthood (153). In addition, there is a suggestion from studies examining trajectories of physical activity into old age that higher levels of education and income are associated with more favourable physical activity trajectories (7, 134, 137). Only a limited number of longitudinal studies have investigated ethnicity as a determinant of physical activity and results have largely been inconsistent (146, 150).

Longitudinal evidence on the impact of marital status is mixed (112, 154). In a recent review of 59 longitudinal studies in adults, the impact of marital status on physical activity maintenance and initiation was inconclusive (151). One recent prospective cohort study investigating physical activity trajectories in older women found that those who never married were less likely to follow a more active trajectory than those who were married (7).

In addition, some studies have observed close concordance between the physical activity of married couples, with an inactive trajectory in one partner strongly predicting a similar trajectory in the other (148, 155).

Marital transitions represent major life events that could affect daily routines. The effects of marital transitions on physical activity appear to be modified by gender, age and the type of marital transition (156). In their review, Engberg and colleagues' found no association between change in physical activity and getting married, divorced, separated or widowed in three out of 12 studies, while other studies showed that these transitions did initiate changes but the direction of these changes were mixed (156). Some studies suggest that getting married is associated with declines in physical activity (157) whereas others studies suggest that it is associated with an increase (158). In addition, one study found that remarriage was associated with decreases in physical activity among men (159). There is also evidence that death of a spouse is associated with increasing physical activity levels in men (160) and women (161), but evidence on the impact of divorce/separation is inconclusive (156).

2.4.2 Behavioural

2.4.2.1 Evidence from cross-sectional studies

Recently, Condello et al., summarised the evidence on the associations between behavioural factors and physical activity. In their review of reviews, the bulk of the evidence came from cross-sectional studies showing a consistent positive association between prior physical activity and current physical activity. Conversely, there were consistent negative associations for language difficulties and smoking with physical activity (162).

There is also a tendency for physical activity to cluster with other health behaviours. A recent systematic review of 56 studies, primarily with a cross-sectional design, highlighted four key health behaviours that are likely to cluster, including not smoking, a healthy diet and healthy levels of alcohol consumption and physical activity (163). Other healthy dietary habits such as breakfast consumption are also correlated with higher levels of physical activity (16). These findings are consistent with other systematic reviews highlighting similar associations (16, 164). However, not all studies find a positive association between healthy behaviours and physical activity. In particular, the association between physical activity and alcohol consumption is the least clear. For example, a recent systematic review of 16 studies, 15 of which were cross-sectional, found a positive association between physical activity and alcohol consumption (165). Causality remains unclear given the cross-sectional design, but

this relationship could be explained by the extra social opportunities that accompany physical activity. Alternatively, additional physical activity could be an attempt to compensate for the negative impact of high levels of alcohol consumption or binge drinking.

2.4.2.2 Evidence from prospective studies

As described above, prior physical activity behaviour is a consistent and strong correlate of current physical activity levels at all ages (16, 112). In their systematic review of 59 longitudinal studies, van Stralen et al., also found convincing evidence that prior physical activity behaviours are positively associated with initiation and maintenance of physical activity levels (151). Evidence from recent studies using GBTM approaches suggest that trajectories of physical activity are largely determined by initial physical activity levels (7, 135). A more detailed discussion of the evidence on physical activity tracking and trajectories across the life course is outlined in Section 2.3.2. In addition, recent evidence using GBTM suggests that other unhealthy behaviours such as high fat intake, low fruit and vegetable intake and smoking also predict unhealthy physical activity trajectories (7, 137). Conversely, higher alcohol consumption increases the odds of following a more active trajectory in old age (7). Further, in the Whitehall II cohort study of 6825 middle-aged adults, 20-year trajectories of health behaviours also appeared to cluster, with 20% of the sample following unhealthy trajectories for multiple health behaviours, including alcohol consumption, smoking and fruit and vegetable consumption (136).

2.4.3 Health status

2.4.3.1 Evidence from cross-sectional studies

Health status is one of the strongest and most consistent correlates of physical activity (112). Cross-sectional analyses from a study in 37,524 European older adults showed an inverse dose-response relationship between physical activity and number of chronic conditions (166). A number of specific age-related health conditions may be implicated in this relationship. Poor physical function (167-170), poor cardiorespiratory fitness (171), overweight and obesity (118, 157, 167), body pain (157, 168, 170), arthritis (118), asthma (170), chronic obstructive pulmonary disease (170), sensory impairments (170), stroke and breathlessness (172) are all associated with lower levels of physical activity in older adults. However, causal relationships between health conditions and physical activity cannot be determined in these cross-sectional studies and should be interpreted with caution.

2.4.3.2 Evidence from prospective studies

The causal relationship between physical activity and good health is widely accepted, but there is also evidence that this relationship is bidirectional; that is, as well as physical activity affecting health, health status also impacts ability and motivation to be active. A systematic review of 59 longitudinal studies in adults found that being in good physical health and fitness are key determinants of physical activity maintenance, but evidence was less consistent for physical activity initiation (151).

Onset of chronic disease represents a major life event that may have long-lasting or even permanent effects on physical activity levels. It is known that physical activity declines from pre to post cancer diagnosis (173) for example, but how a CVD event impacts physical activity has not yet been quantified. Following a CVD diagnosis, patients are initially recommended rest and only light physical activity, with gradual increments thereafter (174). Such events may also prompt positive lifestyle changes, (157) including uptake of cardiac rehabilitation services, although the impact of these programmes on long-term physical activity are inconclusive (175, 176).

It was recently shown in a study exploring physical activity trajectories that onset of functional limitations was associated with a decline in physical activity in those who followed decreasing and stable active trajectories, but this was the only time-varying physical health-related exposure that was explored (134). In addition, similar studies have shown that baseline health indicators, such as poor overall health, overweight and obesity, depressive symptoms, CHD, chronic obstructive pulmonary disease, poor physical function and a larger total number of diseases are associated with an increased risk of following unfavourable physical activity trajectories (7, 137). Nevertheless, it should be considered that the onset of these conditions is likely influenced by prior physical activity. Extended follow up from birth cohort studies might help shed some light on the temporality of these associations.

2.4.4 Environmental

2.4.4.1 Evidence from cross-sectional studies

Over the last two decades, growing use of the ecological model to understand physical activity has led to a rise in research into environmental correlates of physical activity. Regional differences within countries have been observed in several nations, including the UK, USA and China (177-179), suggesting that there may be some underlying environmental

factors involved. At the macro-level, environmental factors such as climate and aspects of the social and economic environment can influence physical activity (180, 181). An umbrella review by Carlin et al., found a consistent positive association between temperature and physical activity, although this was only examined in one review. However, findings for weather conditions were mixed. Overall environment quality and living in rural areas were consistently positively associated with physical activity. In addition, land use mix was positively associated with active transport, but results were inconsistent for overall and leisure-time physical activity (182).

Three recent umbrella reviews identified a number of (182) micro-level environmental features that are also related to physical activity (112, 146). Micro-level aspects of the environment seem to be important for certain types of physical activity but not others. Walkability and street connectivity are consistent positive correlates of transport activity (112, 146, 182), whereas proximity/access to recreational facilities is most important for leisure-related physical activity (112). Associations with aspects of safety such as crime and traffic are inconsistent (112, 146, 182).

The above reviews also highlight a lack of evidence on these relationships in older adults (112). Specific features of the environment may become more relevant later in the life course, when functional limitations may restrict movement to the local neighbourhood (183). A recent review and meta-analysis of 72 studies reported similar environmental correlates exclusively in older adults, but stronger relationships were observed for land-mix use and good access to public transport (184). Given that this is a fairly new area of research, nearly all of the studies included in these reviews are cross-sectional, and so cannot determine the temporality of these associations.

2.4.4.2 Evidence from prospective studies

As highlighted above, longitudinal studies assessing the impact of environmental factors on physical activity are particularly scarce. Indeed, in a recent review and meta-analysis, 94% of included studies were cross sectional in nature (185). In van Stralen's review of prospective studies, access to leisure facilities and neighbourhood safety were associated with physical activity initiation and maintenance (151). Pleasant scenery and living in rural locations were also associated with physical activity initiation, while crime and unattended dogs were negatively associated. These findings are, however, based on only a small number of longitudinal studies. More recent updated umbrella reviews confirm that the evidence on causal links between many of these environmental factors and physical activity is

inconclusive (146, 182). Only a few prospective studies have explored how environmental factors are associated with physical activity trajectories. These studies suggest that baseline and changes in region of residence are important determinants of long-term physical activity, but other environmental factors have yet to be examined (7, 134).

2.4.5 Major life events

Life events refer to occurrences throughout the life course that disturb or affect an individual's daily routine (186). Life events can be broken down into five key categories: change in employment status; change in residence; change in physical status; change in relationships; and change in family structure (187). Many life events falling under these categories coincide with the transition to old age, such as retirement, changes to income, birth of grandchildren, onset of disease, moving to sheltered accommodation, changes to marital status and bereavement. A recent systematic review found that accumulating multiple stressful life events is associated with decreasing physical activity (156). However, some life events may provide additional opportunities for physical activity and could initiate positive changes. Onset of disease and marital transitions have already been discussed above, so this section focusses on some of the other life events that typically coincide with later life.

2.4.5.1 Retirement

In their review, Engberg and colleagues found an increase in leisure-time physical activity following retirement in six out of seven studies (156). However, there is also a suggestion that the effects of retirement may be modified by previous physical activity levels (162). Findings from a prospective study examining trajectories of physical activity into old age suggested that retirement can initiate increases in physical activity in those who are doing at least some physical activity but not in the least active (134). One explanation is that retirement offers additional free time for leisure activities, such as sport and exercise. Conversely, it may have the reverse effect on occupational and transport-related physical activity, which could be the primary source of physical activity for some individuals. Indeed, a prospective cohort study of 971 Dutch older adults showed that those who remained employed were more physically active than those who retired, which was largely driven by physical activity from work-related travel (188). Most of these findings are based on short-term follow up and so the impact of retirement on long-term physical activity trajectories remains unclear.

2.4.5.2 Change in residence

Only one study was identified by Engberg and colleagues that had examined the impact of residential changes to physical activity (156). In approximately 7000 Australian women, moving to institutional care was associated with increased odds of decreasing physical activity (161). Further, in their study examining physical activity trajectories, Pan et al., showed that moving to rural areas was associated with an increase in physical activity across all trajectory groups except the least active (134).

2.4.5.3 Change to family structure

There is fairly consistent evidence that pregnancy or having a child is associated with decreases in physical activity among women (146, 156). Although the impacts in fathers have been rarely studied, the existing evidence suggests that having a first child is associated with decreases in physical activity (189). Birth of a grandchild has also been associated with decreased odds of having increasing physical activity levels in middle-aged Australian women (161). Nevertheless, the association between parenthood and physical activity in old age has yet to be explored.

Overall, the effects of many life events occurring during old age are not fully understood, particularly how they impact on specific types of physical activity and, importantly, how they impact long-term trajectories.

2.4.6 Psychosocial factors

A wide range of psychosocial factors are known to be related to physical activity. Two of the most consistent psychosocial correlates of physical activity are self-efficacy (a person's belief in their capabilities to be physically active) and intention to exercise (112). Self-efficacy drives perceived ability to overcome barriers and subsequently mediates the relationships between many other exposures and physical activity (168, 190). Intentions are a key component of the theory of planned behaviour and increase the likelihood of achieving behavioural targets (190). Consequently, these factors are central in initiating behaviour change (112). In addition, several other psychosocial factors have been shown to be related to physical activity in adults including attitudes, action planning, state of change, stress, perceived effort, physical and psychological outcome realisations (112). There are also some factors that emerge specifically in old age, such as fear of falling (190). For instance, in 1680 men from the BRHS, fear of falling was associated with 1766 fewer steps/day compared to men who

were not fearful (191). Fear of falling may lead to a continuing cycle of fear and increasing levels of inactivity. Findings from longitudinal studies have been mixed; however, there is a suggestion that personality traits, motivational factors and self-efficacy are probable determinants of physical activity (192). Given that psychosocial measures have not been routinely recorded in the BRHS, these factors will not be explored in this thesis.

2.5 Physical activity and cardiovascular disease

Physical inactivity is well established as a major risk factor for CVD morbidity and mortality, with numerous studies showing a dose-response relationship between volume of physical activity and incidence of CVD (66, 193-198), as illustrated in Figure 2.2. A number of potential mediators have been implicated in this relationship including a range of cardiometabolic, inflammatory, hemostatic and cardiac risk factors. This section reviews the evidence from observational prospective studies examining the association between physical activity and CVD risk factors, CVD events and all-cause mortality, with a particular focus on how adult life course and changes in physical activity impact on these outcomes in later life.

2.5.1 Physical activity and cardiometabolic risk factors

Physical activity is strongly associated with improved levels of cardiometabolic risk factors, including lipids, blood pressure, adiposity and glucose metabolism (199-207). The majority of studies examining the effects of physical activity on cardiometabolic risk factors have been experimental in design (205). However, there are also numerous observational studies that have shown that higher levels of physical activity are associated with a more favourable cardiometabolic risk profile, but these have predominantly been cross-sectional studies (201, 204, 205).

2.5.1.1 Prospective studies

2.5.1.1.1 Baseline physical activity only

Numerous prospective studies examining the relationship between physical activity and cardiometabolic risk factors consider physical activity at a single time point only. These studies have consistently shown an inverse dose-response relationship between a single measurement of physical activity and risk of hypertension, obesity, unfavourable lipid levels and markers of diabetes (199, 200, 203, 206, 207). In a prospective study in 2548 Japanese men aged 35 to 59 years, being in the highest physical activity quartile almost halved the risk

of hypertension seven years later compared to those in the lowest activity quartile (200). Dose-response relationships have also been observed for the risk of developing high blood lipids and diabetes (199, 203). Most of these studies were conducted over a relatively short time period and do not capture the impact of physical activity changes on subsequent CVD risk factors.

2.5.1.1.2 Changes in physical activity across two time points

Studies that have examined physical activity changes have typically done so over two time points. For example, in the Inter99 study, a cohort comprising of 4039 Danish adults aged 30 to 60 years, 5-year changes in physical activity were associated with changes in diastolic blood pressure, lipids, weight and waist circumference (208). Compared to those who maintained moderate or high physical activity, an increase in physical activity in the least active was associated with a decrease of 0.11 kg in body weight. By contrast, a decrease in physical activity was associated with a 1.19 kg increase in body weight, a 1.33 cm increase in waist circumference and a 0.79 mmHg increase in diastolic blood pressure, but no associations were observed for systolic blood pressure. Positive changes in physical activity were also associated with favourable changes to lipid levels. In addition, numerous studies have linked favourable changes in physical activity to improved glucose homeostasis. In the Uppsala Longitudinal Study of Adult Men (ULSAM), a prospective study in 1860 Swedish men aged 50 years, 20-year increases in physical activity into old age were associated with improved glucose and insulin metabolism over time (209). Overall, there is consistent evidence in middle-aged and older adults that increases in physical activity and maintenance of higher volumes of physical activity are favourably associated with adiposity (209-214), lipids (209, 213-215) and diabetes risk markers (209, 216, 217) in later life. There is also a suggestion that changes in lower intensity activities such as walking are similarly associated with favourable changes in metabolic markers independent of high intensity activity (218).

However, findings relating to some markers have been inconsistent, particularly for blood pressure. Some studies observed decreases in systolic and diastolic blood pressure in obese adults following increases in physical activity (219), whilst others report no significant associations (214, 220). In the BRHS, 4-year physical activity changes were examined in men aged 56 to 75 years at baseline in relation to a number of CVD risk factors at follow up. At follow up, those who were persistently active or who had increasing levels of activity had a lower BMI and more favourable cholesterol levels but systolic and diastolic blood pressure

were similar across all physical activity change groups (214). It is possible that the benefits of physical activity on blood pressure are only observed in 'high risk' individuals.

2.5.1.1.3 Changes in physical activity across the adult life course

As described earlier, there is a paucity of observational studies utilising physical activity data across more than two time points to examine relationships with CVD risk markers. Subsequently, the impact of underlying fluctuations in physical activity on these risk markers is largely unknown. One study in 15,634 middle-aged Finnish adults, used physical activity data across 3 time points spanning an 8-year period to classify change (213). The mean physical activity across time points 1 and 2 was considered as the baseline measure to define change up to the third time point. Compared to those who had persistently high physical activity levels, decreases in physical activity almost doubled the odds of developing hypertension, dyslipidaemia and obesity. In contrast, increased physical activity was associated with reduced odds of accumulating such risk factors. In the Coronary Artery Risk Development in Young Adults Study of 4995 men and women aged 18-30 years at baseline, the effects of changes in walking on weight change over 15 years were assessed across 6 time points using repeated measures regression modelling (221). Increases in walking were associated with less weight gain over time, particularly in the heaviest at baseline.

Studies using data-driven approaches to examine these relationships are even rarer. One such study in 5964 older men aged ≥65 years simultaneously modelled the trajectories of physical activity and body composition across 3 time points using GBTM. Trajectories of physical activity and of body composition were fairly stable across 7 years of follow up. The trajectories of body composition measures were similar across trajectories of physical activity, suggesting that body composition is largely determined by prior measurements of body composition rather than changes in physical activity (222).

2.5.1.2 Mechanisms linking physical activity and cardiometabolic risk factors

The mechanisms linking physical activity and cardiometabolic risk factors are complex and interrelated. Many mechanisms are involved, but one of the key pathways that mediate the relationship between physical activity and cardiometabolic risk factors is weight status. Many experimental studies suggest that exercise-induced improvements to lipid profiles are not independent of weight loss (205). Although some of the observational studies mentioned above do not adjust for adiposity (199), most of the favourable changes in cardiometabolic risk factors were observed regardless of adiposity. In adults from NHANES, associations for

moderate and vigorous physical activity with lipids and insulin were substantially but not completely attenuated after adjustment for waist circumference (223), suggesting that adiposity and changes in adiposity may only partially explain these associations. Similar independent associations have been observed for blood glucose (201) and hypertension (200). Other pathways that could explain these associations include reductions in total peripheral resistance, promotion of lipolysis and improved insulin sensitivity (216, 224-226). Even after adjustment for all of the common cardiometabolic risk factors, many of these associations still persist (200), which indicates that other pathways must be involved. Recently, more novel risk factors have also been identified as potential mediators of these associations, including inflammation, endothelial dysfunction and cardiac injury.

2.5.2 Physical activity and inflammation

Chronic low-grade inflammation is associated with the onset of several major age-related conditions, including CVD (227). While numerous cross-sectional and experimental studies have shown an inverse association between physical activity and inflammatory markers (228, 229), prospective observational studies assessing the impact of physical activity changes are scarce. Table 2.1 summarises the prospective studies that have assessed the impact of physical activity and physical activity changes on subsequent inflammatory markers.

2.5.2.1 Prospective studies

2.5.2.1.1 Baseline physical activity only

Very few prospective studies examine the impact of physical activity at baseline only on subsequent inflammatory markers, with the majority examining the effects of physical activity changes across two time points. However, one study using data from the Whitehall II cohort study showed an inverse association between baseline physical activity and markers of inflammation over ten years of follow up, including CRP and IL-6, but there was no association between baseline physical activity and changes in these markers over time (230). Data from the MRC National Survey of Health and Development (NSHD), a prospective cohort of British men and women, was used to examine the association between leisure-time physical activity across 28 years of adulthood, measured at 4 separate time points, and inflammatory markers at ages 60 to 64. Baseline physical activity, measured at 36 years of age, was inversely associated with CRP and IL-6 at age 60 to 64 (119). Importantly, including baseline physical activity resulted in an improved model fit when compared to models that

only included current physical activity, suggesting that prior physical activity is important for inflammation.

2.5.2.1.2 Changes in physical activity across two time points

Longitudinal analysis of BRHS data showed a significant association between self-reported 4-year physical activity changes and CRP, with a clear linear trend in favour of persistent activity and increasing physical activity levels (214). Similar findings were reported in this same cohort when 20-year changes in self-reported physical activity and 1-year changes in objectively measured physical activity were considered (231, 232). Another study among 5030 Brazilian adults also showed that compared to persistent inactivity, continuous activity over a median follow up of 3 years was associated with the lowest odds of elevated CRP levels, with stronger associations evident in older adults. Similar associations were observed for those who were active at either baseline or follow up, but the magnitude of these associations were smaller and less consistent (233).

2.5.2.1.3 Changes in physical activity across the adult life course

Prospective studies examining the impact of physical activity measured at several time points on subsequent inflammation are particularly scarce. In the NSHD, becoming active and greater accumulation of leisure-time physical activity across adulthood was associated with more favourable levels of CRP and IL-6 in old age (119). Associations were predominantly but not completely mediated by BMI, suggesting that other pathways are involved. This is also consistent with findings from the Whitehall II cohort study, another cohort study of British adults, aged 49 years at baseline, which reported favourable levels of CRP and IL-6 in those who regularly adhered to physical activity guidelines and those who increased their leisure-time physical activity over three measurements across ten years of follow up (230). Within all the aforementioned studies, participant groupings to describe the trajectories or change in physical activity were created a priori based on observed data. To my knowledge no study has used data-driven methods to identify physical activity trajectories and examined their associations with markers of inflammation.

2.5.2.2 Mechanisms linking physical activity and inflammation

Although the exact pathways explaining how physical activity exerts benefit are not clearly understood, one possible mechanism is that habitual physical activity prevents accumulation of body fat, a key cause of chronic low-grade inflammation (234). Indeed, adjusting for

adiposity largely attenuates the association between physical activity and inflammation (119, 230). However, recent systematic reviews of observational studies show that associations between physical activity or fitness and inflammation still persist independently of adiposity (229). It is also known that acute bouts of physical activity trigger the release of IL-6 from skeletal muscles, which in turn improves glucose and lipid metabolism and insulin sensitivity (235). Release of IL-6 from skeletal muscles during exercise supresses subsequent release of pro-inflammatory cytokines and promotes release of anti-inflammatory cytokines. A pro-inflammatory state is also linked to dysfunction of the endothelium, the cells that form the inner cell lining of the blood vessel walls. The inflammatory system also regulates a number of coagulatory functions.

2.5.3 Physical activity, endothelial dysfunction and other hemostatic factors

Endothelial dysfunction and elevated levels of procoagulant factors and fibrinolytic activity are associated with an increased risk of CHD (79). Cross-sectional studies suggest an inverse association between physical activity and markers of endothelial dysfunction and fibrinolytic activity (232, 236), but causal associations remain unclear. Table 2.1 summarises the existing prospective studies that have assessed the impact of physical activity and physical activity changes on subsequent markers of endothelial dysfunction and fibrinolytic activity.

2.5.3.1 Prospective studies

2.5.3.1.1 Baseline physical activity only

To my knowledge no previous studies have explored prospective associations with endothelial and hemostatic markers using just a single measurement of baseline physical activity. However, in their study, Elhakeem and colleagues explored the association between physical activity across the adult life course on endothelial markers at age 60-64 years. Physical activity at age 36 was inversely associated with tPA levels at age 60-64 (119). However, inclusion of physical activity measured at age 36 did not improve model fit when current physical activity was included in the models.

2.5.3.1.2 Changes in physical activity across two time points

In the BRHS, persistent and increasing physical activity over 4-years of follow up were associated with more favourable levels of vWF and d-dimer when compared to those who were persistently inactive (214). Similar associations were reported in this cohort when

physical activity changes were captured across 20 years of follow up, with additional favourable associations observed for tPA and procoagulant factor IX (231). These findings were also replicated in this cohort with objective measures of physical activity (232).

2.5.3.1.3 Changes in physical activity across the adult life course

In the NSHD, greater accumulation of leisure-time physical activity across 28 years of adulthood was associated with more favourable levels of tPA in old age (119). There was also a significant linear trend in favour of increasing and more persistent activity, but these associations were markedly attenuated after adjusting for BMI and other lifestyle factors.

2.5.3.2 Mechanisms linking physical activity and markers of endothelial dysfunction and hemostasis

Some of the studies above have shown that the impact of physical activity on markers of endothelial function are largely independent of BMI (231) and other lifestyle factors (231, 232). It is thought that habitual physical activity preserves endothelial function through several pathways (237), including by increasing nitric oxide bioavailability, a key regulator of vasodilation in the blood vessels, and by reducing oxidative stress (237). The endothelium is also implicated in the regulation of inflammatory markers, such as CRP, and in the release of tPA, an important mediator of the fibrinolytic process (237). It is hypothesised that the benefits of physical activity on endothelial function accumulate with continuous engagement, which in turn supresses chronic low-grade inflammation (234).

2.5.4 Physical activity and cardiac biomarkers

Cardiac biomarkers NT-proBNP and TnT are now frequently measured in clinical settings. TnT is a marker of myocardial damage and is routinely used to diagnose acute MI but it is also increasingly used in risk prediction (238). NT-proBNP is another biomarker that is released under increased cardiac stress and can also be used in the prediction of heart failure (239). Elevated and increasing levels of these markers are known to play a role in the onset of CVD events (238). As the incidence of heart failure increases rapidly with age (240), there has been increasing attention on the potential of physical activity to prevent this condition in older adults.

Much of the evidence linking physical activity with cardiac markers such as NT-proBNP and TnT has come from studies examining the acute effects of a single bout of exercise or in

intervention trials. For example, in a randomised controlled trial in 307 sedentary older adults, a 1-year physical activity intervention induced more favourable changes in TnT concentrations than a health education programme (241). Similar improvements have been observed in trials examining the effects of exercise on NT-proBNP but these have predominantly been in heart failure patients (242).

Very few studies, however, have been conducted in free-living settings and most of those have been cross-sectional. For example, in the Atherosclerosis Risk in Community study, a prospective cohort study in 9427 middle aged adults, cross-sectional analyses showed that low levels of physical activity were associated with increased odds of elevated hs-TnT when compared to recommended physical activity levels (243). These findings are consistent with observational studies using objective measures of physical activity (244).

2.5.4.1 Prospective studies

2.5.4.1.1 Baseline physical activity only

The prospective association between physical activity and cardiac biomarkers is even less studied. Findings from the Cardiovascular Heart Study, a cohort of 2933 American older adults, showed that higher levels of baseline physical activity were associated with reduced odds of subsequent increases in NT-proBNP and TnT over 2 to 3 years of follow up (245).

2.5.4.1.2 Changes in physical activity across two time points

To my knowledge, only one prospective study has examined the impact of physical activity changes on these markers in free-living settings. Longitudinal data from the BRHS showed that self-reported persistent activity over four years was associated with the lowest levels of NT-proBNP at follow up, whereas those who became inactive had the highest (214). The mechanisms linking physical activity and cardiac biomarkers are not fully understood, but the associations have been shown to be independent of BMI and other routine risk factors (245).

This section summarised the associations between physical activity and a range of established and novel CVD risk factors. The next section will review the association of physical activity changes and adult life course physical activity with CVD and all-cause mortality and the role of the CVD risk factors in these relationships.

2.5.5 Physical activity, CVD risk and all-cause mortality

Since the pioneering work in the 1950s linking physical activity and CVD risk, (246) the survival benefits of physical activity have now been well established. More is now known about the volume and types of physical activity that can achieve such benefits and, as will be highlighted in this section, the mechanisms that explain these survival benefits. The accumulated evidence highlights a dose-response relationship between moderate-to-vigorous leisure-time physical activity and CHD, as shown in Figure 2.2. Although we know that physical activity may be sensitive to change, the majority of studies exploring relationships with CVD and mortality measure physical activity at a single time point only. This section reviews the evidence from prospective studies investigating associations of adulthood physical activity, physical activity changes and adult life course physical activity on subsequent CVD and all-cause mortality.

2.5.5.1 Prospective studies

2.5.5.1.1 Baseline physical activity only

Recent prospective studies have helped develop our understanding of the longer-term benefits of physical activity to survival. Prospective studies with a substantial follow up have consistently shown a dose-response relationship between physical activity and risk of CVD and all-cause mortality (66, 193-195). In their meta-analysis of nine prospective cohort studies, Sattelmair and colleagues showed that 150 min/week of moderate-to-vigorous intensity physical activity was associated with a 14% lower CHD risk compared to those who reported no leisure-time physical activity, while 300 min/week was associated with a 20% risk reduction. Similar risk reductions have been observed in prospective studies with more than 4 decades of follow up (247) and in studies using objectively measured physical activity (248-250).

Furthermore, the latest evidence suggests that the observed survival benefits are largely driven by leisure-time physical activity. A 2012 meta-analysis including more than 650,000 adults, found that high levels of leisure-time physical activity were associated with approximately a 25% reduction in risk of CVD compared to low levels of leisure-time physical activity (66). In contrast to leisure physical activity, an update of this meta-analysis 2 years later including 23 new prospective cohort studies reported that high levels of occupational activity were associated with a 10-30% increase in the risk of CVD (66, 193). These findings are consistent with observations from a prospective study of 17,663 Swiss adults reporting

no survival benefits in relation to transport and occupational physical activity but significant reductions in the risk of all-cause mortality, CVD and cancer mortality for leisure and sporting activity (251). In the Whitehall Study, a British cohort following 7456 middle-aged men and women, only sport and do-it-yourself activities in midlife were associated with a reduced risk of mortality after adjusting for all other types of physical activity, sociodemographic factors, health status and health behaviours (252). There is also evidence that specific types of sport may be more beneficial than others. Data from the Health Survey for England and Scottish Health Survey including 80,306 middle-aged and older adults showed significant reductions in all-cause mortality for those participating in cycling, swimming, racquet sports and aerobics, but no associations were observed for football and running. Likewise, swimming, racquet sports and aerobics were associated with a reduced risk of CVD mortality, but no associations were observed for cycling, running or football (253). The majority of these studies adjust for established CVD risk factors, such as hypertension, BMI, lipids and behavioural factors, suggesting that the association between physical activity and CVD mortality is independent of these risk factors. However, few studies adjust for more novel factors that could also mediate these associations, such as inflammation, endothelial function and cardiac biomarkers. One study found that the association between physical activity and CVD mortality was not markedly attenuated after adjusting for inflammation (254). In contrast, another study showed that associations with stroke were attenuated towards the null after adjusting for established risk factors and markers of inflammation, endothelial dysfunction and hemostasis (255).

2.5.5.1.2 Changes in physical activity across two time points

Table 2.2 summarises relevant prospective cohort studies examining the association between changes in physical activity with CVD events and all-cause mortality. Paffenbarger and colleagues were among the first researchers to examine the effects of physical activity changes across two time points on survival. In their prospective study following 10,269 middle-aged and older men, those who took up or continued to participate in a moderately vigorous sports activity over 11-15 years had a 20-30% lower risk of death over the subsequent 8 years than those who did not take part in a moderately vigorous sport at baseline and follow up (256).

More recent studies examining changes in physical activity across two time points have produced similar findings. A prospective study of 2205 men aged 50 years at baseline examined the impact of 10-year physical activity changes on subsequent mortality over the

ensuing 25 years and found that increased physical activity was associated with a similar survival benefit as those who maintained high levels of physical activity after 10 years of subsequent follow up (257). Conversely, 10-year decreases or stable low levels of activity were associated with an increased risk of mortality compared to those with stable high levels of physical activity (257). These findings are consistent with observations from prospective studies examining physical activity changes specifically in the later life period and in studies of the oldest old (258, 259). For example, in the BRHS, 12-year decreases in physical activity from midlife to old age (mean age, 63 years) were associated with an increased risk of CVD mortality during 3 years of follow up, whereas increases were associated with a 50% lower risk of all-cause mortality (260). Men who became active had a similar risk of all-cause and non-CVD mortality as those who were persistently active; however, persistent activity proved optimal for CVD mortality (260). Comparable findings were also reported in a study of 472 older Dutch men, with similar mortality risks observed in men who became active and men who maintained high levels of physical activity over 5 years (261). In a Spanish Cohort of 2836 older adults, continuous physical activity over 2 to 3 years of follow up was most favourable for preventing CVD deaths and was associated with a 58% reduced risk of CVD mortality compared to those who were continually inactive. By comparison, increased physical activity was associated with a 25% risk reduction (262). However, some studies suggest that becoming active may even be more favourable than maintaining high levels of activity. In a sample of 803 older Mexican adults, a 10-year increase in physical activity was associated with a more favourable survival rate (HR 0.57, 95% CI 0.34, 0.97) than those who maintained high levels of physical activity (HR 0.77, 95% CI 0.53, 1.10) after adjusting for established CVD risk factors (263). Similarly, in a large cohort of 9518 older women from the USA, increased physical activity provided optimal survival benefits for all-cause mortality; however, the risk of CVD mortality was similar among those who remained active and those who increased their activity (264). Persistent and increasing physical activity levels have also been shown to protect against re-infarction and all-cause mortality in MI patients (265).

Although attenuated slightly, the associations reported in these studies remained significant after adjusting for established risk factors and pre-existing disease. Despite an increasing body of research assessing the effects of physical activity on CVD and mortality, defining change across two time points may not capture important fluctuations in physical activity behaviour.

2.5.5.1.3 Changes in physical activity across the adult life course

Only a handful of studies have examined how physical activity measured across several time points is associated with subsequent CVD and mortality in older adults, and there is a large amount of heterogeneity in the approaches used to handle repeated measures data, as shown in Table 2.2. In one large prospective cohort study of 9953 German adults, subjects reported physical activity levels at age 20, 30, 40 and 50 years. Subjects reporting no and extremely high levels of heavy physical activity, defined as sports and hard labour, on average across adulthood were at an increased risk of major CVD events when compared to those who did a moderate amount of heavy physical activity (266).

Recently, more advanced approaches for handling repeated measures data have been adopted for examining this relationship. In the BLSA, a prospective cohort study of men and women aged 19-90+ years, random effects (or multilevel) models were applied to incorporate multiple repeated measures over a mean follow up of 21 years. Men reporting increases or a fractional decline in total and high-intensity leisure-time physical activity across follow up were at a reduced risk of all-cause mortality than those with steeper declines (267). In the Alameda County Study, a prospective cohort study in American adults, 6131 subjects reported leisure-time physical activity over 18 years at 3 separate time points. Cox models treating physical activity as a time-dependent exposure variable showed that for every four-point increase in the physical activity score the risk of mortality was 28% lower. Importantly, associations were stronger when physical activity was treated as a time-dependent exposure as opposed to the baseline measurement only (268).

Using a GBTM approach, Laddu and colleagues identified three patterns of physical activity among 3767 older men, all of which showed declining physical activity over time. Compared to the low-activity declining trajectory group, moderate- and high-activity declining trajectories were associated with a reduced risk of all-cause, CVD and non-CVD non-cancer deaths. However, these associations were largely explained by the most recent/current physical activity measure (135). Another study using data from the Women's Health and Aging Study applied a joint latent class and survival mixture model and identified four distinct trajectories over a median follow up of 12 years: always active, fast declining, stable moderate and always sedentary. Compared to the always active group, the mortality hazard ratios were 2.34 times higher in the fast-declining group and 3.34 times higher in the always sedentary group. No differences were observed between the always active and stable moderate groups (137). Associations were markedly attenuated after adjusting for

established risk factors, including BMI, hypertension, lipids and blood glucose, but typically remained significant. To my knowledge no studies examining the relationship between changes or patterns of physical activity and survival have adjusted for more novel confounders, such as inflammation, endothelial function and cardiac biomarkers.

2.6 Summary of literature review

CVD remains a major cause of mortality and morbidity, particularly in older adults who make up an increasing proportion of the population. Section 2.2 describes the underlying causes of CVD, including established and novel risk factors. Physical activity is one of the most important potentially modifiable risk factors for preventing CVD. Physical inactivity is ranked as the fourth leading risk factor for all-cause mortality worldwide, yet the majority of adults do not engage in sufficient activity to induce benefit. Furthermore, inactivity tends to increase with age. Trend data also highlight declines in occupational, transport and household activity over recent decades. Taken together physical activity promotion efforts are a high priority, particularly in older adults.

Understanding the patterns of physical activity across the life course is crucial for informing the development and timing of interventions. Previous cohort studies have reported that total physical activity tracks moderately across the life course; however, specific types of physical activity may track differently and very few studies have extended into old age. There are also life periods when physical activity is potentially more modifiable, but the transition to old age has been less studied. In addition, few longitudinal studies have utilised repeated measures data to explore life course physical activity in more detail. Those that have done so typically use approaches that cluster trajectory groups in a subjective manner or that describe population-level changes, and thus do not adequately describe sub-groups of the sample nor do they capture fluctuations in physical activity in any detail. Emerging evidence using data-driven approaches, such as latent class growth analysis, suggests that the most naturally occurring trajectories may not be comparable to the pre-determined groups that are commonplace using traditional approaches (i.e. increasers, decreasers, persistently active or inactive). Studies using GBTM have typically identified more stable trajectories across the life course.

The correlates and determinants of physical activity are discussed in section 2.4. A broad range of factors have been associated with physical activity levels, some of them age specific, ranging from individual to wider environmental influences. Aside from age and gender which

are non-modifiable, previous physical activity, self-efficacy and health status are among the most consistent correlates of physical activity. Many of these factors also appear to be important for long-term physical activity behaviour. Major life events can initiate changes in physical activity but the direction and magnitude of their impact and their effects on long-term physical activity remain unclear. Retirement appears to be a crucial window in old age when physical activity is potentially modifiable but its effect appears to be modified by a range of factors, including past physical activity behaviour. Further, the effects of these events in old age on specific types of physical activity and on long-term patterns are unclear.

As reviewed in section 2.5, physical activity lowers CVD risk via a number of pathways. Generally prospective studies have shown that becoming active or remaining active is associated with more favourable levels of cardiometabolic, inflammatory, hemostatic and cardiac risk markers. In contrast, declining and persistent inactivity seem to be associated with the least favourable risk profiles. This review also highlighted a paucity of studies examining physical activity changes using repeated measures data to explore life course patterns, particularly in relation to more novel risk factors. Moreover, there is a lack of data focussing specifically on physical activity changes and CVD risk factors in the later life period. In addition, many studies use rather crude methods for defining change in physical activity, with limited use of data-driven methods, such as GBTM.

Numerous prospective studies have shown a dose-response relationship between physical activity measured at a single time point and risk of CVD and all-cause mortality, including recent studies using objectively measured physical activity. This relationship seems to be largely driven by leisure-time physical activity and not by other domains such as occupational or transport. This review also identified several studies examining the impact of physical activity changes across two time points on subsequent risk of CVD and all-cause mortality. The majority of these studies show similar survival benefit for older adults becoming and remaining active, suggesting that current physical activity is crucial. Fewer studies have utilised repeated physical activity measures covering the adult life course, especially using a data-driven approach, to examine this relationship; in those that have, comparisons are challenging due to the diverse approaches used to classify trajectories. Overall, there is consistent evidence that these associations are partially explained by established CVD risk factors but the extent to which more novel risk factors mediate this relationship remains unclear. Therefore, additional research investigating the association of adult life course physical activity and physical activity type trajectories with subsequent CVD and mortality in later life with additional adjustment for novel CVD risk factors is needed.

This thesis addresses the key gaps in the literature on the role of adult life course physical activity on subsequent CVD and mortality in old age, when the risks of these events are at their highest. Several key questions have come to light in this review:

I. Firstly, how stable is participation in physical activity and physical activity types from midlife to old age?
II. What do the most naturally occurring trajectories of physical activity and physical activity types from midlife to old age look like?
III. How do important physical activity correlates and major life events predict physical activity trajectories?
IV. How do physical activity trajectories from midlife to old age predict subsequent CVD risk factors, major CVD events and all-cause mortality?

This thesis attempts to answer these questions by focussing on the objectives laid out in section 1.2.

Figure 2.1. Socio-ecological model of physical activity behaviour

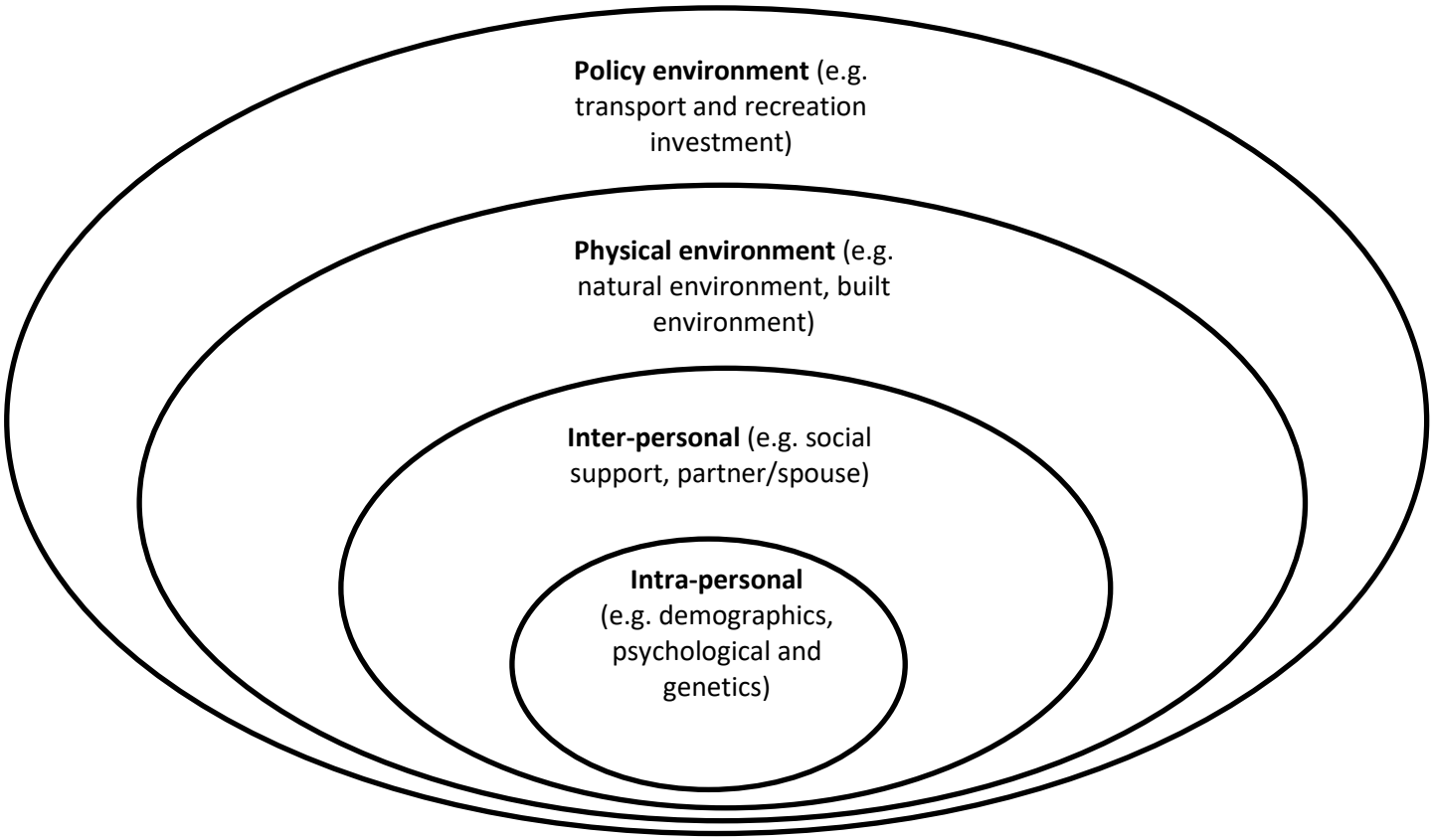


Figure 2.2. Dose-response relationship between leisure-time moderate- to-vigorous-intensity physical activity and CVD mortality [adapted using data from Arem et al., 2015]

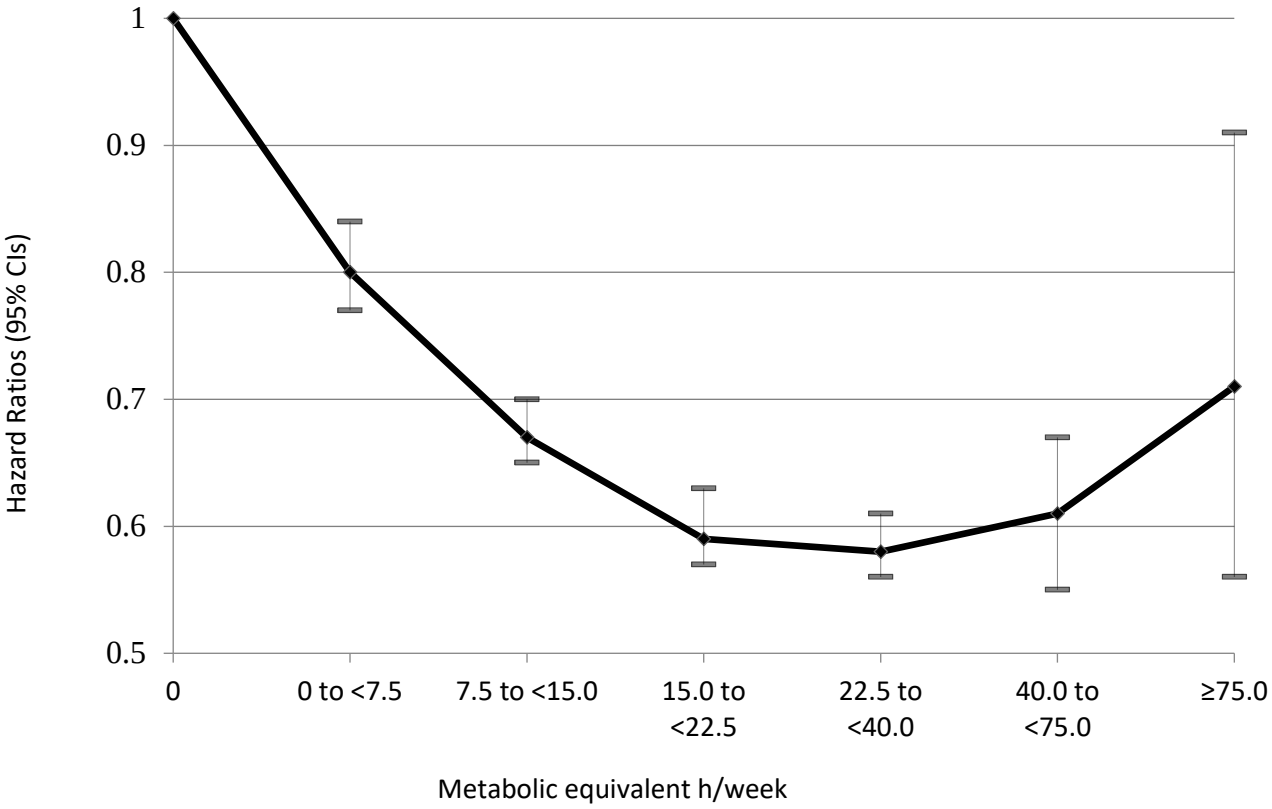


Table 2.1. Summary of prospective studies investigating the longitudinal association between physical activity and novel CVD risk factors

Author, year	Study/location	Trajectory/change period	Population	Physical activity measure	Trajectory/change method	Main findings
Jefferis, 2014	British Regional Heart Study	4-year change	N=3320 men, aged 60 to 79 at follow up	Self-reported	Subjectively defined change. 4 physical activity change groups: 1. Persistently low; 2. Decreasers; 3. Increasers; 4. Persistently high	Compared with men with persistent low activity, men who maintained at least light physical activity had lower levels of inflammatory, endothelial dysfunction and cardiac biomarkers.
Parsons, 2017	British Regional Heart Study	1-year change	N=490 men, mean age 78 at baseline	Objective	Linear regression models with change in physical activity variables as the exposure	A 30-minute increase in light intensity physical activity was associated with a 3.9 unit decrease in vWF. 30 minute increases in sedentary time were also associated with

Author, year	Study/location	Trajectory/change period	Population	Physical activity measure	Trajectory/change method	Main findings
						marked increases in vWF and IL-6.
Fernandes, 2018	Brazil	Change across a median follow up of 2.9 years	N=5030 adults, aged 18 to 60 at baseline	Self-reported	Subjectively defined change. 3 physical activity change groups: 1. Persistently low; 2. High activity at either time point 3. Persistently high	Compared to persistent low activity, persistently active participants had the lowest odds of elevated CRP.
deFilippi, 2012	Cardiovascular Heart Study	Baseline physical activity only, outcome measurement 2-3 years later	N=2933 adults, aged ≥65 years at baseline	Self-reported	N/A	Odds of increasing levels of NT-proBNP and TnT were more than halved in highly active adults compared to the least active.

Author, year	Study/location	Trajectory/change period	Population	Physical activity measure	Trajectory/change method	Main findings
Elhakeem, 2018	MRC National Survey of Health and Development	28-year physical activity, from age 36 years, 4 time points	N=1754 adults, age 36 years at baseline	Self-reported	Subjectively defined change. 4 physical activity change groups: 1. Persistently low; 2. Decreasers; 3. Increasers; 4. Persistently high Accumulation of LTPA across adulthood (i.e. sum of scores across 4 time points)	Greater accumulation of LTPA across adulthood was associated with lower levels of inflammatory and endothelial markers. Persistent activity was most favourably associated with biomarkers, but increasing physical activity was also better than persistent inactivity.
Wannamethee, 2002	British Regional Heart Study	20-year change	N=3810 men, aged 60-79 at follow up	Self-reported	Subjectively defined change. 4 physical activity change groups: 1. Persistently low; 2. Decreasers; 3.	Men who were persistently active had the lowest levels of CRP. Markers of endothelial dysfunction were similar among those who were

Author, year	Study/location	Trajectory/change period	Population	Physical activity measure	Trajectory/change method	Main findings
					Increasers; 4. Persistently high	persistently active and those who increased their PA.
Hamer, 2012	Whitehall II cohort study	10-year change across 2 and 3 time points	N=4289 adults, aged 49 years at baseline	Self-reported	Subjectively defined change across 2 time points. 4 physical activity change groups: 1. Persistently low; 2. Decreasers; 3. Increasers; 4. Persistently high Across 3 time points: 1. Rarely; 2. Sometimes; 3. Always meeting	Increases in physical activity were associated with declines in inflammatory markers. Always and sometimes meeting physical activity guidelines were similarly associated with lower levels of inflammation compared to rarely meeting guidelines.

Author, year	Study/location	Trajectory/change period	Population	Physical activity measure	Trajectory/change method	Main findings
					physical activity guidelines	
Peterson, 2010	Health, Aging, and Body Composition Study	5-year change	N=1496, mean age 74 years at baseline	Self-reported walking	Subjectively defined change, based on meeting 150 min/week guideline. 4 physical activity change groups: 1. Persistently low; 2. Decreasers; 3. Increasers; 4. Persistently high	Compared to the persistently low group, the persistently high group was associated with the most favourable levels of a range of metabolic risk factors and a lower presence of metabolic risk factors. Increasing and decreasing patterns were not significantly associated with levels of metabolic risk factors when compared to the persistently low group.

Table 2.2. Summary of studies investigating longitudinal associations of physical activity with CVD events and all-cause mortality in old age

Author, year	Study/location	Trajectory/change period	Population	Physical activity measure	Trajectory/change method	Outcome	Main findings
Paffenbarger, 1993	Harvard Alumni Study	11 to 15-year change	N=10,269 men, aged 45-84 years at follow up	Self-reported energy expenditure, moderately vigorous sports activity (≥4.5 METs)	Subjectively defined change. 4 sport activity change groups: 1. Persistently no sport; 2. Dropping out; 3. Adopters; 4. Persistent sporting activity	All-cause mortality	Adopting sport was associated with a 23% lower risk of mortality and persistent sporting activity was associated with a 29% lower risk of mortality compared to persistent inactivity.
Byberg, 2009	Uppsala Longitudinal Study of Adult Men	10-year change	N=2205 men, aged 50 at baseline	Self-reported	Subjectively defined change. 4 physical activity change groups: 1. Persistently low; 2. Decreasers; 3. Increasers; 4. Persistently high	All-cause mortality	After 10 years of follow-up for mortality increased physical activity was associated with a similar reduction in mortality as those with persistently high physical activity.

Wannamethe e, 1998	British Regional Heart Study	12-year change	N=4311 men, aged 40-59 years at baseline	Self-reported	Subjectively defined change. 4 physical activity change groups: 1. Persistently low; 2. Decreasers; 3. Increasers; 4. Persistently high	All-cause, cardiovascular and non-cardiovascular mortality	Increased physical activity was associated with a similar reduction in mortality as those with persistently high physical activity. Persistent high activity was optimal for CVD mortality.
Bijnen, 1999	The Zutphen Elderly Study	5-year change	N= 472 men, mean age 75 years at baseline	Self-reported	Subjectively defined change. 4 physical activity change groups: 1. Persistently low; 2. Decreasers; 3. Increasers; 4. Persistently high	All-cause mortality	Increased physical activity was associated with a similar reduction in mortality as those with persistently high physical activity. Decreasing and persistently low activity was associated with an increased risk of mortality in comparison to those with persistently high physical activity.

Higueras-Fresnillo, 2017	Universidad Autónoma de Madrid Cohort Study	2 to 3-year change	N= 2836 men and women, aged ≥ 60 years at baseline	Self-reported	Subjectively defined change. 4 physical activity change groups: 1. Persistently low; 2. Decreasers; 3. Increasers; 4. Persistently high	CVD mortality	Compared to persistent low activity, increased physical activity and persistent high activity was associated with a 25% and 58% lower CVD mortality.
Lewis, 2018	Hispanic Established Population for the Epidemiologic Study of the Elderly	10-year change	N = 803 men and women, aged ≥ 67 years at baseline	Self-reported	Subjectively defined change. 4 physical activity change groups: 1. Persistently low; 2. Decreasers; 3. Increasers; 4. Persistently high	All-cause mortality	Compared to persistent low activity, increased physical activity was associated with a 43% lower risk of all-cause mortality. No associations were observed for persistently high activity.

Gregg, 2003	Study of Osteoporotic Fractures	6-year change	N= 9518 women, aged ≥ 65 years at baseline	Self-reported	Subjectively defined change. 4 physical activity change groups: 1. Persistently low; 2. Decreasers; 3. Increasers; 4. Persistently high	All-cause, CVD and cancer mortality	Compared with women with persistently low activity, women who increased and women who were persistently active had a lower risk of all-cause and CVD mortality. Increased activity proved optimal in relation to all-cause mortality.

Aijo, 2016	Evergreen Project	5-year change	N=357 men and women, aged 80-85 years at baseline	Self-reported	Subjectively defined change. 4 physical activity change groups: 1. Persistently low; 2. Decreasers; 3. Increasers; 4. Persistently high	All-cause mortality	Compared to those who were persistently active, those who decreased their physical activity level had higher all-cause mortality. Persistent low activity had the highest all-cause mortality risk. The risk of all-cause mortality was not statistically significant between those who increased and those who were persistently active.

Stessman, 2009	Jerusalem Longitudinal Cohort Study	7-year change	N=1861 men and women aged 70-85 years at baseline	Self-reported	Subjectively defined change. 4 physical activity change groups: 1. Persistently low; 2. Decreasers; 3. Increasers; 4. Persistently high	All-cause mortality	Survival rates were lowest in the persistently active and increasing physical activity groups. Mortality was similar in the persistently low and decreasing groups.
Raum, 2007	ESTHER study	30-year physical activity from age 20 to 50 years, 4 time points	N=9330 men and women aged 50 to 74 years at baseline	Retrospectively self-reported weekly heavy physical activity	Weekly heavy physical activity averaged across 30-year follow up	Non-fatal doctor diagnosed myocardial infarction or stroke	Compared with participants with moderate amounts of heavy physical activity, those with no or ≥40 hours per week had an increased risk of major CVD events.

Talbot, 2007	Baltimore Longitudinal Study of Aging	38-year physical activity for men, 18-year for women. Biennial measurements (mean n.o. of repeated measurements, 6.5 in <70 and 3.8 in ≥70 year olds, respectively)	N= 2092 men and women aged 19-90+ years at baseline	Self-reported, time spent in physical activity intensities	Linear mixed-effects regression models	All-cause mortality	Those reporting increases or negligible declines in overall and high-intensity physical activity had lower all-cause mortality risk than those with steeper declines. Similar associations were observed in younger and older adults.
Kaplan, 1996	Alameda County Study	18-year physical activity, 3 time points	N= 6,131 men and women, mean age 43 years at baseline	Self-reported	Cox proportional hazard models, with a time-varying physical activity variable	All-cause and CVD mortality	An increase in physical activity was associated with a 28 percent lower risk of death. The effect of physical activity was stronger when using a time-varying variable compared to a time-stable variable.

Laddu, 2018	Osteoporotic Fractures in Men Study	9-year physical activity, 4 time points	N= 3,767 men, aged ≥65 years at baseline	Self-reported	Group-based trajectory modelling	All-cause, CVD, cancer, non-cancer non-CVD mortality	Three trajectory groups identified: low-activity declining, moderate-activity declining and high-activity declining. Compared to the low-activity declining group, following a moderate- or high activity declining trajectory was associated with a lower risk of all-cause and CVD mortality. Associations were largely explained by the most recent physical activity measure.

Xue, 2012	Women's Health and Aging Study	15-year physical activity, 7 time points	N=433 women, aged 70-79 at baseline	Self-reported	Joint latent class and survival mixture model	All-cause mortality	Four trajectory groups identified: always active, fast declining, stable moderate and always sedentary. The risk of mortality in the fast declining and always sedentary classes was more than double the risk in women who were always active. No difference was observed between the stable moderate and always active groups.

Willey, 2017	California Teachers Study	10-year change	N=61,256 women, aged 26-94 at baseline	Self-reported	Subjectively defined change. 4 physical activity change groups: 1. Persistently low; 2. Decreasers; 3. Increasers; 4. Persistently high	Incident stroke	Those who were persistently active and who increased their physical activity were at a lower risk of all stroke than those who were persistently inactive. Associations were driven by achieving moderate doses of physical activity.

CHAPTER 3. METHODOLOGY

This chapter describes the BRHS and how the data are used to address the objectives of this thesis. The first section describes the design of the BRHS, which is followed by a description of the variables used in this thesis, including the main variable of interest (habitual physical activity), the main distal outcomes including CVD risk factors, CVD morbidity and mortality and all-cause mortality, and other covariates and confounders. The strengths and weaknesses of this data source are then discussed, followed by an overview of the statistical methods applied.

3.1 Introduction to the British Regional Heart Study

The BRHS is a large prospective cohort study of CVD, in a socioeconomically and geographically representative sample of British men aged 40 to 59 years, who were randomly recruited from a single General Practice in each of 24 towns across Great Britain. A total of 7735 men were recruited in 1978-80 and attended a physical examination. Men have been repeatedly followed up for morbidity, mortality and lifestyle behaviours until the present. The BRHS was initially conceived to investigate the regional variations in CVD mortality in Great Britain, by examining relationships with environmental, socioeconomic and behavioural risk factors. Since the conception of the study, findings from the BRHS have contributed to a more comprehensive understanding of the aetiology and prevention of CVD in older adults. Funding to support the BRHS since its inception has reached in excess of £10 million, resulting in more than 500 published articles. All participants provided written informed consent to participate, obtained in compliance with the Helsinki Declaration. Ethical approval was obtained from the National Research Ethics Service Committee London.

3.1.1 Recruitment procedures

Towns were selected to cover all major regions of Britain (including England, Scotland and Wales) based on the following key criteria:

I. Two towns from each of the 12 regions in Britain should be included.
II. Populations of 50,000-100,000 at the 1971 Census. Some smaller Scottish towns below 50,000 and a larger town in England (Ipswich) were also considered to achieve sufficient recruitment.
III. Towns should be representative of the region in terms of socioeconomic activity and reflect variations in CVD mortality and water hardness.

IV. Towns with high mobility (i.e. new towns) were excluded

V. When similar towns met the above criteria, a random selection was made.

Figure 3.1 displays a map of the 24 towns included in the BRHS. Table 3.1 shows standardised mortality ratios for CVD in 1969-73 in men aged 35-64 years, the number of men examined in each of the 24 towns and the corresponding response rate.

Participants were recruited from a single General Practice from each of the 24 towns. Criteria for selecting General Practices included adequate size (practice population >7500), representative of the socioeconomic composition of the town and a willingness to participate. 400 men from each practice were randomly selected from age-sex registers, stratified by four five-year age categories (40-44, 45-49, 50-54 and 55-59 years). After excluding men with severe mental or physical disabilities (6-10% per practice), just under 10,000 men were sent invitations, signed by their General Practitioner, encouraging them to attend a CVD health check at a local venue, usually at the practice premises. From nearly 10,000 men invited, 7735 men agreed to take part in the study, equating to approximately 300 men per town and a response rate of 78% (Table 3.1).

3.1.2 Baseline examination

Between 1978 and 1980, 7735 men attended a physical examination conducted in each town. A team of three trained nurses conducted a series of anthropometric and physiological measurements including height, weight, blood pressure, electrocardiogram and lung function. Blood samples were also collected and men completed a questionnaire on their medical history, health and lifestyle.

3.1.3 Follow up of participants

Since the baseline examination, men have been regularly followed up for health and lifestyle factors via postal questionnaires, morbidity outcomes obtained from General Practitioners and patients' medical records, and mortality through National Health Service Central Registers, as shown in Figure 3.2. Men were also invited to physical examinations at 20 (1998/2000; mean age 69 ± 6 years), 32 (2010/12; mean age 79 ± 5 years) and 40 year follow ups (2018/19; mean age 85 ± 4 years). Figure 3.3 shows a flowchart of participant attrition over the course of follow up.

3.1.3.1 Mortality

Information on cause of death was collected through the tagging procedures of the National Health Service Central Registers in Southport for England and Wales, and in Edinburgh for Scotland. Death certificates were sent by the Central Register including identifying information, date and place of death and cause of death coded using the International Classification of Diseases, Ninth Revision (ICD-9). Deaths were also confirmed by General Practices as part of a periodic review, as described in section 3.1.3.2.

3.1.3.2 Morbidity

Information on non-fatal events was obtained from General Practitioners and by biennial reviews of the patients' medical records. Every two years each General Practice was sent a standard medical review (see Appendix 3A) requesting data on each man's continuing registration, current address, and any new CVD events (including MI, angina, stroke, transient ischaemic attack and heart failure), new diagnoses of cancer or diabetes or CVD treatments (coronary artery bypass graft, coronary angioplasty) occurring within the last two years. Newly reported non-fatal MI and stroke events were confirmed via an enquiry form sent to the General Practitioner or hospital consultant to verify that WHO diagnostic criteria had been met. The WHO diagnostic criteria for MI require the presence of at least two of the following: prolonged chest pain, positive electrocardiogram findings and raised cardiac enzyme levels (269, 270). Non-fatal stroke events required an acute disturbance of cerebral function of vascular origin causing a neurological deficit for >24 hours.

Men re-registering with a new General Practice were traced to their new practice using information provided by local authorities. From the original 24 practices, more than 850 practices have been involved in the study, helping to maintain follow up for 98% of surviving men.

3.1.3.3 Follow up questionnaires

Regular postal questionnaires have been sent out to participants from baseline until present, providing information on health and lifestyle factors and personal and socioeconomic circumstances, see Appendix 3B-E. The first follow up questionnaire was sent out after 5 years (in 1983-85), followed by questionnaires after 12 (1992), 16 (1996) and 20 years (1998-2000). At the 20-year follow up, questionnaires were administered at the re-examination. Postal questionnaires were also sent out in 2003, 2005 and 2007. Questionnaires were also completed

at the 32-year re-examination (2010-12). From 2014, questionnaires have been sent out annually.

3.1.3.4 Twenty-year re-examination

At the twenty year follow up, surviving men (then aged 60-79 years) were invited for a re-examination (271). From the 5565 surviving men, a total of 4252 (77%) attended the re-examination. Nurses conducted physical examinations (see Appendix 3F) and administered a questionnaire. All men were asked to provide a fasting blood sample collected using the Sarstedt Monovette system (Sarstedt, Numbrecht, Germany). Men without diabetes were asked to fast for at least 6 hours prior to a pre-arranged appointment between 08:00 and 18:00 hours. On the day of collection, plasma and serum samples were centrifuged and stored at -20°C. Samples were transferred for storage at -70°C until analysis.

3.2 Data used in this thesis

This thesis uses data from the BRHS to identify the patterns of physical activity from midlife to old age, examine the predictors of the identified patterns and the relationship between these patterns and subsequent CVD morbidity and mortality. The data used to identify the patterns of physical activity come from baseline (mean age 50 ± 6 years), 12 (mean age 63 ± 6 years), 16 (mean age 67 ± 6 years) and 20 year follow ups (mean age 69 ± 6 years). Socioeconomic, health, lifestyle and physical measurement data collected at baseline were used to identify the potential predictors of these patterns. Some data that were collected at multiple waves were used to identify major life events, such as retirement, marital transitions and disease onset. Outcome data were obtained from the 20-year physical re-examination and subsequent follow up for morbidity and mortality up until 2016. The following section provides a detailed description of how the physical activity variable, other exposure variables and major outcome variables were defined.

3.2.1 Physical activity measures

Self-reported physical activity data from baseline, 12-, 16- and 20-year follow ups were used to examine the tracking and patterns of physical activity. At each wave, participants were asked about their habitual physical activity, including time spent making journeys by foot or by bicycle, participating in recreational activities and participating in sport/exercise (see Appendix 3B-E). Responses were used to generate a total physical activity score using published procedures

(272). Specifically, each activity was assigned a numerical value based on the Minnesota intensity codes (273). Scores were strongly weighted for vigorous activities and their frequency. Assigned scores for each type and frequency of activity are reported in table 3.2. For walking and cycling men were asked to report whether they used these modes of transport to get to work ("do you usually walk or cycle in the course of your journeys to or from work each day?") and time spent on these journeys ("If yes, how many minutes do these journeys take?"). The same questions were asked for journeys made for reasons other than work. For recreational activity, men were asked "compared to a man who spends four hours on most weekends on activities such as walking, gardening, household chores, do-it-yourself projects, how physically active would you consider yourself?". Response options were much more active, more active, similar, less active and much less active. For sport and exercise participation, men were asked "do you take physical exercise such as running, swimming, dancing, golf, tennis, squash, bowls, cycling, hiking etc.?" Response options were none, occasional (less than once a month) and frequent (once a month or more). Men who reported frequent sport/exercise participation were also asked to state what type of sport/exercise they engaged in.

Scores for each item were summed to give a total physical activity index, ranging from 0 to 46. The physical activity index was used to derive a 6-point total physical activity score by classifying men into six categories: inactive (0-2), minimal activity across all types; occasional (3-5), regular walking or recreational activity only, or sporting activity less than once a week only; light (6-8), more frequent recreational activities plus sporting activity less than once a week, or regular walking plus some recreational activity; moderate (9-12), cycling very frequently only, or very frequent recreational activities plus regular walking, or sporting activity once a week; moderately vigorous (13-20), sporting activity 2-4 times a week, or sporting activity once a week plus regular walking/cycling and recreational activity; or vigorous (>21), sporting activity more than 4 times a week, or less frequent sporting activity plus frequent walking/cycling and recreational activities. The total physical activity score has been validated against heart rate and forced expiratory volume in 1 second (FEV_1) and objectively measured physical activity in the same sample (272, 274). The six-point physical activity score was also dichotomised to categorise participants as either active (at least light activity) or inactive (occasional or less).

The core questions used to generate the score remained virtually identical throughout follow up. Some amendments were made to the types of sport/exercise that were listed in the later waves and the questions regarding walking and cycling to get to work were dropped at the 20-year follow up as few men remained in employment. Instead, at the final wave, walking time per day was derived from reported walking time across the whole week (hours), which included

weekend days. Similarly, a question regarding occupational activity was dropped after the 12-year follow up, but this did not contribute to the physical activity score at any time point.

3.2.2 Socioeconomic and sociodemographic factors

At baseline men were asked to report their longest-held occupation (Appendix 3B). Occupational social class was determined using the Registrar General's Classification of Occupations (275), from which men were classified into six categories: I (professional occupations e.g. physicians, engineers), II (managerial occupations e.g. teachers, sales managers), III non-manual (skilled non-manual occupations e.g. clerks, shop assistants), III manual (skilled manual occupations, e.g. bricklayers, coalminers), IV (partly skilled occupations e.g. bus conductors, postmen) and V (unskilled occupations e.g. porters, general labourers). The six categories were dichotomised into manual (social classes III manual, IV, V) and non-manual occupations (social classes I, II, III non-manual). The proportion of manual and non-manual workers in the BRHS is similar to those reported in census data (271). At each wave, men also reported their employment status, from which men were classified as in employment (part/full-time) or not in employment (retired, unemployed) and their marital status (single; married; widowed/divorced/separated). At baseline, region of residence was derived from the 24 towns that practices were recruited from. Towns were grouped into four regions: Scotland, North, Midlands and South of England. Men were also asked at baseline to report their number of children, which was dichotomised as either no children or ≥ 1 child.

3.2.3 Lifestyle variables

3.2.3.1 Smoking status

In each questionnaire, men were asked detailed questions about their current and previous smoking habits. Men were asked whether they have ever smoked, whether they currently smoke and, if they had stopped, at what age they had given up. From these data, men were classified as either current/recent ex-smokers or non-smokers/long-term ex-smokers (>15 years).

3.2.3.2 Diet and alcohol

In each questionnaire, men were asked in depth questions about their alcohol consumption. Men were asked about the frequency (none; on special occasions only; once or twice a month; weekends; daily/most days) and quantity (2 drinks a day or less; 3-6 drinks a day; more than 6

drinks a day) of their drinking. One drink was defined as 1 unit of alcohol (i.e. a single whisky, gin or brandy, a glass of wine, sherry or port or half a pint of beer). From this information, men were classified into five groups: none (0 units/week); occasional (<1 unit/week); light (1-15 units/week, which included weekend 1-2 units, weekend 3-6 units and daily 1-2 units); moderate (16-42 units/week); heavy (>42 units/week). At baseline, men were asked how often during an average week they consume a range of foods. Breakfast habits were derived from reported consumption of breakfast cereal (none, occasional [1-2 times/week] or regular [>3 times/week]).

3.2.4 Physical measurements

3.2.4.1 Anthropometric measurements

Height and weight were measured by trained nurses at baseline and at the 20-year re-examination. Measurements were made while the men were standing, in light clothing and without shoes. Height was measured using a Harpenden stadiometer to the nearest 0.1cm with the head oriented in the Frankfort plane. Weight was measured using a Soehnle digital electronic scale (Critikon Service Center). For measurements falling between two 0.1 kg marks, the lower value was recorded. From these data BMI was derived (kg/m^2). Waist circumference was also measured in light clothing, whilst men were standing, using an insertion tape (CMS Ltd, London, United Kingdom). Measurements were taken at the midpoint between the iliac crest and the lower ribs. At the 12- and 16-year follow ups men self-reported their weight via the postal questionnaires and their BMI was calculated based on their reported current weight and on their height measured at baseline. Strong correlations (r=0.8-0.9) were observed between the self-reported measurements and the nearest objective measures.

3.2.4.2 Blood pressure

At the 20-year re-examination, systolic and diastolic blood pressure were each measured twice with the subject seated, using a Dinamap 1846SX blood pressure recorder. The mean of two readings was used for analysis. These data were used to identify hypertensive subjects (i.e. high systolic [≥160 mmHg] or diastolic [≥100 mmHg] blood pressure or taking anti-hypertensive medication) (276).

3.2.4.3 Lung function

At the 20-year re-examination, FEV_1 was measured using a Vitalograph Compact spirometer, which was calibrated using a precision syringe at least twice daily.

3.2.5 Self-reported health and morbidity

In each questionnaire, men were asked about their medical history. At baseline, men were asked if they had ever been told by a doctor that they have or have had a range of conditions including a heart attack (including coronary thrombosis and MI), angina, stroke, arthritis, bronchitis and high blood pressure. Men were also asked whether they suffer from chest pain on exertion and breathlessness when walking. Response options were a yes or no. Similar questions were asked at each questionnaire. At the 20-year re-examination, the questionnaire also asked men to report any medications they were currently taking, from which patients taking anti-coagulants, anti-hypertensives and lipid-lowering drugs could be identified.

3.2.6 Blood measurements

At the 20-year re-examination, fasting blood samples were collected using the Sarstedt Monovette system. Blood lipids and glucose were measured at the Department of Chemical Pathology, Royal Free Hospital and insulin was measured at the Department of Diabetes and Metabolism, University of Newcastle. Total, HDL cholesterol and triglyceride levels were measured using a Hitachi 747 automated analyser (Hitachi, Tokyo, Japan). Total and HDL cholesterol were determined using methods described by Siedel et al., (277) and Sugiuchi et al., (278) and LDL was calculated using the Friedrickson-Friedwald equation. Plasma glucose was measured using a glucose oxidase method (Falcor 600 automated analyser, A. Menarini Diagnostics, Wokingham, UK). Serum insulin was measured using an enzyme-linked immunosorbent assay (ELISA) that does not cross-react with proinsulin (279). Haemoglobin A1c was determined using a Drew Hb Gold HPLC analyser (Drew Scientific Group Plc, Barrow in Furness, UK). Blood was anticoagulated with 0.109 mol/L trisodium citrate (9:1 vol:vol) for measurement of coagulation factor VIII in an MDA-180 coagulometer (Organon Teknika, Cambridge, UK). Plasma levels of tPA and D-dimer were measured with ELISAs (Biopool AB, Umea, Sweden), as was vWF (DAKO, High Wycombe, UK). CRP was assayed by ultrasensitive nephelometry (Dade Behring, Milton Keynes, UK). IL-6 was assayed using a high-sensitivity ELISA (R&D Systems). NT-proBNP was measured using the Elecsys 2010 (Roche Diagnostics, Burgess Hill, UK) (81). TnT was measured using a high-sensitivity method on an e411 analyser (Roche Diagnostics, Burgess Hill, UK).

3.2.7 Incident disease

The main distal disease outcomes examined in this thesis include incident CHD events (fatal and non-fatal), stroke events (fatal and non-fatal), CVD mortality and all-cause mortality. Fatal MI was defined as ICD-9 codes 410–414 and fatal stroke was defined as ICD-9 codes 430–438. Fatal CVD was defined as ICD-9 codes 390–459. Non-fatal MI was defined as heart attack or coronary thrombosis in accordance with the WHO diagnostic criteria and non-fatal stroke events were defined using the criteria described in section 3.1.3.2. This thesis uses follow up data from the 20-year re-examination, in 1998-2000, to the 30th June 2016.

3.2.8 Outcomes

The key outcomes assessed in relation to physical activity patterns were:

- Established and novel CVD risk factors measured at the 20-year follow up including:
  - Cardiometabolic risk factors (blood lipids, hypertension, diabetes risk markers and waist circumference)
  - Lung function
  - Inflammatory/hemostatic risk factors (IL-6, CRP, Factor VIII, vWF, tPA and d-dimer)
  - Cardiac markers (Hs-TnT and NT-proBNP)
- Major CHD events (fatal and non-fatal)
- Major stroke events (fatal and non-fatal)
- CVD mortality
- All-cause mortality

3.3 Statistical methods

Detailed explanations of specific statistical methods are provided in relevant chapters, but some of the common methods used throughout this thesis are outlined below. Evidence from the literature on physical activity and CVD was used to identify potential predictors, confounders and covariates in respective analyses. All analyses were performed in Stata 14 (Stata Corp., College Station, Texas).

3.3.1 Descriptive analysis

Initially, distributions of continuous variables were examined graphically using histograms and distributions of categorical variables were examined using frequencies. Descriptive analyses

were then performed for each variable. For normally distributed continuous variables, means and standard deviations were used to describe the central tendency and dispersion of the data, whereas medians and interquartile ranges were used for non-normally distributed data. Proportions were used to summarise categorical data.

3.3.2 Estimates of tracking

The tracking of physical activity measures from baseline to the 20-year follow up was assessed in three ways:

1) Cohen's kappa was used to assess the level of agreement of the binary categorisation of physical activity (i.e. active or inactive) between baseline and subsequent time points. Cohen's Kappa is a measure of agreement comparing the observed agreement to the expected agreement, as shown in the calculation below.

$$K\ \text{Cohen} = \frac{P\text{o} - P\text{e}}{1 - P\text{e}}$$

*P*o is the proportion of observed agreement and *P*e is the proportion of random/expected agreement.

2) Random effects models (also known as multilevel, mixed or hierarchical models) are appropriate for analysing longitudinal data as they account for the clustering of repeated measures (Level 1) within individuals (Level 2) and can accommodate for confounding variables. Key outcomes of random effects models include the intercept (i.e. the average initial score at baseline) and slope (i.e. the average rate of change of the outcome variable over age or time). A major advantage of using random effects models for studies with repeated measures data compared to more traditional omnibus tests such as repeated measures analyses of variance is their ability to separate within- and between-person variability. Random effects models produce intra-class correlation coefficients (ICCs) which indicate the proportion of variance explained by within-person variability (Level 1), and are calculated as the variance between subjects (Level 2 variance) divided by the total amount of variance explained by the model (Level 1+2 variance) (283). Random effects models have typically been used with continuous data but recent advances have extended their use for binary data (284). In this thesis, random effects models were used to calculate ICCs, maximising the use of available physical activity data whilst adjusting for a range of confounders.

3) Logistic regression is appropriate for analysing the relationship between one or more exposure variables and a dichotomous outcome variable (285). Logistic regression calculates the odds of a binary outcome in those exposed to a particular factor, the odds of a binary outcome in those not exposed to this factor and the ratio between these two odds. Many of the assumptions of linear regression, such as linearity, normality and homoscedasticity do not apply for logistic regression, as the outcome is linked to the predictors via a sigmoid non-linear function. This thesis uses logistic regression to estimate the odds ratio for being active compared to being inactive at the 20-year follow up according to a range of prior physical activity measures, whilst adjusting for a range of confounders.

3.3.3 Linear regression

Linear regression is used to examine the relationship between one or more explanatory variables and a continuous outcome variable. Linear regression estimates an intercept, which is the predicted value of the outcome when the exposure equals zero, and a slope, which is the predicted rate of change in the outcome for a one unit increase in the exposure. Linear regression assumes a linear relationship between exposure and outcome, normally distributed residuals and homoscedasticity (i.e. constant variance). Linear regression was used to examine the association between physical activity trajectories and continuous CVD biomarker variables at the 20-year follow up.

3.3.4 Survival analysis and Cox proportional hazards regression analysis

Survival analysis is used to analyse time-to-event data when time to a binary event is the outcome of interest (285). The length of time is calculated from a fixed time point (i.e. entry to the study) until the time the event occurs or until death. Censoring occurs when subjects do not experience the event by the end of the follow up period, before dropping out of the study or if they died from a cause other than the event of interest. The Kaplan-Meier method can be used to estimate probabilities of experiencing an event by a certain time point and to generate survival curves.

This analysis can be extended by performing cox proportional hazards regression models, which are used to examine the association between one or more exposure variables and a time-to-an-event outcome. These models estimate a hazards rate in those exposed and those not exposed to a particular factor and the ratio between the two, which can be interpreted much like an odds ratio or risk ratio. The key assumption of these models is that hazard ratios for each covariate are constant over time, i.e. the proportional hazards assumption. This assumption can be

examined graphically using survival plots and more formally by inspecting the Schoenfeld residuals. Survival analysis and Cox proportional hazards models were performed to investigate the association between 20-year physical activity trajectories and risk of CVD events and mortality over 16 years of subsequent follow up.

3.3.5 Classifying subjects with different physical activity trajectories

This thesis uses two approaches to categorise participants based on their physical activity trajectories. These can be broadly categorised as 'observed trajectories', which utilise more conventional techniques, and 'group-based trajectory modelling' which is a more advanced data-driven modelling approach using latent variables to represent groups of participants.

3.3.5.1 Trajectories based on observed binary exposure measurements

One of the more traditional methods for classifying trajectories is to group subjects based on observed data. This is typically done using a binary exposure measurement, derived from a clinically meaningful cut point. Binary data can be used to address two common hypotheses of life course epidemiology, risk accumulation and sensitive period models. The former involves generating a cumulative score across repeated measures, thus providing an overall index of physical activity levels across the study period. One of the caveats of accumulation models is that they do not account for the possibility that exposures during specific life stages might have a particularly strong effect on an outcome but have little or no effect at other life stages (30). The approach adopted in this thesis is based on the idea of sensitive periods, allowing for the explicit modelling of the relative effect of physical activity at different ages on specified outcomes. Trajectories were defined according to whether participants were active or inactive across three follow up measurements. At each of the three time points, men were classified as active (1) if they had at least 'light' activity or inactive (0) if they were classified as inactive or occasional. Men were allocated to one of eight possible trajectories, which are indicated by combinations of zeros and ones (e.g. '0-0-0' represents participants that were inactive at all three time points, while '1-0-0' describes participants who were active at baseline only). The time points used to define these trajectory groups will be outlined in each relevant chapter.

3.3.5.2 Group-based trajectory modelling

There are a variety of data-driven methods that have been developed for identifying developmental trajectories, which largely rely on growth curve models (GCM), a statistical model similar to random effects models (286), which uses an alternate parameterisation. GCM

make use of latent variables which capture the development of a variable over time and represent the intercept and slope of the trajectory (a quadratic term capturing non-linear change can also be derived as an additional latent variable) (286, 287). Traditional GCM applies this approach to estimate an average developmental trajectory over time. Deviations from this mean trend and how one or more exposure variables can predict the growth parameters can also be estimated. Previous physical activity research reviewed in section 2.3.2 suggests that change in physical activity over time is not uniform and there may be sub-groups of the population that follow very different trajectories compared to the mean population trajectory. Hence other modelling approaches may be more appropriate for capturing physical activity trajectories.

LCGA otherwise known as GBTM and latent class growth mixture modelling (LCGMM) are techniques that are founded in the growth curve modelling approach. They extend on traditional growth curve modelling by grouping individuals who share similar patterns of behaviour over time, with each group having its own growth parameters (286). Although these related techniques group individuals who share similar intercepts and slopes, there are some technical differences. The main difference is that LCGMM allows for within-class variation or, in other words, trajectories are allowed to differ within classes, whereas GBTM does not allow for within-class variation. In GBTM, individual trajectories are assumed to be similar within each class so the focus is more on between-group differences in the intercepts and slopes (117, 287). This often results in a larger number of trajectory groups or classes when compared to LCGMM. However both approaches tend to yield comparable trajectories, although LCGA has been shown to outperform LCGMM in terms of its ability to detect linear trajectories (288). A schematic description of the modelling framework applied to address the objectives of this thesis is shown in Figure 3.4.

This thesis uses a GBTM approach, applied using the Stata TRAJ plugin (289), to identify the shape and optimal number of trajectories in the BRHS sample for a range of physical activity measures. The trajectory groups can then be used to study the predictors and associated outcomes. To identify the optimal number of trajectory groups, models with 2 to 5 groups were tested and compared using goodness of fit criteria including the Bayesian information criterion (BIC), whereby a lower BIC (or the least negative in the case of negative numbers) (290) represents a better fitting model; the requirement of at least 5% of the total sample size to be allocated in each trajectory group; close agreement between the estimated probability of group membership and the actual proportion of the sample assigned to that group; odds of correct classification based on posterior probabilities exceeding 5; and posterior probabilities (estimates

of likelihood that an individual belongs to their assigned trajectory group) exceeding 0.70 (117). Higher posterior probabilities indicate greater certainty that individuals are accurately assigned to trajectory groups. The models provide probabilities of belonging to each of the identified trajectory groups for each individual and assigns them to the trajectory group that they have the highest probability of belonging to. GBTM also allows for the inclusion of time-varying and time-stable predictors simultaneous to class selection in order to increase classification accuracy and to adjust the shape of each group's trajectory. Time-stable variables are used to predict trajectory group membership while time-varying covariates predict the slope and intercept of the trajectories. A multinomial logit function estimates the odds of trajectory group membership according to time-stable predictors (289). Estimates for time-varying covariates represent the shift in the trajectory per unit change in the exposure variable. The effects of time-varying predictors on the trajectory shapes are estimated for each trajectory group, and thus the effects could differ in each trajectory group. Wald tests were performed to test whether the effects of time-varying covariates differed by trajectory group. To examine the potential presence of multicollinearity among predictor variables, variance inflation factors (VIF) were calculated. Mean VIFs not considerably larger than 1.00 indicate no multicollinearity issues (291). After the optimal number of trajectory groups had been established, the level of the polynomial function for each group was determined. First, the models were fit with the highest order function possible, starting with a quadratic growth factor, followed by linear and intercept only models, until each parameter estimate was statistically significant based on the t statistic ($p<0.05$). Examples of these trajectory shapes are provided in Figure 3.5. As GBTM analyses are conducted using the maximum likelihood estimation method, all available data are used to estimate parameters and standard errors, under the assumption that missingness is at random. Subsequently these models can include all subjects with at least one measure of physical activity, minimising the bias caused by non-responders.

Figure 3.1. Map of 24 British Regional Heart Study towns in Great Britain

Figure 3.2. Timeline showing follow up of the British Regional Heart Study cohort

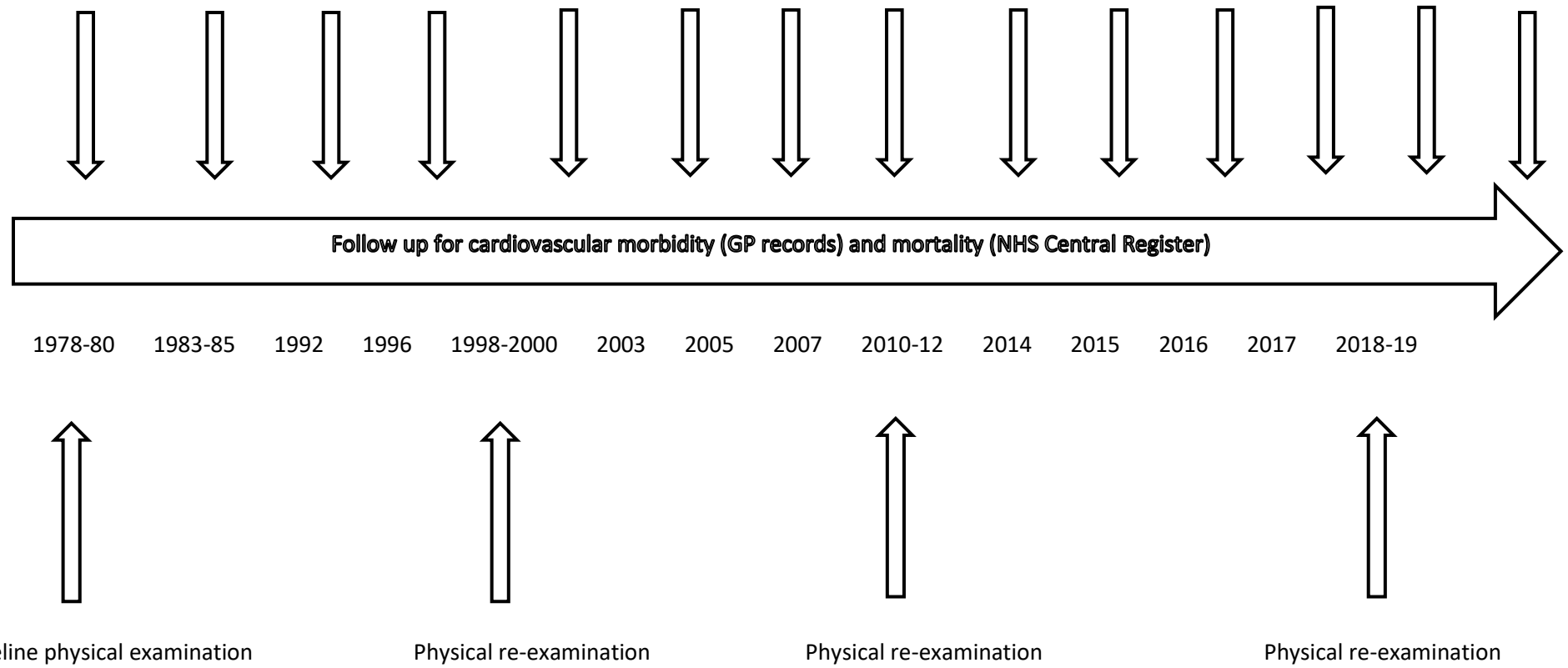


Figure 3.3. Flow chart illustrating subject attrition over follow up

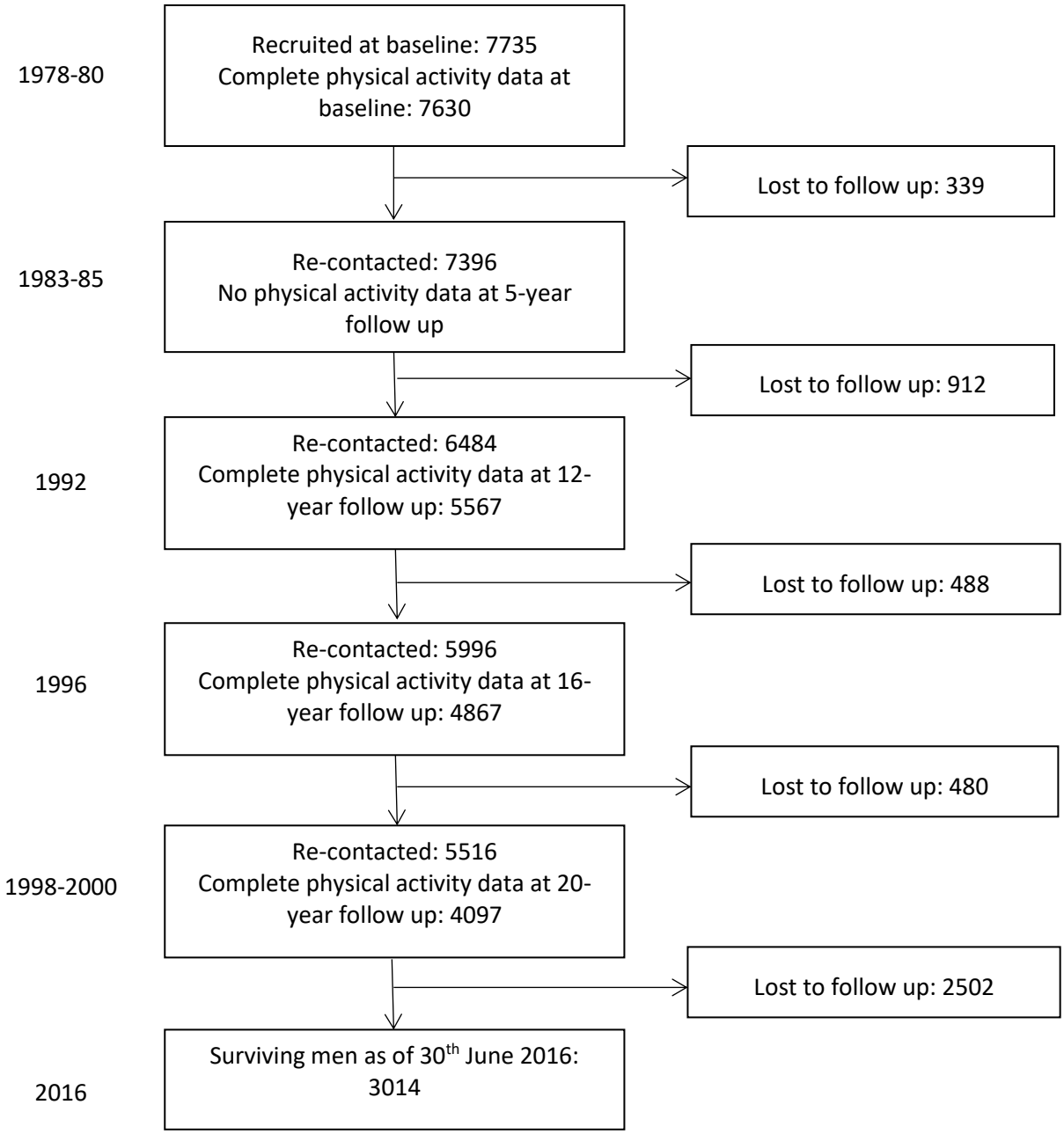


Figure 3.4. Schematic diagram of the latent modelling framework. Rectangles represent the four waves with repeated physical activity measurements, i and s represent the intercept and slope, c represents the latent trajectory class and squares represent the predictors and distal outcomes

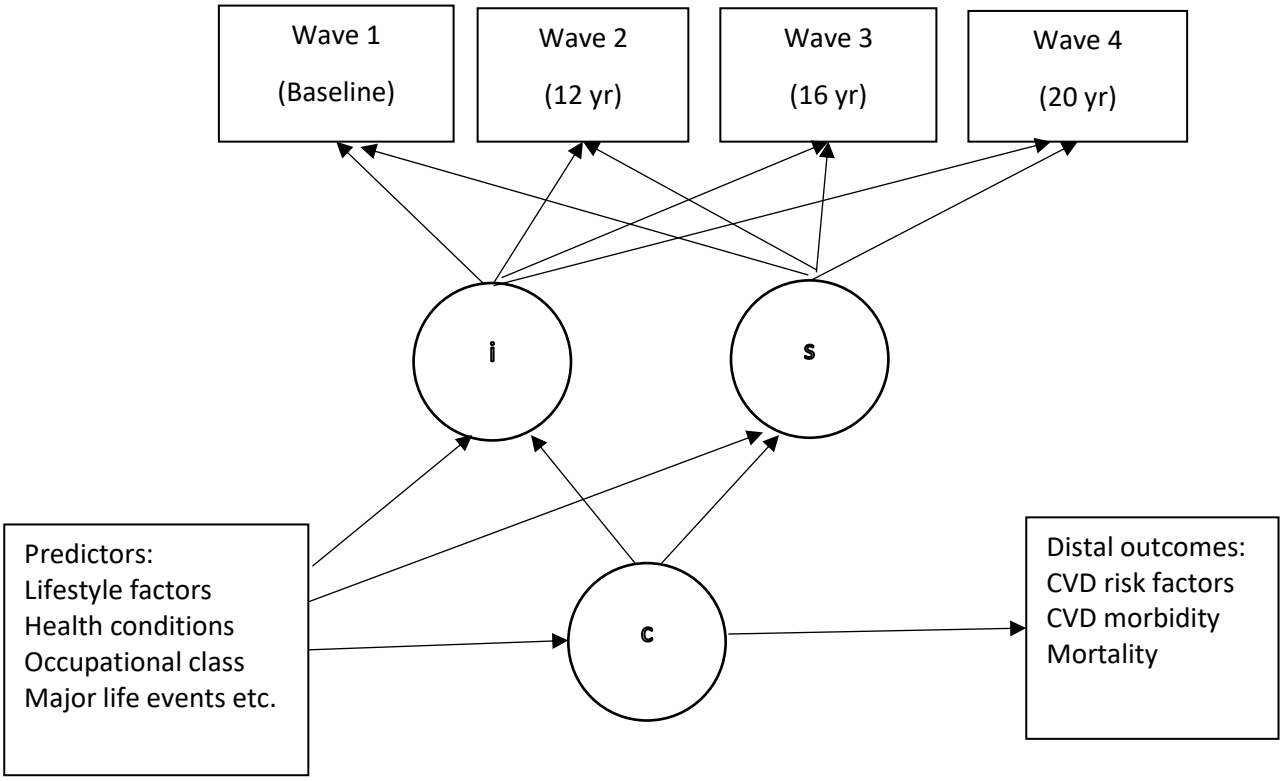


Figure 3.5. Types of trajectory shape

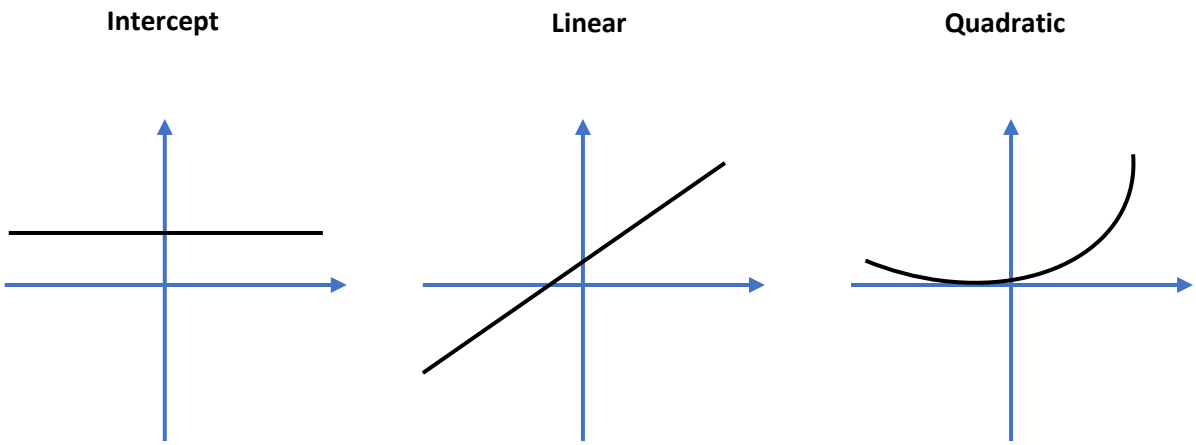


Table 3.1. Towns included in the British Regional Heart Study

Town	Standardised mortality ratios for cardiovascular disease in men aged 35-65 years in 1969-73	Men examined (n)	Response rate (%)
Ayr	140	301	70
Bedford	80	303	73
Burnley	114	286	80
Carlisle	121	389	85
Darlington	109	382	82
Dewsbury	142	326	79
Dunfermline	118	350	80
Exeter	90	332	84
Falkirk	98	308	75
Gloucester	84	309	73
Grimsby	96	318	71
Guildford	78	335	82
Harrogate	82	280	77
Hartlepool	101	334	70
Ipswich	92	362	85
Lowestoft	85	324	83
Maidstone	99	319	72
Mansfield	95	321	80
Merthyr Tydfil	135	282	76
Newcastle-upon-Lyme	115	293	77

Town	Standardised mortality ratios for cardiovascular disease in men aged 35-65 years in 1969-73	Men examined (n)	Response rate (%)
Scunthorpe	109	313	76
Shrewsbury	95	310	83
Southport	114	322	80
Wigan	134	337	77

Data source: adapted from Shaper et al. 1981 (292)

Table 3.2. Type and duration/frequency of physical activity with assigned scores

Activity	Score
Regular walking	
None	0
≤ 20 min/day	1
21-40	2
41-60	3
61-90	4
>90	5
Cycling	
None	0
≤ 15 min/day	2
16-30	4
31-45	6
46-60	8
>60	10
Recreational activity	
Very inactive	0
Fairly inactive	1
Average	3
Fairly active	5
Very active	7
Sporting activity	
None	0

Activity	Score
Occ (< 1 month)	2
1-3 times/month	4
4-7	8
8-11	12
12-15	16
16-19	20
≥ 20	24

Scores for low intensity sports such as fishing and bowls were capped at 4.

CHAPTER 4. TRACKING OF PHYSICAL ACTIVITY FROM MIDLIFE TO OLD AGE

4.1 Summary

Adopting an active lifestyle in old age may bring similar health benefits as those who have been persistently active across the life course. Identifying life stages when physical activity behaviour is modifiable could inform intervention strategy. Prior physical activity is one of the most consistent correlates of current physical activity; however, the stability of physical activity and specific types of physical activity in later life is unclear. In this chapter, the tracking of physical activity and specific types of physical activity from midlife to old age was examined. A total of 3413 men, aged 60-79 years, from the BRHS had completed the physical activity questionnaire at baseline, 12-, 16- and 20-year follow ups. Tracking coefficients for total physical activity, walking, sport/exercise and recreational activity were estimated across the four waves. Logistic regression was used to estimate the odds of being active compared to inactive at the 20-year follow up according to previous engagement in physical activity and physical activity types. Tracking coefficients indicated moderate levels of tracking for total physical activity, with 17% becoming active and 17% becoming inactive between baseline and 20-year follow up. Sport/exercise tracked stronger than other physical activity types, due to high levels of drop out for recreational activity and high uptake of walking. Golf was the most popular and most stable sport/exercise throughout, whereas bowls, walking/hiking and dancing were less common at baseline but frequently adopted during follow up. Conversely, cycling and racquet sports were common at baseline but were frequently dropped during follow up. Being active in midlife more than doubled the odds of being active at 20-year follow up. High levels of walking and recreational activity at baseline were also associated with increased odds of being active at 20-year follow up, but the magnitude of association was strongest for high sport/exercise. More persistent physical activity throughout adulthood, earlier uptake of sports/exercises and a greater diversity of sports/exercises further increased the odds of being active in old age.

4.2 Introduction

Although there is some evidence suggesting that maintenance of a physically active lifestyle throughout the life course provides optimal health benefits (257, 259, 260), adopting an active lifestyle later in life may induce similar benefits as those who have been persistently active (257-261, 263, 264). As described in Chapter 3, tracking refers to the stability of an outcome or behaviour over time. Examining the tracking of physical activity may help identify critical periods

when physical activity is particularly important for future physical activity and when it may be modifiable.

As reviewed in Chapter 2, physical activity tracks moderately throughout the life course; however, most of the evidence comes from younger cohorts. Recent reviews have suggested that tracking may be lower during transitionary periods (17, 89, 93), but tracking during the transition to old age, which often coincides with a number of major life events that could impact physical activity, such as retirement, birth of grandchildren, onset of health conditions and disability etc, has been little studied. These events may present additional opportunities for physical activity or may equally present a barrier to physical activity. There is also a suggestion that specific types of physical activity track more strongly than others (90, 98, 293). For example, there is evidence to suggest that sport tracks more strongly and is a stronger predictor of physical activity later on in life than other types of physical activity (90, 101, 293), but this has been less studied in older adults. Even less researched is the tracking of specific types of sport and exercise. It may be possible that certain sports/exercises, or multiple sports/exercises (102), are fundamental for establishing a lifelong habit for sport and physical activity. Moreover, as the health benefits of sport and exercise are specific to type (294, 295), it may be important to identify the most acceptable types of sport/exercise for adoption or continued participation in ageing adults. However, very few prospective studies have collected sufficient data to be able to track participation in specific types of sport/exercise.

The aim of this chapter is therefore to investigate the tracking of physical activity and specific types of physical activity from midlife to old age. Specifically, the stability of total and various types of physical activity are estimated between baseline and subsequent follow-up measures up to the 20-year follow up. In addition, the predictability of being active and engaging in sport/exercise are estimated according to various markers of prior physical activity.

4.3 Objectives

To examine the tracking of physical activity and physical activity types from midlife to old age in British men, this Chapter addresses the following key objectives:

I. Examine the levels of participation in physical activity and specific types of physical activity from midlife to old age in British men.
II. Estimate the stability of overall and specific types of physical activity from midlife to old age.

III. Determine the predictability of physical activity and sport/exercise engagement in old age from measures of prior physical activity.

4.4 Methods

4.4.1 Subjects and methods of data collection

This chapter uses longitudinal data from the BRHS collected from questionnaires completed by study participants at baseline in 1978-80, and at the 12-, 16- and 20-year follow ups. Analyses were conducted on men, aged 60-79 in 2000, who had self-reported their habitual physical activity, as described in Chapter 3, at all four waves and who had complete data on relevant covariates outlined below.

4.4.2 Physical activity measures

Self-reported physical activity data from all four waves were used, including measures of total physical activity, sport/exercise, walking and recreational activity. Each physical activity variable was dichotomised into high or low categories, allowing comparisons across all physical activity measures. For total physical activity, men were classified as active or inactive (high/low) at each wave based on the six-point total physical activity score (<light=inactive; ≥ light= active). Recent validation of the total physical activity score in BRHS participants suggests that this cut point is appropriate for differentiating between active and inactive men (274). Participants were also classified according to high or low engagement in sport/exercise (none or occasional=low; frequent [once a month or more=high), walking (≤20 mins/day=low; >20 mins/day=high) and recreational activity (≤4 hours/weekend=low; >4 hours/weekend=high).

Men who reported frequent participation in sport/exercise also stated the types of sport/exercise they engaged in. Men reporting activities not deemed to be sport or exercise (e.g. snooker) were reclassified as low sport/exercise. Walking/hiking was retained as a sport/exercise but did not include men who reported walking for transport purposes only. Cycling participation was considered as a sport/exercise and combined all forms, including men who reported frequent cycling for transport purposes. As participation in some sports/exercises was low, similar sports/exercises were grouped together. For example, bowls, curling and skittles were combined to form ‘bowling games’. A full list of sports/exercises that were combined can be viewed in Appendix 4A. Sports/exercises that were extremely rare (≤0.5%) were also combined into an ‘Other’ category. Men were also classified according to the number

of sports/exercises they engaged in (none, one, two and three or more). At baseline men also retrospectively reported how many years they had been involved in these sports/exercises, from which men were classified as participating for ≤ 4 years, 5-11 years, 12-24 years and ≥ 25 years.

4.4.3 Sociodemographic and lifestyle factors

Age was self-reported at baseline. Occupational class was derived from each participant's longest held occupation reported at baseline and categorised as manual or non-manual using the Registrar General's occupational classification, as described in Chapter 3. Participants were classified as current/recent ex-smokers or never smokers/long-term ex-smokers. Men were also categorised as overweight/obese (BMI: ≥25.0 Kg/m2) or healthy weight (BMI:<25.0 Kg/m2). Season of questionnaire completion was classified as summer or winter.

4.4.4 Statistical methods

Descriptive statistics were initially used to calculate the proportion of men classified as active or inactive, participating in high or low levels of each physical activity type and participating in each sport/exercise type across all four waves. The proportion of men adopting, dropping out and sustaining low and high levels of participation between baseline and 20-year follow up was also determined. Cohen's kappa was used to assess the observed agreement compared with the expected agreement from baseline up to each subsequent wave. Interpretation of K coefficients was based on suggestions by Munoz and Bangdiwala: <0.00 indicates poor agreement, 0.00-0.20 fair agreement, 0.21-0.45 moderate agreement, 0.46-0.75 substantial agreement and 0.76-1.0 indicates near perfect agreement (296). As Kappa statistics vary in magnitude depending on how the outcome measure is categorised, initial analyses were performed using the binary physical activity variables across all four time points, as described above. However, to make use of the available data, additional analyses were performed to estimate tracking coefficients using 3 categories where possible. Random effects models were used to calculate ICCs, across all repeated assessments, whilst also controlling for confounding factors, as described below. ICCs less than 0.4 indicate poor to fair agreement, between 0.4 and 0.6 indicate moderate agreement, between 0.6 and 0.8 indicate good agreement and above 0.8 indicate excellent agreement (297). Random effects models included a larger sample as inclusion required physical activity data at only two assessments.

Multiple logistic regression was used to estimate odds ratios and 95% CIs for being active compared to being inactive at 20-year follow up according to various measures of prior physical activity behaviour including 1) overall activity levels at baseline, 2) engagement in specific types

of physical activity at baseline, 3) participation in specific types of sport/exercise, 4) duration of sports/exercise participation, 5) number of sport/exercises and 6) long-term trajectories of physical activity participation based on the observed binary data from baseline through 12- and 16-year follow ups, as described in Chapter 3. To examine linear trends, the number of sports/exercises and the duration of participation in these sports/exercises were entered into regression models as continuous variables. Additional models were conducted to estimate the odds ratios of frequent sport/exercise participation at the 20-year follow up (compared to occasional or no sport/exercise participation) according to participation in sport/exercise types at baseline. All random effects and logistic regression models were adjusted for age at baseline (model 1). Additional confounding variables were also added including occupational class, BMI (healthy vs. overweight/obese) and smoking habits at baseline (model 2). Analyses including sporting/exercise types as the exposure also adjusted for season of questionnaire completion to account for seasonal variation in sport/exercise participation (model 2). Additional models were introduced adjusting for participation in other types of physical activity to determine whether the associations of specific types of physical activity or sport/exercise were independent of each other.

In additional exploratory analyses, kappa statistics were calculated according to changes in employment status to examine whether the transition to retirement reduced the stability of physical activity and physical activity types. Men were classified as no change in employment status (representing continuous employment/seeking employment and continuously retired) or retiring (i.e. retired between baseline and the respective follow up) and kappa statistics were presented separately. Logistic regression models were also run to estimate the odds of being active at 20-year follow up according to physical activity and physical activity types categorised with 3 levels rather than a dichotomous variable to determine whether greater levels of physical activity more strongly predicted physical activity in old age. In addition, to understand whether the tracking of specific sports/exercises differed according to occupational class, participation and change in participation (adopters and drop outs) was also estimated for men from manual and non-manual occupations separately.

4.5 Results

Among the 7735 men who responded to the baseline survey, a total of 3413 men had complete physical activity data at all four waves, accompanied with complete covariate data. Compared to men in the analytic sample assessing the tracking of total physical activity (n=3413), men excluded from the analyses due to insufficient physical activity or covariate data were

significantly older (baseline age, 48.6 vs. 51.5 years, p<0.001), had a higher BMI (baseline BMI, 25.3 vs. 25.7, p<0.001) and were less likely to be active at baseline (proportion active at baseline, 66.1% vs. 55.5%, p<0.001). A larger sample was included in random effects models, as men were only excluded if they did not provide physical activity measures on at least two assessments and have valid covariate data. Sample sizes for random effects models are reported in the respective tables. Mean age was 49 years at baseline rising to 69 years at the 20-year follow up. Baseline characteristics and the proportion classified as active and with high levels of participation in physical activity types are presented in table 4.1. Around two thirds of men were classified as active at baseline, 16- and 20-year follow ups. Physical activity peaked at the 12-year follow up with 71% being classified as active. The proportion of men participating in sport/exercise remained fairly consistent with just over a third classified with high levels of participation throughout follow up. Recreational activity declined with follow up. A total of 56.0% reported high levels of recreational activity at baseline dropping to 40.2% at 20-year follow up. The proportion of men reporting high levels of walking increased from 26.9% at baseline to 61.5% at 20-year follow up (p<0.001).

4.5.1 Change and stability of physical activity measures

4.5.1.1 Overall and specific types of physical activity

Table 4.2 presents the proportion of men who changed and sustained their level of physical activity and participation in specific types of physical activity between baseline and 20-year follow up. Almost half remained active, while 17% remained inactive, 17% became active and 17% became inactive. Further exploratory analyses showed that out of the 589 men who became active, 67% adopted high levels of walking, 45% adopted high levels of sport/exercise and 33% adopted high levels of recreational activity. Among the 562 men who became inactive, 65% dropped out of high recreational activity, 44% dropped out of sport/exercise and 20% dropped out of high walking. For sport and exercise, more than two thirds retained their initial level of participation, with 22% sustaining high levels of participation between baseline and 20-year follow up and 46% sustaining low levels. By comparison, there was far more change in walking and recreational activity. Walking was frequently adopted with 42% adopting high levels between baseline and 20-year follow up, whereas recreational activity frequently decreased with 29% dropping their level of participation.

Table 4.3 presents tracking statistics for physical activity and physical activity types across follow up. Kappa statistics were highest for sport/exercise participation ranging between 0.33 and 0.38,

indicating moderate agreement. Moderate agreement was also observed for total physical activity with Kappa statistics ranging from 0.23 to 0.26. Kappa statistics were lower for recreational activity (0.26-0.16) and walking (0.15-0.11), suggesting fair agreement. Kappa statistics tended to be lower for longer follow up periods. ICCs, estimating consistency across all available measures, were comparable with Kappa statistics. ICCs indicated good agreement for sport/exercise participation, moderate for total physical activity and poor to fair agreement for walking and recreational activity. After adjusting for baseline age, BMI, social class and smoking status, ICCs were only marginally weakened. Kappa statistics were slightly lower when they were estimated using 3 category variables for each measure but interpretations remain unchanged (see Appendix 4B).

Additional analyses indicated similar levels of tracking between those who reported no change in working status and those who retired between baseline and subsequent follow ups, as shown in Table 4.4. However, further exploration, showed that a higher proportion of men who retired had increased their physical activity between baseline and subsequent follow ups in comparison to those who maintained their employment status (e.g. 21.3% vs. 15.7% of men increased their total activity levels between Wave 1 and Wave 2 in the retiring group and the no change group, respectively).

4.5.1.2 Sport and exercise types

Table 4.5 presents the proportion of men who were participating in specific sports/exercises at each wave and the proportion that sustained or changed their participation from baseline to the 20-year follow up. Golf was the most common sport/exercise throughout, with around 12% participating at all waves. Racquet sports were the next most common at baseline (9%), but participation declined substantially thereafter, with only 2.2% participating at the 20-year follow up. Notable declines were also observed for cycling, surface water sports, football, rugby, running/jogging, cricket and other sports. In contrast, important increases were observed for swimming, dancing, bowls, aerobics/fitness classes and gym/muscle strengthening between baseline and the 20-year follow up. The most frequently adopted sports/exercises between baseline and 20-year follow up were bowls (8.0%), walking (7.5%) swimming (7.4%), golf (4.8%), cycling (4.7%) and dancing (4.5%). Racquet sports had the highest proportion of dropouts (7.9%), followed by cycling (5.9%), swimming (5.1%) and golf (4.5%). Although drop out was high among these specific sports/exercises, many of these men took part in another sport/exercise at the 20-year follow up. For example, 62% of men who dropped out of racquet sports took part in another sport/exercise at the 20-year follow up, while only 39% of golf dropouts, 38% of

swimming dropouts and 28% of cycling dropouts took part in another sport/exercise at 20-year follow up, respectively. Golf was most common sport/exercise to be sustained between baseline and 20-year follow up, with 6.9% of men participating at both time points.

Additional exploratory analyses revealed some important differences in sport/exercise participation between occupational classes, as shown in tables 4.6 and 4.7. For example, golf was played by 14.2% of men from non-manual classes compared to 8.8% of men from manual classes at baseline. Racquet sports, swimming, gym/muscle strengthening and running/jogging were also more prevalent among those from non-manual classes. In addition, golf (6.5% vs. 3.1%), racquet sports (11.9% vs. 4.0%), walking/hiking (9.5% vs. 5.6%) and swimming (8.9% vs. 6.0%) were more frequently adopted in men from non-manual occupations compared to men from manual occupations, but adoption was comparable for bowls (8.5% vs. 7.5%), dancing (4.0% vs. 4.9%) and cycling (4.8% vs. 4.6%).

Table 4.8 presents tracking statistics for sport/exercise types across follow up. Golf participation was the most stable across follow up with Kappa statistics ranging from 0.55 to 0.60, indicating substantial agreement. Kappa statistics were lower for all further sports/exercises, indicating fair to moderate levels of agreement. ICCs were also highest for golf and were suggestive of excellent agreement. ICCs were only fractionally lower for bowling games, also indicating excellent agreement. ICCs for all other sports/exercises indicated moderate to good agreement. Adjusting for age, BMI, social class, smoking status and season only slightly reduced ICCs.

4.5.2 Predictability of physical activity in old age according to prior engagement

4.5.2.1 Predictability of physical activity at 20-year follow up according to total physical activity and physical activity types at baseline

Table 4.9 presents the odds of being active at 20-year follow up compared to being inactive according to various physical activity measures in midlife. Compared to being inactive at baseline, being active more than doubled the age-adjusted odds of being active at 20-year follow up. Odds of being active at the 20-year follow up were similarly raised for men who had high levels of sport/exercise at baseline. High levels of walking and recreational activity at baseline were also associated with increased odds of being active at 20-year follow up, but the magnitude of association was greater for high sport/exercise. ORs were only marginally attenuated after additionally adjusting for social class, BMI and smoking status at baseline. High levels of sport/exercise at baseline remained the strongest predictor of being active at 20-year follow up after mutually adjusting for other physical activity types at baseline. The odds of being active

increased in a linear fashion with greater volumes of overall and specific types of physical activity, as shown in Appendix 4C.

In addition, a strong positive linear trend was observed between years of sport/exercise participation reported at baseline and odds of being active at 20-year follow up, as shown in table 4.10. Indeed, ORs for being active at 20-year follow up were greater with earlier sport/exercise uptake. For example, compared to those who were not participating in sport/exercise at baseline, participation for 25 years or more was associated with more than a four-fold increase in the odds of being active at 20-year follow up. However, more recent uptake (≤ 4 years) was associated with double the odds of being active at 20-year follow up.

4.5.2.2 Predictability of physical activity at 20-year follow up according to prior long-term patterns of physical activity

More persistent activity increased the odds of being active by the 20-year follow up even further, as shown in Table 4.11. Being persistently active was optimal and was associated with more than a 30-fold increase in the odds of being active at 20-year follow up compared to those who were persistently inactive. Being active at later waves was also more favourable than being active at earlier waves. For example, no associations were observed for men who were active at baseline only, while being active at the 16-year follow up alone was associated with more than a 5-fold increase in the odds of being active at the 20-year follow up compared to the persistently inactive.

4.5.2.3 Predictability of physical activity at 20-year follow up according to sport and exercise type participation at baseline

Table 4.12 presents the ORs for having high participation in sport/exercise (i.e. monthly or more) compared to low participation (i.e. none or less frequent than once a month) and the ORs for being active compared to inactive at the 20-year follow up according to participation in specific types of sport/exercise at baseline. Among all the sports/exercises reported at baseline, golf and bowling games were the strongest predictors of high participation in sport/exercise at 20-year follow up. Golf and bowling participation were associated with more than a six-fold increase in the age-adjusted odds of high sport/exercise participation at 20-year follow up, which was only marginally attenuated after adjusting for social class, BMI, smoking status at baseline and season. ORs for golf and bowls were similar after simultaneously adjusting for participation in all other sports/exercises, suggesting that these associations are independent of participation in all other sports/exercises. Odds of sport/exercise participation at 20-year follow up were also

raised for participation in dance, racquet sports, running/jogging, other sports, surface water sports, walking/hiking and swimming at baseline after adjusting for participation in all other sports/exercises, but the magnitude of association was greater for golf and bowls. Participation in cycling, cricket and gym/muscle strengthening at baseline was only weakly associated with high sport/exercise at 20-year follow up after accounting for participation in all other sports. Many of these associations were attenuated, some to non-significant levels, after adjusting for total physical activity score at baseline. Only associations for golf, bowling and racquet sports remained significant after adjusting for total physical activity, suggesting that these associations are independent of all forms of physical activity.

Similar associations were observed when being active at the 20-year follow up was considered as the outcome. Golf in midlife was the strongest predictor and was associated with more than a four-fold increase in the odds of being active at 20-year follow up after adjusting for age, BMI, social class, smoking status, season and participation in other sports/exercises. ORs of being active were also raised for cricket, running/jogging, dancing, bowls, racquet sports, swimming, cycling and other sports after adjusting for health and lifestyle factors and other sports/exercises. Initially, ORs were raised for walking/hiking but these were attenuated to non-significance after additionally adjusting for all other sports/exercises. Only golf participation at baseline remained significant after additionally adjusting for total physical activity score at baseline, and was associated with a two-fold increase in the odds of being active at the 20-year follow up.

Further, a strong positive linear trend was observed between the number of sports/exercises reported at baseline and the odds of participating in sport/exercise and being active at the 20-year follow up, with the odds increasing in a dose-response fashion. Participation in three or more sports/exercises proved to be optimal and was associated with a 14- and 12-fold increase in the odds of high sport/exercise and being active at the 20-year follow up, respectively, after adjusting for health and lifestyle factors. Further exploratory analyses revealed that multiple sport participation (i.e. taking part in 2 or more sports/exercises) at baseline was most common among men who took part in swimming (53.2%), running (66.7%), racquet sports (54.4%) and cricket (66.1%).

4.6 Discussion

4.6.1 Summary of main findings

The aim of this chapter was to examine how physical activity and physical activity types track from midlife to old age in British men. Total physical activity tracked moderately, while the tracking of physical activity types varied, with sport/exercise tracking more strongly than walking and recreational activity. Physical activity in midlife proved to be an important predictor of physical activity levels in old age. Persistent physical activity across adulthood and sport/exercise participation were strongly associated with physical activity in old age, particularly when participation was initiated earlier in life and included engagement in several sports/exercises. Tracking also varied by sport/exercise types. Notably, golf was the most common sport/exercise throughout follow up and tracked the strongest, while participation in bowling games was less stable owing to a high proportion of uptake.

4.6.2 Comparisons with previous studies

4.6.2.1 Tracking of total physical activity

The proportion of men classified as active remained at around two thirds over the 20-year follow up, which conflicts the common suggestion that physical activity declines with age (122, 123). It is possible that significant declines occur later in the life course. Indeed, many of the men were under the age of 75 at the 20-year follow up, which is reportedly when more rapid declines in physical activity begin to occur (11). Furthermore, the observed lack of decline in the proportion classified as active may simply be due to attrition. Men with less data were typically unhealthier and less active. When considering changes in physical activity between baseline and 20-year follow up, almost half of the men were active at both time points, while approximately 17% became inactive, 17% became active and 17% were inactive at both time points. Although there are some discrepancies, other cohort studies have also identified groups of older adults with changing physical activity levels over a similar time frame (119, 257, 262). In the NSHD 1946 British cohort, physical activity was tracked over a similar period of the life course with similar follow-up, however less than a third were classified as active at both time points, only 8% became active and 37% became inactive (119). Discrepancies may be due to the different physical activity measures and cut offs used for defining a person as active.

Total physical activity tracked moderately from midlife to old age. Comparisons with previous tracking studies are not straightforward given the various measures, cut off points, time frames and statistical approaches used between studies. However, the finding that physical activity tracks moderately is consistent with previous reviews suggesting that physical activity tracks fair to moderately across the life course (17, 89, 90, 93). Similar correlations have been reported in the limited number of tracking studies that have extended over prolonged periods into old age, with correlations declining for longer follow up periods (94-97). One Norwegian study tracked physical activity in men and women aged 20-54 years at baseline and found moderate correlation (Spearman correlation coefficient: 0.25-0.32) and agreement (weighted kappa: 0.24-0.29) over 28 years of follow up (94).

Tracking coefficients in retiring men were comparable with men who maintained their employment status across waves. However, a greater proportion of retiring men increased their physical activity rather than decreased, suggesting that retirement may be a sensitive period when physical activity might be positively modified. This is in line with a recent systematic review suggesting that retirement is associated with increases in leisure-time physical activity (156). However, the evidence on the effects of retirement on physical activity is not uniform, with some studies showing that retirement may have an adverse effect (188).

The tracking of physical activity was also examined using logistic regression to estimate the odds of being active in old age according to baseline measures of physical activity. Being active in midlife more than doubled the odds of being active in old age. In addition, greater volumes of physical activity in midlife further increased the odds of being active in old age. This is consistent with a Finnish study of men and women aged 18-64 years at baseline that showed that being inactive at baseline doubled the odds of being inactive 28 years later (97). Similarly, a Norwegian cohort study of adults aged 20-54 years at baseline showed that being non-sedentary at baseline more than trebled the odds of being non-sedentary 28 years later, with odds increasing for higher physical activity levels at baseline (94).

Odds of being active in old age were substantially raised for more persistent activity across adulthood. To my knowledge, only the Young Finns study has been used to investigate the effects of continuous physical activity on activity at a later time point, but the Young Finns cohort is in a younger population focussing on the transition from childhood into adulthood (298, 299). Specifically, the Young Finns study showed that six years of being continuously active from late adolescence to early adulthood was associated with a 19-fold increase in the odds of being active in mid-adulthood (298).

4.6.2.2 Tracking of physical activity types

The proportion of men reporting high levels of sport/exercise was fairly stable across follow up, whereas the proportion reporting high recreational activity decreased and the proportion reporting high walking increased. Within-person changes between baseline and 20-year follow up seem to be explaining these findings. Approximately 70% of men sustained the same level of sport/exercise from baseline to 20-year follow up, whereas recreational activity had the highest proportion of dropouts at almost a third and walking had the highest proportion of adopters at more than 40%. These findings support previous literature suggesting that age-related physical activity changes are specific to physical activity types (140). These findings are also comparable with previous research suggesting that a large proportion of retiring adults can increase their walking during this transition (141, 142). However, it contradicts some research that suggests that a number of recreational activities, such as gardening and household activity increase during retirement (140, 300). Plausibly, increases in some physical activity types after retirement are temporary and are therefore not observed with longer intervals between follow ups.

The changes observed between baseline and 20-year follow up are reflected in the tracking coefficients. Sport/exercise tracked strongest at moderate levels, whereas recreational activity and walking tracked at a fair level. Few studies have estimated tracking coefficients for specific types of physical activity and those that have done so have typically been in children. For example, findings from the Young Finns study suggest stronger tracking for sport/exercise compared to other physical activity types during childhood (301). One previous study in older adults tracked specific types of physical activity and found that outdoor, strength, flexibility, walking and leisure physical activity were moderately stable, whereas indoor physical activity and shopping were less stable (98).

Participating in high levels of sport/exercise in midlife trebled the odds of being active in old age and was a stronger predictor than recreational activity and walking. Several previous studies have shown that prior sport/exercise participation strongly predicts being active in old age (99, 100) and is more strongly associated than other physical activity types (101). This finding is also comparable with tracking studies in younger cohorts (293, 302). Further, consistent with the 'habit formation' and 'ability and readiness' hypotheses (17), findings from this chapter suggest that earlier uptake of these sports/exercises substantially increased the odds of being active in old age.

There may be a number of reasons why participation in sport/exercise in midlife is a stronger predictor of overall activity in older age than other types of activity. Sport/exercise is typically

carried out for enjoyment purposes and thus may be more likely to persist into old age when individuals have a lot more free time to do the activities they enjoy. Sport/exercise may also help develop and preserve fundamental movement skills, physical function and physical activity self-efficacy in later life, increasing psychological and physical readiness for physical activity in old age.

4.6.2.3 Tracking of sport/exercise types

Golf was the most common sport/exercise throughout follow up, with approximately 11% of men participating at each wave. Dance, swimming and cycling also ranked highly. These sports/exercises were also among the most commonly reported in older adults from the 2016 Sport England Active People Survey and in a study of Scottish adults (303, 304). Bowling games and walking/hiking were the most common sports/exercises to be adopted between baseline and 20-year follow up, whereas racquet sports and cycling were among the most frequently dropped sports/exercises. Swimming was both one of the most commonly adopted and most commonly dropped sports/exercises. The stability of golf participation was also reflected in the tracking coefficients, indicating excellent levels of tracking. Tracking estimates were also excellent for bowling when all time points were considered in random effects models. Tracking estimates were lower for all other sports/exercises generally suggesting fair to moderate levels of tracking. To my knowledge, no previous prospective studies have tracked participation in specific sports/exercises. Nonetheless, these findings do support cross-sectional data from the recent Active People Survey where bowls was enjoyed by 0.4% of 55-64 years olds compared to 1.9% of 65 and overs, suggesting uptake is common around this period of the life course (304). Similarly, racquet sports, swimming and cycling were lower in the 65 and overs compared to the 55-64 year olds, indicating there may be some dropout (304). Findings from this chapter are also consistent with another study in Scottish adults that asked participants to retrospectively report past and current participation in specific sport/exercises, from which proportions who had persistently participated in individual sports/exercises could be determined (303). The most commonly sustained sports/exercises were golf, bowls and walking/rambling, with more than half of men who had ever participated since school still participating at the age of 58. In contrast, less than 10% who had ever participated in racquet sports and cycling still participated at age 58. Small increases in aerobic/fitness training and gym activities were also observed in this chapter. This could reflect genuine age-related changes or could be as a result of secular shifts in preference for these kinds of activity and increased access to leisure facilities over recent

decades. Temporal increases in gym and fitness-based activities have previously been reported in UK adults over a similar period (87).

This chapter also found that participation in most, but not all, types of sport/exercises were higher in men with more favourable socioeconomic circumstances. This finding is consistent with a large body of evidence suggesting an association between higher socioeconomic status and higher sport/exercise participation (305, 306). There were clear inequalities for golf, racquet sports and swimming participation, but not for other sports, such as bowls. This is consistent with other reports showing a social gradient for some sports/exercises but not others (303, 304, 307).

Consistent with the tracking coefficients, golf participation in midlife strongly predicted sport/exercise participation and being active at 20-year follow up. Odds of being active and participating in sport/exercise were also raised for several other sports/exercises but the strongest and most consistent associations were found for golf and bowls. These findings reflect the strong levels of tracking and continued participation rates for golf and bowls into old age. Anecdotally, there may be a number of explanations for the higher levels of tracking for golf and bowls. Plausibly, the age-related health conditions may not limit these lower intensity sport/exercises, there may be a lower risk of injury and the social benefits may be greater.

Despite tracking coefficients for racquet sports suggesting lower levels of tracking, participation in midlife still strongly predicted being active and participating in sport/exercise at 20-year follow up. One possible explanation is that the skills acquired from racquet sports are more easily transferred to other types of sport/exercise. Indeed, men who dropped out of racquet sports were likely to switch to another type of sport/exercise or were already engaged in other sports/exercises. Importantly, participating in multiple sports/exercises further increased the odds of being active and participating in sport/exercise at 20-year follow up when compared to participating in a single sport/exercise. This is consistent with previous studies suggesting that a greater diversity of sports/exercises in early life raises the odds of being active later in life (102, 103). In addition, previous research in youth populations has shown that multiple sports participation is associated with greater neuromuscular control than single sport participation (102). Acquiring skills in multiple sports/exercises may enhance physical and psychological readiness to maintain or take up activities later on in life.

4.6.3 Strengths and limitations

One of the main strengths of this study is the large, geographically and socioeconomically representative sample. Also, the follow up extends over a long period, capturing data on an understudied period of the life course. The physical activity measure was validated at baseline against resting heart rate (272) and more recently against accelerometer-measured physical activity (274). In addition, the same questionnaire and response options were administered at each wave ensuring comparability between waves. Self-reports also allowed investigation into how specific types of physical activity and sport/exercise track, which may provide useful insight for intervention strategy. An additional strength is the use of random effects models which provide estimates of tracking using all available data, whilst also accounting for factors that may influence tracking strength.

The general limitations of the BRHS are that the sample consists of only males predominantly of white ethnicity and so the findings are not generalisable to women and non-white ethnic groups. Also, the findings may not be generalisable to different countries/cultures where the popularity of specific sports/exercises differs from the UK. For example, Europe is home to 22% of the world's golf facilities while only 3% are located in Africa (308). Furthermore, there have been some shifts in the popularity of specific sports/exercises since the final follow up in 2000, which limits the generalisability of the findings to current sport/exercise trends. For example, we know that dance participation has declined since the turn of the century (309), but golf, bowls, swimming and cycling remain among the most common sports in older British men (304). In addition, men who left the study were generally less active and healthy than men who continued to participate, which may have resulted in attrition bias. Physical activity may be more liable to change in men who were lost to follow up, possibly as a result of an increased risk of developing chronic health conditions. Consequently, the levels of physical activity, proportion remaining active and tracking of physical activity may have been overestimated in this sample. However, the levels of stability were similar in random effects models that accommodated for missing data, reducing the bias caused by attrition. Nevertheless, the proportion who became inactive during follow up is likely underestimated. Although the self-reported physical activity measure has been validated, self-reported physical activity may still be prone to bias. Social desirability bias may lead to an overestimation of physical activity. Several studies have shown that physical activity is much higher when it is self-reported compared to objectively measured (310). Further, self-reported physical activity data were collapsed into a binary or ternary format, which allowed comparability across physical activity measures but also resulted in loss of information. As a result, some fluctuations in physical activity may have been missed. Further, individuals who

make considerable changes in their physical activity are potentially classified in the same way as those making a small change across the cut off value.

Although our sample is fairly large, only a small number of men took part in some specific sports and exercises. Consequently, the tracking of certain sports and exercises could not be reliably estimated. Moreover, the questionnaire design meant that there may have been some overlap between physical activity types. For example, recreational walking was listed as an example recreational activity, so it may be possible that men did not report walking/hiking under the sport/exercise question. In addition, physical activity during early life was not reported but could be crucial in predicting future physical activity. Men reporting frequent sport/exercise were asked how long they had been participating in the reported activities, but this did not capture sports/exercises from early life that were subsequently dropped in adulthood. There may be specific types of physical activity in early life that were particularly important for lifelong physical activity but these could not be identified from the questionnaire.

4.7 Conclusion

The findings of this chapter show that total physical activity tracks moderately from midlife to old age, but tracking of physical activity types varies. Being active in midlife increased the odds of being active in old age. Persistent activity from mid- to late-adulthood and greater volumes of physical activity further increased the odds of being active in old age. High levels of walking, recreational activity and sport/exercise were also independently associated with increased odds of being active in old age. Sport/exercise was more strongly associated with being active in old age than other physical activity types, particularly if participation began earlier in life. Among sport/exercise types, golf participation tracked strongest and was the strongest predictor of being active in old age. There were also some sports/exercises that were regularly adopted, such as bowling, walking/hiking, dancing and swimming. Sampling a range of sports/exercises was more favourably associated with physical activity in old age than single sports/exercise participation. Overall, these findings suggest that physical activity in midlife, particularly if it is more diverse, regular, and persistent and involves sport/exercise, develops physical and psychological readiness for physical activity in old age. Now that a degree of instability in physical activity and physical activity types has been established between midlife and old age, the next chapter of this thesis attempts to identify the trajectories of physical activity and physical activity types using more sophisticated techniques. It also examines the predictors of these trajectories.

Table 4.1. Sample characteristics and physical activity levels at baseline, 12-, 16- and 20-year follow up

	Baseline	12 year	16 year	20 year
Age (years, mean ± SD)	48.6 ± 5.4	62.2 ± 5.4	66.2 ± 5.4	68.5 ± 5.4
Overweight/Obese (%, n)†	52.2 (1783)			
Current smoker (%, n)†	30.6 (1043)			
Manual Occupation (%, n)†	50.2 (1713)			
Physically active[a] (%, n)	66.1 (2257)	71.0 (2422)	63.7 (2173)	66.9 (2284)
High sport participation[b] (%, n)	38.2 (1292)	36.8 (1244)	37.1 (1254)	37.8 (1279)
High recreational activity[c] (%, n)	56.0 (1912)	58.4 (1994)	41.2 (1407)	40.2 (1372)
High walking[d] (%, n)	26.9 (918)	51.6 (1754)	50.9 (1735)	61.5 (2097)

Analytic sample consisted of 3413 participants with a valid physical activity score at all four time points. Data on walking was missing for an additional 15 participants at 12 year follow up, 3 participants at 16-year follow up and 1 participant at 20-year follow up. Data on sport participation was missing for 29 participants.

[a] Physically active was classified as reporting at least light activity.

[b] High sport was classified as reporting frequent participation (once a month or more)

[c] high recreational activity was classified as >2hours/weekend day on recreational activities

[d] high walking was classified as >20 mins/day

†Data on BMI, smoking status and occupational class were utilised at baseline only

Table 4.2. Change in physical activity and physical activity types between baseline and 20-year follow up

Physical activity change Q1 to Q20 (n=3413)	**% (n)**
Remained inactive	16.6 (567)
Became active	17.3 (589)
Became inactive	16.5 (562)
Remained active	49.7 (1695)
Sport/exercise change Q1 to Q20 (n=3384)	
Remained low	46.4 (1569)
Adopters	15.5 (523)
Dropouts	15.8 (536)
Remained high	22.3 (756)
Recreational activity change Q1 to Q20 (n=3413)	
Remained low	30.5 (1041)
Adopters	13.5 (460)
Dropouts	29.3 (1000)
Remained high	26.7 (912)
Walking change Q1 to Q20 (n=3412)	
Remained low	31.1 (1060)
Adopters	42.0 (1434)
Dropouts	7.5 (255)
Remained high	19.4 (663)

Table 4.3. Stability of physical activity types across 4 waves up to the 20-year follow up

				Random Effects Models	
	Wave 1 to 2	Wave 1 to 3	Wave 1 to 4	Univariate	Multivariate[a]
	Kappa	Kappa	Kappa	ICC (95% CI)	ICC (95% CI)
Physically active	0.26	0.23	0.24	0.46 (0.43, 0.48)	0.44 (0.41, 0.46)
Sport participation	0.38	0.35	0.33	0.66 (0.64, 0.68)	0.64 (0.62, 0.66)
Recreational activity	0.24	0.19	0.16	0.38 (0.36, 0.40)	0.36 (0.34, 0.39)
Walking	0.15	0.12	0.11	0.32 (0.30, 0.35)	0.32 (0.30, 0.34)

Kappa statistics are presented for participants with a valid physical activity score at all four time points (n=3413). Data on walking was missing for an additional 15 participants at 12 year follow up, 3 participants at 16-year follow up and 1 participant at 20-year follow up. Data on sport participation was missing for 29 participants. Random Effects Models included men with at least two assessments for each domain accompanied by valid covariate data (Physical activity: n= 5962; Sport participation: n= 6122; Recreational activity: n=6093; Walking: n=6040). ICC = Intraclass correlation coefficients from random effects models

[a] adjusted for age, BMI, social class and smoking status at baseline

Table 4.4. Stability of physical activity variables over time by changes in working status

	Wave 1 to 2	Wave 1 to 3	Wave 1 to 4
	Kappa	Kappa	Kappa
Total Physical Activity			
No change in working status	0.28	0.18	0.24
Retired between follow ups	0.25	0.25	0.25
Sport participation			
No change in working status	0.36	0.32	0.33
Retired between follow ups	0.40	0.35	0.35
Recreational activity			
No change in working status	0.26	0.18	0.27
Retired between follow ups	0.22	0.19	0.14
Walking			
No change in working status	0.18	0.16	0.13
Retired between follow ups	0.12	0.09	0.11

Analytic sample consisted of 3288 participants with a valid physical activity score at all four time points and valid data on working status. 46.4% (n=1526) of men retired between wave 1 and 2; 71.5% (n=2352) of men retired between wave 1 and 3; and 79.4% (n=2611) were retired between wave 1 and 4.

Table 4.5. Participation and change in specific sports and exercises over 20 years of follow up

Sport/exercise type	Baseline	12 year	16 year	20 year	Change between baseline and 20-year follow up			
					Participating at both	Adopters	Drop outs	Not participating at both
	% (n)							
Golf	11.4 (387)	11.8 (400)	11.7 (397)	11.7 (396)	6.9 (234)	4.8 (162)	4.5 (153)	83.8 (2835)
Bowling	2.2 (74)	8.4 (285)	9.5 (322)	9.5 (321)	1.5 (51)	8.0 (270)	0.7 (23)	89.8 (3040)
Dancing	1.2 (42)	1.7 (59)	2.0 (68)	5.1 (172)	0.6 (20)	4.5 (152)	0.7 (22)	94.3 (3190)
Racquet sports	9.3 (314)	3.6 (123)	2.2 (74)	2.2 (73)	1.4 (48)	0.7 (25)	7.9 (266)	90.0 (3045)
Swimming	6.9 (235)	9.6 (324)	9.0 (305)	9.2 (312)	1.8 (62)	7.4 (250)	5.1 (173)	85.7 (2899)
Cycling (any purpose)	7.3 (246)	8.9 (300)	8.2 (276)	6.1 (206)	1.4 (46)	4.7 (160)	5.9 (200)	88.0 (2978)
Surface water sports	2.1 (71)	1.0 (32)	0.7 (25)	0.4 (15)	0.2 (6)	0.3 (9)	1.9 (65)	97.6 (3304)
Aerobics/fitness training	0.2 (5)	0.7 (24)	0.8 (27)	1.5 (52)	0.0 (1)	1.5 (51)	0.1 (4)	98.4 (3328)
Gym/muscle strengthening	1.1 (38)	1.6 (55)	2.2 (75)	1.9 (65)	0.1 (4)	1.8 (61)	1.0 (34)	97.1 (3285)
Football	0.7 (25)	0.1 (4)	0.2 (6)	0.1 (2)	–	0.1 (2)	0.7 (25)	99.2 (3357)

Sport/exercise type	Baseline	12 year	16 year	20 year	Change between baseline and 20-year follow up			
					Participating at both	Adopters	Drop outs	Not participating at both
	% (n)							
Rugby	0.2 (6)	0.0 (0)	0.0 (0)	0.0 (0)	–	–	0.2 (6)	99.8 (3378)
Running/jogging	2.3 (77)	1.2 (42)	1.0 (35)	1.1 (36)	0.4 (14)	0.7 (22)	1.9 (63)	97.1 (3285)
Cricket	1.6 (54)	0.3 (9)	0.2 (6)	0.1 (4)	0.1 (3)	0.0 (1)	1.5 (51)	98.4 (3329)
Walking/hiking	1.4 (47)	6.5 (219)	7.4 (251)	8.0 (272)	0.6 (19)	7.5 (253)	0.8 (28)	91.1 (3084)
Other	3.3 (113)	2.2 (74)	1.9 (65)	1.7 (58)	0.4 (12)	1.4 (46)	3.0 (101)	95.3 (3225)

Analytic sample consisted of 3384 participants

Table 4.6. Participation and change in sports participation over 20 years of follow up in non-manual occupational classes

Sport/exercise type	Baseline	12 year	16 year	20 year	Change between baseline and 20-year follow up			
					Participating at both	Adopters	Drop outs	Not participating at both
	% (n)							
Golf	14.2 (235)	15.6 (259)	15.8 (262)	15.8 (262)	9.3 (154)	6.5 (108)	4.9 (81)	79.3 (1314)
Bowling	1.9 (31)	8.0 (132)	9.1 (150)	9.7 (161)	1.2 (20)	8.5 (141)	0.7 (11)	89.6 (1485)
Dancing	0.8 (13)	1.7 (28)	1.8 (29)	4.2 (69)	0.1 (2)	4.0 (67)	0.7 (11)	95.2 (1577)
Racquet sports	14.2 (235)	5.9 (98)	3.5 (58)	3.4 (57)	2.3 (38)	1.2 (19)	11.9 (197)	84.7 (1403)
Swimming	8.8 (145)	12.1 (200)	11.7 (193)	11.5 (190)	2.6 (43)	8.9 (147)	6.2 (102)	82.4 (1365)
Cycling (any purpose)	5.3 (87)	8.6 (142)	8.0 (133)	5.6 (93)	0.8 (13)	4.8 (80)	4.5 (74)	89.9 (1490)
Surface water sports	3.1 (52)	1.4 (23)	1.0 (16)	0.6 (10)	0.3 (5)	0.3 (5)	2.8 (47)	96.6 (1600)
Aerobics/fitness training	0.2 (4)	1.2 (20)	1.3 (21)	1.9 (32)	0.1 (1)	1.9 (31)	0.2 (3)	97.9 (1622)
Gym/muscle strengthening	1.7 (28)	1.9 (31)	3.0 (50)	2.9 (48)	0.2 (3)	2.7 (45)	1.5 (25)	95.6 (1584)
Football	0.8 (13)	0.1 (1)	0.2 (4)	0.1 (2)	–	0.1 (2)	0.8 (13)	99.1 (1642)

Sport/exercise type	Baseline	12 year	16 year	20 year	Change between baseline and 20-year follow up			
					Participating at both	Adopters	Drop outs	Not participating at both
	% (n)							
Rugby	0.1 (2)	0.0 (0)	0.0 (0)	0.0 (0)	–	–	0.1 (2)	99.9 (1655)
Running/jogging	3.2 (53)	1.8 (29)	1.4 (23)	1.3 (21)	0.5 (8)	0.8 (13)	2.7 (45)	96.1 (1591)
Cricket	2.2 (36)	0.2 (3)	0.2 (4)	0.2 (3)	0.1 (2)	0.1 (1)	2.1 (34)	97.8 (1620)
Walking/hiking	2.2 (37)	8.0 (132)	9.7 (161)	10.4 (173)	1.0 (16)	9.5 (157)	1.3 (21)	88.3 (1463)
Other	3.7 (62)	2.6 (43)	2.4 (40)	1.5 (25)	0.3 (5)	1.2 (20)	3.4 (57)	95.1 (1575)

Analytic sample consisted of 1657 participants

Table 4.7. Participation and change in sports participation over 20 years of follow up in manual occupational classes

Sport/exercise type	Baseline	12 year	16 year	20 year	Change between baseline and 20-year follow up			
					Participating at both	Adopters	Drop outs	Not participating at both
	% (n)							
Golf	8.8 (152)	8.2 (141)	7.8 (135)	7.8 (134)	4.6 (80)	3.1 (54)	4.2 (72)	88.1 (1521)
Bowling	2.5 (43)	8.9 (153)	10.0 (172)	9.3 (160)	1.8 (31)	7.5 (129)	0.7 (12)	90.0 (1555)
Dancing	1.7 (29)	1.8 (31)	2.3 (39)	6.0 (103)	1.0 (18)	4.9 (85)	0.6 (11)	93.4 (1613)
Racquet sports	4.6 (79)	1.5 (25)	0.9 (16)	0.9 (16)	0.6 (10)	0.4 (6)	4.0 (69)	95.1 (1642)
Swimming	5.2 (90)	7.2 (124)	6.5 (112)	7.1 (122)	1.1 (19)	6.0 (103)	4.1 (71)	88.8 (1534)
Cycling (any purpose)	9.2 (159)	9.2 (158)	8.3 (143)	6.5 (113)	1.9 (33)	4.6 (80)	7.3 (126)	86.2 (1488)
Surface water sports	1.1 (19)	0.5 (9)	0.5 (9)	0.3 (5)	0.1 (1)	0.2 (4)	1.0 (18)	98.7 (1704)
Aerobics/fitness training	0.1 (1)	0.2 (4)	0.4 (6)	1.2 (20)	–	1.2 (20)	0.1 (1)	98.8 (1706)
Gym/muscle strengthening	0.6 (10)	1.4 (24)	1.5 (25)	1.0 (17)	0.1 (1)	0.9 (16)	0.5 (9)	98.5 (1701)
Football	0.7 (12)	0.2 (3)	0.1 (2)	0.0 (0)	–	–	0.7 (12)	99.3 (1715)

Sport/exercise type	Baseline	12 year	16 year	20 year	Change between baseline and 20-year follow up			
					Participating at both	Adopters	Drop outs	Not participating at both
	% (n)							
Rugby	0.2 (4)	0.0 (0)	0.0 (0)	0.0 (0)	–	–	0.2 (4)	99.8 (1723)
Running/jogging	1.4 (24)	0.8 (13)	0.7 (12)	0.9 (15)	0.4 (6)	0.5 (9)	1.0 (18)	98.1 (1694)
Cricket	1.0 (18)	0.4 (6)	0.1 (2)	0.1 (1)	0.1 (1)	–	1.0 (17)	99.0 (1709)
Walking/hiking	0.6 (10)	5.0 (87)	5.2 (90)	5.7 (99)	0.2 (3)	5.6 (96)	0.4 (7)	93.9 (1621)
Other	3.0 (51)	1.8 (31)	1.5 (25)	1.9 (33)	0.4 (7)	1.7 (29)	2.6 (45)	95.3 (1646)

Analytic sample consisted of 1727 participants

Table 4.8. Stability of sport and exercise type participation across 4 waves up to the 20-year follow up

Sport/exercise type	Wave 1 to 2	Wave 1 to 3	Wave 1 to 4	Random Effects Models	
				Univariate	Multivariate[a]
	Kappa	Kappa	Kappa	ICC (95% CI)	ICC (95% CI)
Golf	0.60	0.57	0.55	0.93 (0.92, 0.93)	0.89 (0.88, 0.90)
Bowling	0.28	0.22	0.23	0.85 (0.84, 0.86)	0.85 (0.84, 0.86)
Dancing	0.29	0.24	0.17	0.71 (0.67, 0.74)	0.80 (0.76, 0.83)
Racquet sports	0.34	0.23	0.22	0.72 (0.69, 0.75)	0.72 (0.66, 0.77)
Swimming	0.17	0.15	0.16	0.65 (0.62, 0.69)	0.64 (0.61, 0.68)
Cycling (any purpose)	0.30	0.23	0.15	0.65 (0.61, 0.68)	0.64 (0.60, 0.68)
Surface water sports	0.34	0.16	0.13	0.79 (0.75, 0.82)	0.70 (0.65, 0.74)
Aerobics/fitness training	0.07	0.06	0.03	0.67 (0.60, 0.74)	0.63 (0.54, 0.72)
Gym/muscle strengthening	0.12	0.13	0.06	0.74 (0.68, 0.80)	0.70 (0.62, 0.78)
Football	0.07	0.00	0.00	0.67 (0.55, 0.77)	0.66 (0.52, 0.78)
Rugby	0.00	0.00	0.00	[b]	[b]

Sport/exercise type	Wave 1 to 2	Wave 1 to 3	Wave 1 to 4	Random Effects Models	
				Univariate	Multivariate[a]
	Kappa	Kappa	Kappa	ICC (95% CI)	ICC (95% CI)
Running/jogging	0.26	0.24	0.24	0.78 (0.74, 0.81)	0.77 (0.65, 0.86)
Cricket	0.19	0.10	0.10	0.73 (0.67, 0.79)	0.71 (0.60, 0.79)
Walking/hiking	0.08	0.09	0.10	0.58 (0.53, 0.63)	0.56 (0.51, 0.61)
Other	0.25	0.15	0.12	0.67 (0.60, 0.74)	0.65 (0.57, 0.72)

Analytic sample consisted of 3384 participants.

[a] adjusted for age, BMI, social class, smoking status at baseline and season.

[b] Models failed to converge

Table 4.9. Odds of being active at 20 year follow up according to activity levels at baseline

		Model 1	Model 2	Model 3
	N	OR (95% CI)	OR (95% CI)	OR (95% CI)
Physical activity				
Inactive	1,156	1.0	1.0	–
Active	2,257	**2.9 (2.5, 3.3)**	**2.8 (2.4, 3.2)**	–
Sport				
Low	2,049	1.0	1.0	1.0
High	1,269	**3.1 (2.7, 3.7)**	**3.0 (2.5, 3.6)**	**3.0 (2.5, 3.5)**
Recreational activity				
Low	1,501	1.0	1.0	1.0
High	1,912	**1.9 (1.6, 2.2)**	**1.8 (1.6, 2.1)**	**1.6 (1.4, 1.9)**
Walking				
Low	2,495	1.0	1.0	1.0
High	918	**1.5 (1.3, 1.8)**	**1.5 (1.3, 1.8)**	**1.6 (1.4, 1.9)**

Analytic sample consisted of 3413 participants. Data on sport/exercise were missing for 95 men, resulting in a sample of 3318 for this analysis.

Model 1 adjusted for baseline age. Model 2, Model 1 + social class, BMI and smoking status at baseline. Model 3 mutually adjusted for all domains of activity respectively. Bold indicates statistical significance ($p<0.05$).

Table 4.10. Odds of being active at 20 year follow up according to duration of sport participation at baseline

		Model 1	Model 2
	N	**OR (95% CI)**	**OR (95% CI)**
Sports participation duration			
Not participating at baseline	2074	1.0	1.0
≤ 4 years	251	**2.3 (1.7, 3.2)**	**2.3 (1.7, 3.1)**
5-11 years	329	**2.7 (2.1, 3.6)**	**2.6 (2.0, 3.5)**
12-24 years	286	**4.1 (2.9, 5.8)**	**3.9 (2.8, 5.5)**
≥ 25 years	296	**4.7 (3.3, 6.6)**	**4.4 (3.1, 6.2)**
p value for trend[a]		<0.001	<0.001

Data on duration of participation were missing for 82 men, resulting in an analytic sample of 3236 participants

Model 1 adjusted for baseline age. Model 2, Model 1 + social class, BMI and smoking status at baseline.

[a] Tests for linear trend were conducted by entering sports duration as a continuous variable into regression models. Bold indicates statistical significance (p<0.05).

Table 4.11. Odds of being active at 20 year follow up according to physical activity trajectory (baseline, 12- and 16-year follow ups)

			Model 1	Model 2
	N	%	OR (95% CI)	OR (95% CI)
Physical activity trajectory[a]				
0-0-0	390	11	1.0	1.0
1-0-0	287	8	1.4 (1.0, 2.0)	1.4 (1.0, 1.9)
0-1-0	206	6	**2.2 (1.5, 3.1)**	**2.1 (1.4, 3.0)**
1-1-0	357	11	**4.6 (3.4, 6.4)**	**4.5 (3.3, 6.2)**
0-0-1	138	4	**5.7 (3.7, 8.7)**	**5.7 (3.8, 8.8)**
1-0-1	176	5	**8.8 (5.8, 13.2)**	**8.5 (5.7, 12.9)**
0-1-1	422	12	**16.6 (11.8, 23.5)**	**16.3 (11.5, 23.0)**
1-1-1	1,437	42	**31.7 (23.6, 42.7)**	**30.2 (22.4, 40.7)**

Analytic sample consisted of 3413 participants

[a] Physical activity trajectories correspond to levels of physical activity from baseline through 12 and 16 year follow ups. 0 and 1 denote physical activity level as low or high at each time point, respectively. For example, (0-0-0) represents low physical activity at all periods, whilst (1-0-0) indicates high physical activity at baseline only.

Model 1 adjusted for baseline age. Model 2, Model 1 + social class, BMI and smoking status at baseline. Bold indicates statistical significance ($p<0.05$).

Table 4.12. Odds of participating in sport and exercise or not and being active or not at 20-year follow up according to type of sport and exercise type participation at baseline

	Participating in sport/exercise at 20-year follow up (n=3384)				Physically active at 20-year follow up (n=3318)			
Sport/exercise type	**Model 1**	**Model 2**	**Model 3**	**Model 4[a]**	**Model 1**	**Model 2**	**Model 3**	**Model 4[b]**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Golf	**6.3 (4.9, 8.0)**	**6.1 (4.8, 7.8)**	**6.6 (5.1, 8.5)**	**3.4 (2.6, 4.5)**	**4.2 (3.0, 5.7)**	**4.1 (3.0, 5.6)**	**4.2 (3.0, 5.7)**	**2.1 (1.5, 2.9)**
Bowling	**5.9 (3.4, 10.1)**	**6.1 (3.5, 10.6)**	**7.7 (4.4, 13.5)**	**3.0 (1.7, 5.3)**	**2.3 (1.3, 4.1)**	**2.3 (1.3, 4.1)**	**2.5 (1.4, 4.6)**	1.0 (0.5, 1.8)
Dancing	**3.1 (1.6, 5.7)**	**3.4 (1.8, 6.4)**	**4.3 (2.3, 8.2)**	1.6 (0.9, 3.2)	**2.2 (1.0, 4.6)**	**2.3 (1.0, 4.8)**	**2.6 (1.2, 5.5)**	1.1 (0.5, 2.3)
Racquet sports	**3.7 (2.9, 4.8)**	**3.4 (2.6, 4.3)**	**3.0 (2.3, 4.0)**	**1.6 (1.2, 2.2)**	**3.0 (2.2, 4.1)**	**2.7 (2.0, 3.8)**	**2.3 (1.6, 3.2)**	1.2 (0.9, 1.7)
Swimming	**2.0 (1.5, 2.6)**	**1.8 (1.4, 2.4)**	**1.6 (1.2, 2.1)**	0.8 (0.6, 1.1)	**2.6 (1.8, 3.7)**	**2.5 (1.7, 3.5)**	**2.1 (1.5, 3.0)**	1.1 (0.8, 1.6)
Cycling (any purpose)	1.2 (0.9, 1.5)	1.2 (0.9, 1.5)	**1.3 (1.0, 1.8)**	**0.6 (0.5, 0.8)**	**1.6 (1.2, 2.1)**	**1.5 (1.1, 2.1)**	**1.6 (1.2, 2.2)**	0.8 (0.6, 1.1)
Surface water sports	**2.4 (1.5, 3.8)**	**2.1 (1.3, 3.4)**	**2.0 (1.2, 3.4)**	1.1 (0.7, 1.8)	1.5 (0.9, 2.6)	1.3 (0.8, 2.3)	1.1 (0.6, 2.0)	0.6 (0.4, 1.1)
Gym/ muscle strengthening	1.7 (0.9, 3.1)	1.4 (0.8, 2.7)	**2.1 (1.1, 4.0)**	0.5 (0.3, 1.0)	1.9 (0.9, 4.2)	1.7 (0.8, 3.7)	1.9 (0.9, 4.2)	0.5 (0.2, 1.2)
Running/jogging	**3.2 (2.0, 5.1)**	**2.9 (1.8, 4.7)**	**2.6 (1.6, 4.3)**	1.1 (0.7, 1.8)	**4.2 (2.0, 8.8)**	**3.9 (1.8, 8.1)**	**3.2 (1.5, 6.8)**	1.4 (0.6, 2.9)
Cricket	**2.3 (1.3, 3.9)**	**2.1 (1.2, 3.7)**	1.6 (0.9, 3.0)	1.2 (0.7, 2.1)	**3.8 (1.6, 9.0)**	**3.7 (1.6, 8.8)**	**3.0 (1.2, 7.2)**	2.0 (0.8, 4.8)
Walking/hiking	**2.7 (1.5, 4.8)**	**2.3 (1.2, 4.1)**	**2.1 (1.1, 3.9)**	1.4 (0.8, 2.6)	**2.6 (1.2, 5.5)**	**2.2 (1.0, 4.7)**	2.0 (0.9, 4.4)	1.3 (0.6, 2.8)
Other	**2.5 (1.7, 3.7)**	**2.5 (1.7, 3.7)**	**2.1 (1.4, 3.1)**	1.1 (0.7, 1.7)	**2.8 (1.6, 4.7)**	**2.7 (1.6, 4.6)**	**2.3 (1.3, 4.0)**	1.1 (0.7, 2.0)

Sport/exercise type	Participating in sport/exercise at 20-year follow up (n=3384)				Physically active at 20-year follow up (n=3318)			
	Model 1	**Model 2**	**Model 3**	**Model 4[a]**	**Model 1**	**Model 2**	**Model 3**	**Model 4[b]**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Number of sports/exercises								
0 (n=2091)	1.0	1.0	-	1.0	1.0	1.0	-	1.0
1 (n=940)	**3.5 (3.0, 4.1)**	**3.3 (2.8, 3.9)**	**-**	**2.0 (1.6, 2.5)**	**2.7 (2.3, 3.2)**	**2.6 (2.2, 3.1)**	**-**	1.1 (0.9, 1.4)
2 (n=276)	**5.7 (4.4, 7.5)**	**5.3 (4.1, 7.0)**	**-**	**2.8 (1.9. 3.9)**	**4.5 (3.2, 6.4)**	**4.2 (3.0, 6.1)**	**-**	1.4 (0.9, 2.1)
3+ (n=77)	**15.8 (8.5, 29.5)**	**14.6 (7.8, 27.3)**	**-**	**7.0 (3.6, 13.7)**	**13.0 (4.7, 35.9)**	**12.2 (4.4, 33.5)**	**-**	**3.6 (1.2, 10.1)**
p value for trend[c]	**<0.001**	**<0.001**	**-**	**<0.001**	**<0.001**	**<0.001**	**-**	**<0.001**

Note. Rugby, football and aerobics were not included in these models as participation at baseline was too low to generate reliable estimates

[a] Total physical activity score at baseline was missing for 37 men resulting in a final sample of 3347

[b] Total physical activity score at baseline was missing for 37 men resulting in a final sample of 3281

[c] Tests for linear trend were conducted by entering sports duration as a continuous variable into regression models. Bold indicates statistical significance $p<0.05$

Model 1 adjusted for baseline age. Model 2, Model 1 + social class, BMI, smoking status at baseline and season. Model 3, Model 2 + participation in all sport and exercises at baseline. Model 4, Model 2 + total physical activity score at baseline. Bold indicates statistical significance ($p<0.05$)

CHAPTER 5. TRAJECTORIES OF PHYSICAL ACTIVITY AND PREDICTORS DURING THE TRANSITION TO OLD AGE

5.1 Summary

It is well established that there is on average a gradual age-related decline in physical activity. However, there is emerging evidence that some groups of individuals follow different patterns of behaviour over time. Identifying and understanding these patterns could help inform intervention strategies to promote lifelong activity. Additionally, very little is known about the patterns of participation in specific types of physical activity over time. Moreover, the literature on the correlates and determinants of physical activity has largely been based on cross-sectional or short-term longitudinal studies and has rarely focussed on specific types of physical activity. This chapter identifies the trajectories of self-reported total and specific types of physical activity using LCGA methods and explores associations with a range of sociodemographic factors, health conditions, behavioural factors and major life events. GBTM, a form of LCGA, was used to identify distinct 20-year trajectories of total physical activity, sport/exercise, recreational activity and walking from midlife to old age. Three trajectories of total physical activity were identified, revealing three distinct trajectories. Similarly, three stable trajectories were identified for sport/exercise. Walking and recreational activity were more variable from midlife to old age. Two out of three walking trajectory groups followed an increasing pattern, comprising more than two thirds of the sample. In contrast, two out of four recreational activity trajectory groups demonstrated a decreasing pattern, making up around half of the sample. Consistent predictors of following more favourable trajectories for total and all physical activity types included not smoking, a healthy BMI and absence of other health conditions. A range of sociodemographic and behavioural factors also predicted trajectories but associations varied according to specific types of physical activity. Retirement and CVD onset proved to be important life events but effects were modified by prior physical activity behaviours and by physical activity types.

5.2 Introduction

Chapter 4 showed that there was some instability in total physical activity and participation in physical activity types between midlife and old age. Further exploration is required to quantify the changes in physical activity during this period and to understand when and why these

changes occur. As described in Chapter 3, more advanced techniques, such as LCGA, have been developed for identifying trajectories of health behaviours. To date, only a handful of studies have used this approach to explore trajectories of physical activity during the transition to old age (7, 134-137) and none to my knowledge have looked at specific types of physical activity. This approach is appropriate when it is hypothesised that there are several underlying subgroups of individuals who share similar patterns of behaviour over time. Given that previous studies suggest that not all older adults share a common physical activity growth curve (14), this approach is appropriate for identifying latent physical activity trajectories.

Conventional approaches to classify change over time would typically involve grouping men based on a clinically relevant cut point, resulting in persistently inactive or active, increasing and decreasing groups (14, 118, 119). In contrast, studies using the LCGA approach generally suggest that physical activity may be more stable than these traditional groupings suggest (7, 135, 136). These studies show that those who are active tend to stay active or become more active and visa verse (7, 134, 136). However, there are some inconsistencies, with a few studies using LCGA identifying trajectories that do overlap to some degree (134, 136, 137). Given the finding that physical activity types track differently, it is important to also explore the trajectories of specific types of activity in more detail, particularly as they will be masked when examining total physical activity.

As highlighted in Chapter 2, a large amount of research, predominantly cross-sectional, has identified a range of correlates and determinants of physical activity (112). The most consistent modifiable correlates and determinants of physical activity include previous physical activity, markers of socioeconomic status, a range of psychosocial factors and health status (112). However, there is a paucity of evidence identifying the predictors of long-term physical activity patterns. In recent years, there has been an increased focus on identifying correlates of specific types of physical activity. The early evidence suggests that many correlates and determinants are specific to physical activity types (311-314), but how they are associated with adult life course patterns remains unclear.

Only a few studies using LCGA have also explored the predictors of the identified physical activity trajectories (7, 134, 137). Such studies are consistent with the previous literature, suggesting that factors related to health and socioeconomic status strongly predict long-term physical activity (7, 134, 137). In addition, one study showed that the effects of some major life events were modified by trajectory grouping. Retirement was associated with increases in physical activity in the most active trajectory groups but was not associated with any change in the least

active. In addition, onset of mobility limitations initiated steeper declines in the more active groups compared to the least active (134). However, the impact of these events on the trajectories of specific physical activity types remains unexplored.

The primary aim of this chapter is to identify the trajectories of self-reported physical activity and physical activity types using LCGA methods. Also, this chapter aims to explore the predictors of these trajectories and how major life events impact trajectory slopes.

5.3 Objectives

I. Identify distinct 20-year trajectories of total physical activity, sport/exercise, recreational activity and walking from midlife to old age in British men
II. Examine associations between a range of sociodemographic, health markers and lifestyle factors at baseline and trajectory group membership
III. Examine the impact of major life events on physical activity and physical activity type trajectory slopes

5.4 Methods

5.4.1 Subjects and methods of data collection

Data in this chapter are drawn from the baseline, 12-, 16- and 20-year follow ups of the BRHS. Primary analyses were performed on men, aged 60-79 in 2000, who had self-reported their habitual physical activity and participation in physical activity types on at least three occasions across the four follow up measurements, with complete data on baseline exposures of interest as outlined below.

5.4.2 Physical activity measures

Habitual physical activity and levels of sport/exercise, recreational activity and walking were self-reported at each wave. For total physical activity, the derived 6-point total physical activity score was used, as detailed in Chapter 3. The six-point score classified men as inactive (minimal activity across all types), occasional (regular walking or recreational activity only, or sporting activity less than once a week only), light (more frequent recreational activities plus sporting activity less than once a week, or regular walking plus some recreational activity), moderate (cycling very frequently only, or very frequent recreational activities plus regular walking, or sporting activity once a week), moderately vigorous (sporting activity 2-4 times a week, or

sporting activity once a week plus regular walking/cycling and recreational activity) or vigorous (sporting activity more than 4 times a week, or less frequent sporting activity plus frequent walking/cycling and recreational activities).

Men also reported their sport/exercise participation. Response options were none, occasional (< 1 a month) and frequent (≥1 a month). For recreational activity, men were asked to report their level of recreational activity at weekends and were classified as low (<4 hours at the weekend), moderate (similar to 4 hours at the weekend) and high (>4 hours at the weekend). For walking men were asked to report the amount of time spent walking for transport and other purposes and were classified as low (<20 minutes/day), moderate (21-60 minutes/day) and high (>60 minutes/day).

5.4.3 Exposure variables

A range of time-stable and time-varying measures were considered based on existing literature suggesting an association with physical activity. Variables that were not routinely measured at each wave could only be included as time-stable predictors of trajectory group membership. Variables that were measured repeatedly at each follow up could be included as time varying, but several factors were considered before including them as time varying in the final model. Time-varying variables were treated as a time-stable baseline predictor if there was limited within-person variability over time, if the effects were similar across trajectory groups and if a change in the variable conceptually did not represent an important life event.

5.4.3.1 Time-stable variables

At baseline, when aged 40-59 years, participants self-reported a range of sociodemographic, health and lifestyle factors. Occupational social class was based on participants' longest-held occupation and was classified as manual or non-manual using the Registrar General's Classification of Occupations (250). Marital status was classified into three categories (single, married or widowed/divorced) and number of children was classified as either none or ≥1.

Men also self-reported whether they ever had a doctor-diagnosis of a range of health conditions including arthritis, bronchitis and high blood pressure. Other health problems including breathlessness and chest pain on exertion were also reported and classified as yes/no. BMI was determined from height and weight measurements (kg/m^2) and was classified as normal weight (BMI <25.0 Kg/m^2) or overweight/obese (BMI ≥25.0 Kg/m^2).

Smoking status was categorised into two groups based on current and prior smoking habits (current/recent ex-smokers or non-smokers/long-term ex-smokers). Alcohol consumption was categorised into five groups based on frequency and quantity of intake (none, occasional [<1 drink/week], light [1-15 drinks/week], moderate [16-42 drinks/week] or heavy [>42 drinks/week]). Each man's region of residence was based on the location of the recruited town and was classified into 4 groups (Scotland, North, Midlands and South). Weekly breakfast cereal consumption was based on frequency of consumption and classified into three groups (none, occasional [1-2 times/week] or regular [>3 times/week]).

5.4.3.2 Time-varying variables

At all four waves men reported doctor diagnosis of CVD (including stroke with symptoms lasting >24 hours, heart attack, myocardial infarction, coronary thrombosis or angina). The number of CVD conditions was summed at each time point to account for accumulation of multiple conditions. Men also reported employment status at each follow up, from which men were classified as in part- or full-time employment (0) or not in employment (1), i.e. retired or unemployed. BMI, marital status, alcohol consumption and smoking status were explored as time-varying but were ultimately included as time-stable using the baseline measurement. The time-varying BMI variable was derived from height and weight measurements (kg/m^2) from the physical examinations at baseline and 20-year follow up and from self-reported data at the 12- and 16-year follow ups. Time-varying marital status was coded as not married (0), i.e. single/divorced/widowed, or married at each wave (1). BMI and marital status were highly correlated throughout follow up (rs ranged from 0.8-0.9 for BMI and 0.4-0.9 for marital status) and were deemed more informative as time-stable predictors of trajectory group membership in final models. Alcohol consumption was classified using the 5-point categorical variable at each wave, as described above. Smoking status was defined as currently (0) or not currently smoking (1) at each wave. As Wald tests revealed similar effects of time-varying alcohol consumption and smoking status across trajectory groups, they were instead treated as time-stable baseline predictors of trajectory groups. Also, due to the complex interrelationship between health behaviours it may not be possible to untangle cause and effect. Supplementary analyses exploring these variables as time-varying are shown in appendix 5C.

5.4.4 Statistical methods

GBTM, a form of LCGA, was used to identify latent homogenous groups of study members with similar trajectories of total physical activity, sport/exercise participation, recreational activity

and walking over 20 years of follow up. Models with 2 to 5 trajectory groups were tested for total physical activity and each physical activity type. The optimal number of trajectory groups was determined using the goodness of fit criteria described in Chapter 3. Models simultaneously estimated the odds of trajectory group membership in relation to time-stable predictors, while the effects of time-varying variables were estimated for each trajectory group. Wald tests were conducted to examine whether the effects of time-varying variables differed by trajectory group. The shape of each trajectory was then determined, starting with the highest order function possible i.e. a quadratic growth factor, which was then reduced by exploring linear and intercept only models, until each parameter estimate was statistically significant ($p<0.05$). The characteristics of each trajectory group according to baseline and time-varying predictors were also determined. Means and standard deviations were used to describe continuous variables, while proportions were used to summarise categorical data. To determine the concordance between total physical activity and physical activity type trajectories, membership of trajectory group types was cross tabulated.

5.4.4.1 Sensitivity analyses

To address potential sources of bias a number of sensitivity analyses were performed. As the age range at baseline was quite broad, important age-related transitions could be masked. Therefore, analyses were also performed stratifying the sample into younger and older men. Also, to understand the impact of attrition on trajectory groups and shapes, GBTM was also conducted including all men, even those with less than 3 measures of physical activity. Finally, as the question on walking changed at the fourth wave (as described in Chapter 3), a sensitivity analysis was performed excluding the fourth time point from the trajectories.

5.5 Results

Out of 7735 men who were recruited at baseline, men with at least three valid total physical activity scores (n=4952) and three measures of sport/exercise (n=5116), recreational activity (n=5085) and walking (n=5106) accompanied by complete covariate data were included in respective analyses. Compared to men in the analytic sample exploring total physical activity trajectories (n=4952), men excluded due to having only 1 or 2 physical activity measures (n=2694) were less active at baseline (53.0% vs. 62.3% classified with at least light activity, respectively), were older (52.2 years vs. 49.1 years, $p<0.001$), were more likely to come from manual occupations (71.6% vs. 54.3%) and had more health conditions (e.g. 10.7% and 3.2% of

men had CVD at baseline, respectively). Similar characteristics were observed in men with missing data for specific physical activity types.

5.5.1 Trajectories of total physical activity

Based on the goodness of fit criteria, a 3-group model was chosen as the best fitting model. The three groups were defined as low, decreasing (24.6%, n=1218), light stable (51.1%, n=2530) and moderate, increasing (24.3%, n=1204) trajectories (see figure 5.1). Although the BIC value was higher for the 4 group model (BIC=-30385.6), it was rejected because the difference in BIC was fairly small compared to the 3-group model (BIC=-30442.9), as shown in appendix 5A, and the addition of a fourth group largely replicated the patterns of the 3-group model but with smaller group sizes. In the 3-group model, posterior probabilities ranged from 0.82 to 0.90 and the estimated group sizes were comparable with the actual group sizes, suggesting a good fit. ORs for correct classification ranged from 10.0 to 49.3, suggesting accurate group assignment. Therefore the 3-group model was selected as the most parsimonious description of the longitudinal patterns in the data.

For the low, decreasing group, the quadratic function was statistically significant (p=<0.001), suggesting a non-linear trajectory (see Figure 5.1). Members of this group were characterised by light/occasional physical activity at baseline remaining stable for the first 12 years, followed by a decrease between 12- and 16-year follow ups and a steep decline towards inactivity by the 20-year follow up. In the light stable group, although the slope was significant (p=<0.001) suggesting a slight decline, physical activity remained consistently light over time. For the moderate, increasing group, the slope, but not the quadratic term, was positive and statistically significant (p<0.001) suggesting a linear increase in physical activity over time (see Appendix 5B).

The distribution of each time-stable and time-varying exposure variables are presented in table 5.1, according to each trajectory group. There was a clear dose-response relationship across trajectory groups, with more favourable characteristics observed in the moderate, increasing group. For example, men in the low, decreasing trajectory group tended to be older and were more likely to come from manual occupations, currently smoke, come from regions other than the south of England and suffer from a range of health conditions.

5.5.1.1 Time-stable predictors of total physical activity trajectory group membership

The odds of trajectory group membership according to time-stable predictors are shown in table 5.2. Being older, residing in the midlands or north of England (vs. southern England), being

overweight or obese (vs. healthy weight), being diagnosed with arthritis or bronchitis or high blood pressure and being a current/recent-ex smoker (vs. non-smoker) were associated with reduced odds of belonging to a more favourable trajectory group (light stable/moderate, increasing) compared to the low, decreasing group. Working in a manual profession (vs. non-manual) was also associated with reduced odds of belonging to the moderate, increasing group when compared to the low, decreasing group. Further, being married or previously married (vs. single), having children (vs. no children), drinking alcohol (vs. none) and eating breakfast cereal (vs. none) were associated with increased odds of belonging to a more favourable trajectory group compared to the low, decreasing group. ORs were highest for light alcohol and occasional breakfast cereal consumption. Borderline associations were also observed between chest pain diagnosis and reduced odds of belonging to more favourable trajectories. Most of the above associations were strongest for the moderate, increasing group, suggesting a dose-response relationship across trajectory groups. Among time-stable predictors, the mean VIF was 1.1, indicating no multicollinearity issues.

5.5.1.2 Time-varying predictors of total physical activity trajectory slopes

Leaving employment was associated with an increase in physical activity in the light stable (β 0.324, p<0.001) and moderate, increasing groups (β 0.847, p<0.001) but was associated with a decrease in the low, decreasing group (β -0.306, p<0.001) (see Table 5.3). Of note, the main reason for leaving employment was retirement (e.g. 97% of men not in employment reported that they had retired at the 20-year follow up). Diagnosis of cardiovascular-related conditions was associated with a decrease in physical activity in the low, decreasing (β -0.408, p<0.001) and light stable groups (β -0.118, p<0.001) but was not associated with changes in the moderate, increasing group. Wald tests showed that the effects of changes to employment status and CVD diagnoses were significantly different between trajectory groups (p<0.001).

Exploratory analyses including BMI, marital status, alcohol consumption and smoking as time-varying covariates instead of time-stable revealed similar results that did not alter conclusions. An increase in BMI was associated with similar declines in physical activity across all trajectory groups. Changes in marital status were not significantly associated with changes in physical activity across all trajectory groups, hence marital status was deemed more informative as a time-stable predictor. An increase in alcohol consumption was associated with an increase in total physical activity in the light stable and moderate, increasing trajectory groups, while quitting smoking was associated with an increase in physical activity across all trajectory groups, see Appendix 5C.

5.5.2 Trajectories of sport/exercise participation

For sport/exercise participation, a three-trajectory group model was selected as the best fitting model. The least negative BIC value was observed for the three-group model, as shown in Appendix 5D. Estimated group sizes were similar to the actual group sizes and posterior probabilities exceeded 0.7. ORs for correct classification also exceeded 5. The three groups were described as consistently none (45.8%, n=2342), consistently occasional (30.4%, n=1555) and consistently frequent (23.8%, n=1219) sport/exercise participation. To determine the shape of each trajectory, quadratic functions were initially tested, but linear trajectories best described the trajectories for all three groups, as shown in Appendix 5E. Gradual increases in sport/exercise were observed for the consistently frequent group, whereas steady declines were observed for the consistently occasional and none groups. Although there were some fluctuations, men in these groups had fairly consistent low, occasional and frequent sport/exercise participation, respectively, as shown in Figure 5.2.

5.5.2.1 Time-stable predictors of sport/exercise trajectory group membership

The odds of sport/exercise trajectory group membership according to time-stable predictors are shown in table 5.4. Being older, being a current or recent ex-smoker, coming from a manual occupation and suffering from breathlessness were associated with reduced odds of belonging to the consistently occasional and frequent groups when compared to the consistently none group. Residing in the Midlands was associated with reduced odds of belonging to the consistently occasional group when compared to the consistently none group, but there were also borderline associations between residing in the Midlands or North of England and reduced odds of belonging to both the consistently occasional and frequent groups. Being overweight or obese was also associated with reduced odds of belonging to the consistently frequent group and having high blood pressure was associated with reduced odds of belonging to the consistently occasional group when compared to the consistently none group. Being married or previously married, consuming light to heavy amounts of alcohol and consuming breakfast cereal were associated with increased odds of belonging to the consistently occasional and frequent groups when compared to the consistently none group. Having children and residing in Scotland were also associated with increased odds of belonging to the consistently frequent group. Associations were typically strongest for the consistently frequent group, suggesting a dose-response relationship.

5.5.2.2 Time-varying predictors of sport/exercise trajectory slopes

The impact of major life events on trajectory slopes are presented in Table 5.5. Leaving employment was associated with an increase in sport/exercise participation in the consistently occasional (β 1.179, p<0.001) and frequent groups (β1.718, p<0.05), but was associated with a decrease in the consistently none group (β-0.940, <0.001). Wald tests revealed significant differences in the effects of leaving employment between the consistently none group and the consistently occasional (p<0.001) and frequent groups (p<0.05). Developing cardiovascular conditions was associated with a decline in sport/exercise participation in the consistently frequent (β -1.307, p<0.05) and consistently none groups (β -1.283, p<0.05) but was not associated with change in the consistently occasional group (β -0.045, p=0.833).

5.5.3 Trajectories of recreational activity

For recreational activity, four trajectory groups proved to be the optimal fit for the data. A five-group model was also tested but this model failed to converge. The least negative BIC value was observed for the four-group model and was therefore selected as the optimal model (see Appendix 5D). Similar estimated and actual group sizes were observed. Posterior probabilities ranged from 0.77 to 0.94, and ORs for correct classification exceeded 5. The four groups were described as moderate, decreasing (14.6%, n=744), consistently moderate (30.5%, n=1550), high, decreasing (33.2%, n=1688) and consistently high (21.7%, n=1103). All four trajectories were defined using quadratic functions (see Appendix 5E). As shown in Figure 5.2, the moderate, decreasing group began with moderate levels of recreational activity at baseline, but participation steadily declined up to the 12-year follow up and rapidly declined thereafter. The consistently moderate group had moderate levels of recreational activity from baseline up to the 20-year follow up. The high, decreasing group had high levels of recreational activity at baseline but participation steadily decreased to moderate levels by 20-years of follow up. The consistently high group had consistently high levels of recreational activity throughout the duration of the study.

5.5.3.1 Time-stable predictors of recreational activity trajectory group membership

The odds of trajectory group membership according to baseline exposures are presented in Table 5.6. Being older, coming from a manual occupation, residing in regions outside of the South of England, being overweight or obese, being diagnosed with arthritis, bronchitis or high blood pressure, suffering from breathlessness and being a current or recent smoker was associated with reduced odds of belonging to the consistently high group compared to the

moderate, decreasing group. In addition, being married or previously married was associated with increased odds of belonging to the consistently high group compared to the moderate, decreasing group. Associations were strongest for the consistently high group but similar associations were observed for membership of the high, decreasing and consistently moderate groups when compared to the moderate, decreasing group, albeit they were less consistent. Having children and consuming breakfast cereal and alcohol were not consistently associated with trajectory group membership.

5.5.3.2 Time-varying predictors of recreational activity trajectory slopes

Leaving employment was associated with a decrease in recreational activity in the moderate, decreasing group (β -0.342, <0.05), but it was not associated with any change in the remaining groups, as shown in Table 5.5. Onset of cardiovascular-related conditions was associated with a decline in recreational activity in the moderate, decreasing (β -0.325, <0.001), consistently moderate (β -0.118, <0.05), high, decreasing (β -0.718, <0.001) and consistently high groups (β-1.192, <0.001). Wald tests revealed that the effects of developing cardiovascular-related conditions was significantly larger in the consistently high group compared to the other groups ($p<0.05$).

5.5.4 Trajectories of walking

For walking, three trajectory groups were identified as the best fitting model. Two to four groups were tested, but the three-group model resulted in the least negative BIC value. Estimated and actual group sizes were comparable and posterior probabilities exceeded 0.7 (see Appendix 5D). ORs for correct classification also exceeded 5. Quadratic functions were initially tested but were not significant. Growth parameters were subsequently reduced until reaching significance, resulting in one intercept and two linear trajectory shapes (see Appendix 5E). The three groups were described as consistently low (27.2%, n=1388), low, increasing (64.6%, n=3297) and moderate, increasing (8.3%, n=421), as shown in Figure 5.2. The consistently low group is characterised by low levels of walking from baseline to 20-year follow up (i.e. intercept only). The low, increasing group had low levels of walking at baseline that increased to moderate levels over the duration of the study. The moderate, increasing group had moderate levels of walking at baseline, which increased towards high levels by the 20-year follow up.

5.5.4.1 Time-stable predictors of walking trajectory group membership

The odds of trajectory group membership according to baseline exposures are presented in Table 5.7. Being overweight or obese, suffering from breathlessness and being a current or recent smoker was associated with reduced odds of belonging to the moderate, increasing and low, increasing groups compared to the consistently low walking group. Being married was also associated with reduced odds of belonging to the moderate, increasing group. In addition, being diagnosed with arthritis and residing in the Midlands were associated with reduced odds of belonging to the low, increasing group when compared to the consistently low group. Working in a manual occupation was associated with increased odds of belonging to the low, increasing and moderate, increasing trajectory groups when compared to the consistently low group. In addition, residing in Scotland and occasionally eating breakfast cereal was associated with increased odds of belonging to the moderate, increasing group when compared to the consistently low group. Regular breakfast cereal consumption was also associated with increased odds of belonging to the low, increasing group. Further, having children was associated with increased odds of belonging to the low, increasing group when compared to the consistently low group. No significant associations were found with age and alcohol consumption.

5.5.4.2 Time-varying predictors of walking trajectory slopes

Leaving employment was associated with an increase in walking in the low, increasing group (β 0.439, $p<0.001$) but was not associated with change in any other group (see Table 5.5). Wald tests confirmed that the effects of leaving employment were greater in the low, increasing group compared to the moderate, increasing group. Development of cardiovascular-related conditions was not significantly associated with change in walking in any trajectory group.

Exploratory analyses examining the impact of alcohol and smoking on physical activity types when they were treated as time-varying variables revealed that the associations were specific to physical activity types. The observed association between increases in alcohol consumption and physical activity were driven by sport/exercise, while the effects of quitting smoking acted mainly through declines in sport/exercise and recreational activity.

5.5.5 Exploring reasons for retirement

As mentioned above, the primary reason for leaving employment was retirement. Further analyses exploring the reasons for retirement revealed that a higher proportion of men in the

least active trajectory groups across all physical activity types were retiring due to health issues, suggesting that the effects of retirement may be modified by the cause/reason for retirement. For example, for total physical activity, more men in the low, decreasing group were retiring due to health issues (30%) than men in the light stable (15%) and moderate, increasing groups (11%).

5.5.6 Concordance between physical activity and physical activity type trajectories

To examine the concordance of trajectories across all physical activity types, total physical activity group membership was cross tabulated with membership of other physical activity type trajectories. There was some evidence of concordance between total physical activity and physical activity type trajectories (See Appendix 5F). Generally, members of the least favourable trajectory for total physical activity were also in the least favourable trajectory for physical activity types. Notably, however, men in the light stable total physical activity group did not typically belong to the most favourable sport/exercise group, with only 9% belonging to the consistently frequent sport/exercise group. Conversely, many of the men in the light stable group increased their walking, with 71% and 10% of these men belonging to the low, increasing and moderate, increasing walking groups, respectively.

5.5.7 Sensitivity analyses

To examine the extent that attrition bias may have impacted the findings, trajectories were also identified after including all men with at least one measure of physical activity. Trajectory groups and shapes remained largely unchanged after including individuals with only one or two physical activity measures across follow up. Associations with exposure variables also remained unchanged, but group sizes were altered. For total physical activity, a higher proportion of men belonged to the low, decreasing trajectory group (31.9%) and a lower proportion belonged to the moderate, increasing trajectory group (19.2%), as shown in Appendix 5G. Similar trends were observed for physical activity types, with more individuals assigned to the least favourable trajectories. This suggests that physical activity levels were lower in men who were lost to follow up. Subsequently physical activity may be overestimated when restricting the sample to participants with more complete data. However, this is unlikely to have affected the trajectory shapes and optimal number of groups.

To understand whether any bias was introduced by analysing the whole age range of the sample, models were also performed after stratifying by age. After stratifying by age, the 3-group model for total physical activity remained optimal for both younger and older men. It also revealed some important life periods of change that were previously masked when observing the

trajectories of the whole sample. Physical activity appeared to be more likely to increase between the ages of 60 and 65 years, while the late sixties/early seventies seemed to be a turning point when physical activity started to decline universally (see Appendix 5H). For sport/exercise, a two-group model was optimal in younger and older men, with similar stable trajectories observed for both younger and older men (see Appendix 5I). For walking, two trajectory groups provided the best fit for the data for younger and older men (see Appendix 5J). Trajectories were comparable between younger and older men, but a higher proportion of older men had increasing levels of walking. For recreational activity, three trajectory groups were optimal for younger men, while two groups provided the best fitting model for older men (see Appendix 5K). Although decreases were more rapid in the older men, the trajectories were largely similar.

In addition, as the walking question was modified at the fourth time point, walking trajectories were estimated across the first three waves. Similar trajectory groups were observed when this fourth time point was excluded.

5.6 Discussion

5.6.1 Summary of main findings

This chapter used GBTM to identify the underlying trajectories of total and specific types of physical activity and examined their associations with a range of predictors and major life events. Three trajectories of total physical activity that were largely stable over time were identified, suggesting that physical activity in old age was largely dictated by physical activity in midlife. For sport/exercise, three trajectories were identified, also revealing fairly constant patterns over time. In contrast, walking and recreational activity were more changeable. Three trajectory groups were identified for walking, two of which displayed increasing levels over the 20-year follow up. For recreational activity, four trajectory groups were identified, two of which showed a decreasing pattern. Men with chronic health conditions, obesity and smoking were less likely to follow more favourable trajectories for total and all types of physical activity. Socioeconomic status, lifestyle and other demographic factors were also important for physical activity trajectories but the magnitude and direction of the associations were specific to each physical activity type. Retirement and CVD onset proved to be important events that could initiate changes to physical activity, but the impact of these events was modified by trajectory group membership and physical activity type.

5.6.2 Comparison with previous studies

This chapter identified three distinct trajectories of total physical activity (low, decreasing [24.6%], light stable [51.1%] and moderate, increasing [24.3%]). Previous studies using similar statistical techniques to identify trajectory groups have also identified a substantial proportion of adults (15-74%) who were inactive in midlife and remained inactive into old age (7, 131, 134-138). The trajectories identified in this analysis also suggested that physical activity levels in old age were largely determined in midlife. This is consistent with GBTM studies identifying trajectory groups using continuous measures of physical activity showing that trajectories do not typically overlap during this life period (7, 131, 135). Discrepancies with other GBTM studies may be due to the type of physical activity measure, with several using fewer categories or binary variables to classify activity (134, 136, 137). The trajectories identified in this chapter varied according to the type of physical activity. To my knowledge, this is the first study to identify the trajectories of specific types of physical activity using GBTM.

The trajectories identified support the findings in Chapter 4 that physical activity levels are fairly stable into old age. Even when men with less physical activity data were included in the models, i.e. those who are typically less healthy and more inactive, trajectories remained fairly stable. These findings are also comparable with other studies exploring tracking/changes across two time points that suggest that sport/exercise is more stable than other types of physical activity (101) and that many retiring adults increase their walking (141, 142). Another study with similar findings showed that transport and occupational activity declined during the transition to retirement, whereas recreational activity (including sport/exercise, walking/cycling for pleasure, do-it-yourself and gardening) and household activities increased (140).

Previous studies using traditional growth curve modelling suggest that there is on average a linear age-related decline in physical activity across adulthood (123). The findings of this chapter suggest that between the ages of 40 and 65 not all men's total physical activity declines. Only a quarter of adults demonstrated a decline in physical activity from midlife to old age, while the remainder remained fairly stable or even increased. From approximately the age of 67 there does, however, seem to be a universal decline. Comparisons with studies using more rudimentary methods to describe change across two time points are challenging given the various measures and cut offs used to define change in activity levels.

The results of this chapter also highlight a number of sociodemographic, behavioural, environmental and health factors that are associated with physical activity trajectories.

Although there were some common predictors across physical activity type trajectories, this analysis showed that many of the predictors were specific to type.

5.6.2.1 Demographic factors

Firstly, men who were older were less likely to belong to an active total physical activity trajectory (light stable or moderate, increasing). This finding is consistent with previous cross sectional (11) and longitudinal studies (123) that suggest older adults are generally less active. A similar pattern of associations was observed for sport/exercise and recreational activity, but no associations were observed between age and walking trajectories. This is in keeping with existing studies that show walking is the predominant type of activity among older adults (315) and is often adopted during retirement (142).

The association between socioeconomic status and physical activity has been widely researched. The finding that men from manual occupations are less likely to belong to favourable total physical activity trajectories is consistent with numerous studies using a variety of socio-economic status measures that have shown that coming from a more disadvantaged background is associated with lower levels of physical activity (112, 146, 147). Studies examining trajectories of physical activity into old age have also shown that higher levels of education and income are associated with more favourable physical activity trajectories (7, 134, 137).

The socioeconomic gradient observed for total physical activity trajectories seems to be largely driven by sport/exercise. Working in a non-manual occupation was strongly associated with increased odds of belonging to a more favourable sport/exercise trajectory. There was also a socioeconomic gradient observed for recreational activity trajectories but it was not as obvious as sport/exercise. By contrast, manual occupations were associated with a more favourable walking trajectory. These findings are largely consistent with a systematic review showing a conclusive social gradient for leisure-time physical activity, but less consistent associations for walking (147). These findings suggest that social inequalities in sport and exercise participation extend into later life; however, these inequalities are not so apparent for other physical activity types during the transition to old age.

The findings of this chapter also showed that men who were married or previously married were more likely to follow an active total physical activity trajectory compared to unmarried men. Evidence on the association between marital status and physical activity in older adults has been somewhat mixed (112, 131, 134, 151). However, the present findings are consistent with two previous studies in older adults that showed that married men and women are more likely to

follow active trajectories compared to unmarried men of the same age (7, 131). This chapter also showed that being married or previously married was associated with more favourable sport/exercise and recreational activity trajectories, but it was associated with reduced odds of belonging to a moderate, increasing walking trajectory group. Conflicting results were reported in a study of more than 20,000 Australian adults suggesting that married adults were less likely to take part in sport and more likely to take part in non-sport physical activity, although these findings were cross-sectional in nature (316). Plausibly, marriage may prevent isolation in old age and provide a companion for sport and other physical activities. Although it may also prove to be a barrier in older adults who are responsible for the care of a spouse (134).

Men who were fathers were more likely to be members of an active total physical activity trajectory group compared to non-fathers. Fatherhood was also associated with more favourable sport/exercise and walking trajectories. To my knowledge, existing studies have only explored associations between parenthood and total or leisure-time physical activity. In addition, very little research has been conducted on the impact of having children on the parent's long-term physical activity levels. These results conflict existing studies exploring relatively acute effects of having children suggesting that parenthood is associated with a decline in physical activity (146, 156, 189). Plausibly, it may become easier for parents to exercise with their children as they become older. Similarly, one study exploring the impact of major life events in women found that having a grandchild was associated with decreased odds of having increasing physical activity over a three year period (161). These results extend on previous research by showing that fathers and most likely grandfathers are more active from midlife to old age. A larger family network including children and possibly grandchildren may create additional social activities that promote physical activity in old age, specifically sport/exercise and walking. Higher levels of physical activity across adulthood may mediate the observed association between parenthood and increased longevity (317).

This chapter also showed that men from the south of England were more likely to follow an active total physical activity trajectory than men residing in other regions of Britain. The impact of region of residence on trajectories was, however, very much specific to physical activity type. Men from the South of England were more likely to belong to more favourable recreational activity trajectories when compared to other regions of Britain. There was also some evidence that residing in southern regions of England was more favourable for sport/exercise trajectories than other regions of England. However, living in Scotland was associated with increased odds of more favourable sport/exercise and walking trajectories when compared to the South of England. Previous data have shown that levels of total physical activity in adults from Scotland

and England are comparable (318), while the northern regions of England are typically more inactive (319). However, few studies have examined regional differences in specific types of activity. That said, these findings are consistent with data from Sport England's Active People Survey that also showed higher sport participation rates in southern regions of England compared to northern regions (304). Comparisons between countries are more challenging given the different survey instruments used in national surveys, but similar rates of sport/exercise participation were recently reported in the Health Survey for England and Scottish Household Survey (63, 320). In addition, these surveys reported that 70% of Scottish adults frequently took part in recreational walking for at least 30 minutes in 2017, while 47% of English men reported moderate intensity walking of at least 10 minutes on at least one day in the last four weeks. A higher level of walking in Scottish men is plausible given the positive association between access to green and large open spaces and physical activity (321, 322) and the proximity to these spaces in Scottish towns. This chapter extends on previous studies by demonstrating that these regional and national inequalities in overall and specific types of physical activity participation endure across the life course into old age.

5.6.2.2 Behavioural

Among the behavioural factors analysed, participation in other healthy lifestyle behaviours including not smoking and occasional or regular breakfast cereal consumption were associated with increased odds of belonging to a more active total physical activity trajectory group. This is consistent with a body of evidence suggesting that healthy behaviours tend to cluster (163). Other studies examining breakfast consumption have also found a positive association with physical activity (16), particularly with physical activity in the morning (323, 324). In addition, skipping breakfast has been found to cluster with other health-compromising behaviours such as sedentary behaviour, smoking and alcohol use (325). Breakfast habits in the elderly may be particularly important given that older adults are generally most active in the mornings (326). It may also be a good indicator of other healthy dietary behaviours. Indeed, Nguyen and colleagues observed that older adults consuming a moderate amount of fruit and vegetables were more likely to follow a more active trajectory. Conversely, high fat intake was associated with reduced odds of belonging to a more active trajectory (7). In contrast to other healthy behaviours, this chapter showed that unhealthy levels of alcohol consumption were in fact associated with increased odds of belonging to a more active trajectory. This is consistent with recent systematic reviews and studies using GBTM approaches that have also found a positive association between alcohol consumption and physical activity (7, 165). Plausibly, physical activity increases exposure

to environmental, contextual and social factors that promote drinking. Alternatively, it could be that adults who drink alcohol may seek to compensate for this unhealthy behaviour by performing more physical activity (327).

The results of this chapter revealed that the observed positive association between total physical activity trajectories and alcohol consumption was driven by sport/exercise. Higher alcohol consumption was strongly associated with more favourable sport/exercise trajectories but was not associated with other physical activity types consistently. Men with light alcohol consumption were the most likely to belong to the most favourable sport/exercise trajectory group but even heavy consumption was a strong predictor. This is consistent with studies in younger populations suggesting that participation in sport is strongly correlated with harmful drinking (328), particularly if participation is at a higher level, persistent and involves team sports (329). Being a current smoker or recent ex-smoker was associated with reduced odds of following more favourable trajectories for all physical activity types.

The association between breakfast cereal consumption and more favourable total physical activity trajectories was largely driven by sport/exercise and walking. Healthier eating habits have previously been reported in sporty adolescents compared to non-sporty adolescents (330, 331). In addition, there is a suggestion from experimental studies that skipping breakfast can reduce physical activity and exercise performance throughout the day (332). This is the first study to my knowledge to highlight that sport/exercise and walking may be most strongly affected by breakfast omission in older adults and to provide evidence in naturalistic settings.

5.6.2.3 Health status

As expected, men suffering from a variety of health problems at baseline were also less likely to be members of an active total physical activity trajectory group compared to their healthy counterparts, with strong inverse associations observed for overweight or obese, arthritis, bronchitis, high blood pressure, chest pain and particularly breathlessness. This is in keeping with a large body of research showing that good physical health and fitness are key determinants of physical activity maintenance (151) and that many of these conditions are independently associated with an increased risk of following unfavourable trajectories (7, 137).

Among the health conditions that were examined, breathlessness and overweight or obesity were the most consistently associated with reduced odds of belonging to more favourable trajectories across all physical activity types. Associations were less consistent for arthritis, bronchitis, high blood pressure and chest pain. The finding that breathlessness is a strong

inverse predictor of physical activity trajectories is consistent with another study in community-dwelling older adults that also highlighted breathlessness as one of the most important health-related barriers to physical activity (172).

5.6.2.3.1 CVD events

Previous studies have also been identified CVD status as an important predictor of physical activity trajectories (7, 137), but this is the first study to my knowledge to explore the impact of CVD as a time-varying event. This chapter showed that diagnosis of CVD was associated with a decline in total physical activity in the light stable and low, decreasing groups but no association was observed in the moderate, increasing group. The finding that CVD onset does not impact physical activity levels in the most active older men is in line with recent trials suggesting that higher pre-stroke physical activity is associated with improved physical function and greater expression of vascular endothelial growth factors after stroke when compared to individuals with lower pre-stroke physical activity (333, 334). Indeed, there is evidence that functional and aerobic capacity can recover to nearly normal levels after CVD events, such as heart attack or stroke, even without intervention (335, 336). One could also speculate that those who are already active have a stronger motivation to return to pre-CVD activity levels. As discussed in detail below, the present analysis shows that in free-living settings the most active men appear to reduce sport/exercise but it would seem they are able to maintain their total physical activity through other types of activity.

Indeed, CVD onset was associated with declines in recreational activity and sport/exercise, especially in the most active trajectory groups. However, CVD onset had no impact in any of the walking trajectory groups. This is in keeping with published exercise recommendations for heart attack and stroke survivors, which advocate only light-to-moderate intensity aerobic activities such as walking, precluding strenuous activities such as sport and recreational activity (174). The recommendations for stroke survivors also state that stroke patients may be able to perform activities at around 50% of the peak oxygen consumption achieved by matched individuals without stroke (337). It is plausible, therefore, that the most active CVD patients compensate for reductions in sport/exercise by increasing walking.

5.6.2.4 Retirement

This chapter also explored the impact of changes to employment status on trajectory shapes. Leaving employment was associated with an increase in total physical activity in the active trajectory groups but a decrease in the low, decreasing group. Further exploratory analyses

revealed that retirement was the primary reason for leaving employment. Hence these findings suggest that retirement can initiate an increase in total physical activity in men who are already at least occasionally active but not in those who have a history of inactivity. These findings are consistent with a recent systematic review that showed a consistent association between retirement and increases in leisure-time physical activity (156). Our findings are also in keeping with existing studies suggesting that the effects of retirement may be modified by previous physical activity levels (134, 162). However, these findings conflict with the results of a previous study that found older adults who remained employed were more physically active than those who retired. Indeed, that study showed that retirement was associated with declines in physical activity from work-related travel and this was not compensated by increases in leisure or sport participation (188). This chapter also suggests that the effects of retirement may be modified by reason for retirement or health issues on retirement. Compared to the more active trajectory groups, a higher proportion of men in the low, decreasing groups were retiring due to health issues. There is also a suggestion from existing studies that the effects of retirement may be modified by a range of other factors, such as occupational class and life stage (162, 338). Retirement from manual professions has been shown to be associated with declines in physical activity, whereas retirement from non-manual professions has been associated with increases in physical activity (338). Plausibly, men in manual occupations may accumulate physical activity primarily from work-related activities during adulthood. Thus, these men are likely to experience a decline in physical activity upon retirement. The findings of this chapter extend on what has previously been investigated in the literature by examining the impacts of retirement in the context of long-term physical activity trajectories and highlighting possible effect modifiers.

Not only were the effects of retirement modified by trajectory group but also by physical activity type. The increases in total physical activity observed in the more active groups following retirement were largely driven by increases in sport/exercise participation in those who already occasionally or frequently participated. Conversely, retirement was associated with a decrease in sport/exercise in those who rarely participated. Retirement was also associated with an increase in walking in the low, increasing group but no associations were observed in the remaining groups. By contrast, retirement was associated with declines in recreational activity in individuals with the lowest recreational activity trajectories. Studies examining the impact of retirement on other forms of physical activity such as transport and occupational activity have either been inconclusive or suggested a decline following retirement (188). Differences in how specific types of activity have been reported or defined could explain these discrepancies.

5.6.3 Strengths and limitations

A main strength of this study is the large, geographically and socioeconomically representative sample. However, the generalisability to women and non-white ethnic groups is uncertain, given that the sample comprises of men predominantly of white ethnicity. Another key strength is the use of a data-driven approach for identifying physical activity trajectories. GBTM identifies underlying trajectory sub-groups, which could not have been identified using traditional growth curve modelling or by subjectively creating trajectory groups. GBTM also estimates the effects of both time-stable and time-varying variables on physical activity trajectories. Consequently, analyses were able to explore the effects of baseline predictors and of major life and health events occurring during follow up. Although some time-dependent variables were included in the models, some factors that were not recorded at each wave may have had time-varying effects on physical activity that were not captured.

This study is limited by the use of self-reported physical activity, which may be prone to recall bias. However, the questionnaire was validated at baseline against heart rate and FEV_1 and more recently against objectively measured physical activity (272, 274). Individual questionnaire items also correlated well with objective measures. Self-reported physical activity could also be viewed as a strength as it provides contextual information, allowing for the trajectories of specific physical activity types to be explored. To my knowledge, this is the first study to apply GBTM for identifying trajectories of specific types of activity and explore their associations with a range of predictors and major life and health events. A limitation of the physical activity type variables is that they were categorised into three simple categories. More continuous variables representing time spent in each physical activity type would have been better to capture minor fluctuations in behaviour.

Using the same questionnaire across waves also ensured comparability and enabled trajectories of physical activity to be determined. There were, however, some minor changes to the wording of the walking question at the final follow up, which may have biased walking estimates. Sensitivity analyses removing this time point revealed similar walking trajectories. In addition, it is possible that walking may have been underestimated in those men who reported walking/hiking as a frequent sport/exercise as this was not included as a sport/exercise nor was it possible to add it to the walking estimate.

Although the 20-year trajectories capture a significant portion of the lifespan, important fluctuations in physical activity may have been overlooked during the 12-year interval between baseline and the next follow up assessment. Other important periods prior to midlife may be

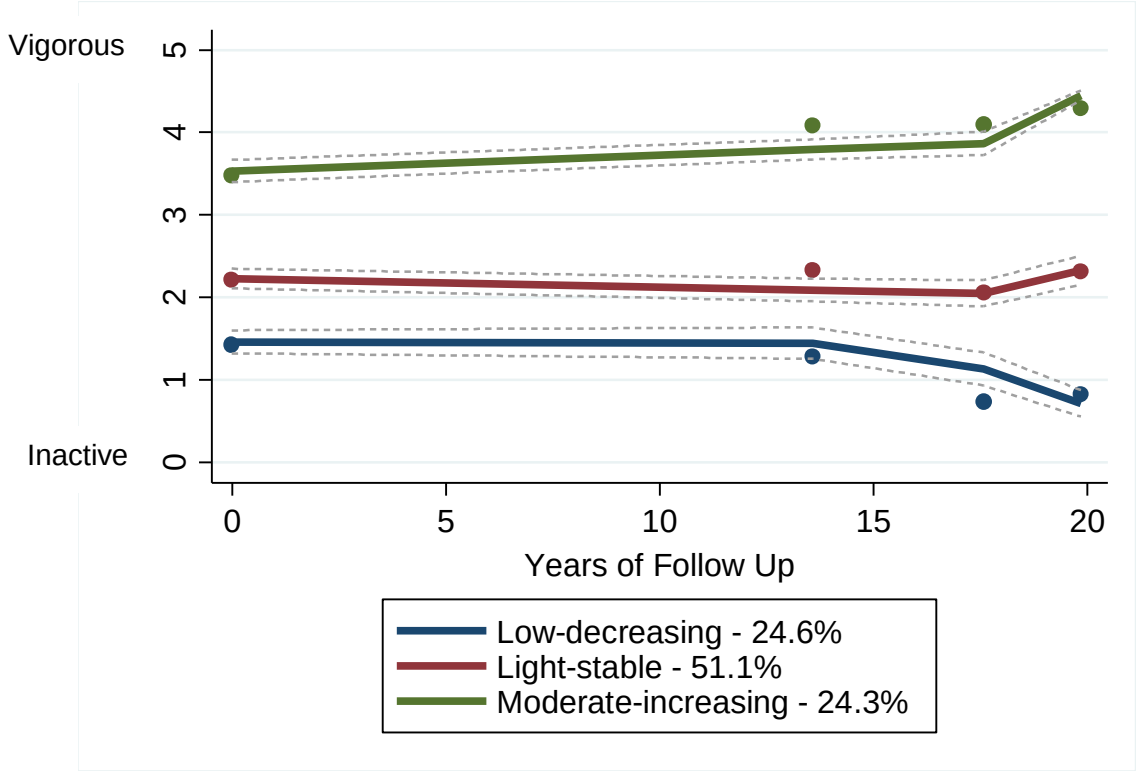
critical for determining lifelong physical activity but were not captured in this study. Physical activity accumulated during childhood and early adulthood may be associated with risk of chronic conditions in midlife so reverse causality is also possible.

There is also the possibility that subject attrition may have biased the estimated trajectories. An important benefit of GBTM is that it incorporates the maximum likelihood method, which utilises all available data to estimate parameters and standard errors, under the assumption that missingness is at random. Sensitivity analyses revealed that the main analyses including men with ≥3 physical activity measures underestimated the proportion of men who followed the least favourable trajectories, highlighting that men with less physical activity data or who were lost to follow up were less active than men with more complete data. However, the number of trajectories and trajectory shapes were similar when men with ≥1 time point were included.

5.6.4 Conclusion

Distinct trajectories of total physical activity, sport/exercise, recreational activity and walking were identified, suggesting that trajectories are specific to type. Trajectories of total physical activity and sport/exercise into old age were largely determined by engagement in midlife, whereas walking and recreational activity were more variable. More than two thirds of men increased time spent walking during the transition to old age, while almost half of men decreased time spent in recreational activities. There were some common predictors of total and physical activity type trajectories, including smoking behaviour, overweight and obesity and breathlessness. The impact of other sociodemographic, health and behavioural factors was specific to type. Retirement and CVD diagnosis are important life events that initiated changes in physical activity behaviour. The impact of retirement and CVD onset are modified by prior physical activity behaviours and by physical activity types. The total physical activity trajectory groups will be used throughout the remainder of this thesis, and the next chapter will explore their associations with CVD risk factors.

Figure 5.1. Physical activity trajectories and 95% CIs from midlife to old age



Analytic sample consisted of 4952 participants

Table 5.1. Participant characteristics at baseline and subsequent follow ups across trajectory groups, mean (SD) or percentage

	Low, decreasing (n=1218)				Light stable (n=2530)				Moderate, increasing (n=1204)			
	1978/80	1992	1996	2000	1978/80	1992	1996	2000	1978/80	1992	1996	2000
Time-stable												
Age (mean ± SD)	50.4 (5.6)				49.0 (5.6)				48.2 (5.3)			
Manual occupation (%, n)	62.7 (764)				57.6 (1457)				38.8 (467)			
Children ≥ 1 at baseline (%, n)	62.9 (766)				71.7 (1815)				73.2 (881)			
Resident in South of England at baseline (%, n)	24.0 (292)				36.1 (913)				34.8 (419)			
Overweight/obese at baseline (%, n)	60.1 (732)				52.9 (1339)				48.1 (579)			
Married/previously married at baseline (%, n)	94.8 (1154)				96.4 (2438)				97.6 (1175)			
Chest pain at baseline (%, n)	8.7 (106)				4.6 (115)				3.2 (39)			
Breathlessness at baseline (%, n)	9.9 (120)				2.2 (55)				0.7 (8)			
Arthritis at baseline (%, n)	13.9 (169)				7.4 (187)				6.6 (79)			
High blood pressure at baseline (%, n)	14.7 (179)				9.1 (229)				8.4 (101)			
Bronchitis at baseline (%, n)	22.2 (270)				13.6 (345)				10.6 (128)			

	Low, decreasing (n=1218)				Light stable (n=2530)				Moderate, increasing (n=1204)			
	1978/80	**1992**	**1996**	**2000**	**1978/80**	**1992**	**1996**	**2000**	**1978/80**	**1992**	**1996**	**2000**
Breakfast cereal consumption ≥2/week at baseline (%, n)	34.7 (423)				53.5 (1354)				58.5 (704)			
Alcohol consumption (≥light[a]) (%, n)	68.1 (829)				68.5 (1734)				77.3 (931)			
Current smokers (%, n)	54.1 (659)				30.0 (760)				22.9 (276)			
Time-varying												
Valid physical activity score[b] (n)	1204	1150	1126	849	2512	2434	2391	2034	1202	1168	1146	1042
≥Light Activity[c] (%, n)	34.6 (417)	26.6 (306)	7.1 (80)	8.4 (71)	66.0 (1659)	74.2 (1806)	65.1 (1557)	72.5 (1475)	90.1 (1083)	98.1 (1146)	98.3 (1127)	98.9 (1030)
High sport participation[d] (%, n)	17.8 (217)	7.5 (87)	4.4 (51)	5.5 (47)	40.1 (1014)	33.4 (814)	32.3 (765)	41.3 (844)	80.1 (964)	92.2 (1090)	93.7 (1089)	94.9 (989)
High recreational activity[e] (%, n)	36.0 (437)	26.7 (315)	7.6 (87)	6.5 (55)	58.0 (1465)	61.4 (1517)	39.5 (949)	39.0 (799)	66.1 (796)	74.5 (880)	61.5 (707)	63.4 (663)
High walking[f] (%, n)	19.4 (234)	32.6 (376)	22.1 (259)	31.9 (276)	29.9 (752)	56.6 (1377)	56.0 (1373)	67.5 (1392)	29.3 (353)	59.7 (688)	58.6 (686)	73.0 (766)
Not in employment† (%, n)	6.5 (79)	71.6 (836)	83.9 (985)	88.2 (751)	2.9 (73)	56.5 (1390)	71.8 (1748)	81.2 (1656)	1.6 (19)	52.0 (611)	69.0 (806)	79.1 (828)
CVD conditions ≥1† (%, n)	5.3 (64)	23.4 (256)	28.5 (334)	32.1 (276)	2.6 (66)	15.5 (366)	19.4 (473)	22.4 (457)	2.5 (30)	12.1 (139)	15.8 (184)	18.6 (194)

Analytic sample consisted of 4952 participants, including 17710 repeated measurements

[a]light classified as ≥1 unit per week

[b] men with a complete physical activity score at each follow up

[c]men classified as having at least light physical activity (scoring ≥2)

[d] high sport was classified as reporting at least occasional participation (less than once a month)

[e] high recreational activity was classified as >4hours/weekend on recreational activities

[f] high walking was classified as >20 mins/day

†total number with complete data on employment, CVD conditions and on physical activity types differs to that of the total number with complete physical activity questionnaire data at each follow up

Table 5.2. Time-stable predictors of trajectory class membership

	Light Stable vs. Low, decreasing[a]	Moderate, increasing vs. Low, decreasing[a]
	OR (95% CI)[b]	OR (95% CI)[b]
Socio-demographic factors		
Baseline age (per year increase)	**0.97 (0.95, 0.98)**	**0.94 (0.92, 0.96)**
Occupational class		
Manual (ref. non-manual)	1.10 (0.88, 1.37)	**0.60 (0.48, 0.74)**
Marital status		
Married (ref. single)	1.41 (0.84, 2.39)	**2.14 (1.22, 3.75)**
Widowed/Divorced (ref. single)	1.98 (0.96, 4.08)	**2.58 (1.20, 5.55)**
Number of children		
≥1 child (ref. no children)	**1.42 (1.13, 1.78)**	**1.45 (1.15, 1.81)**
Region		

	Light Stable vs. Low, decreasing[a]	Moderate, increasing vs. Low, decreasing[a]
	OR (95% CI)[b]	OR (95% CI)[b]
Midlands (ref. south)	**0.67 (0.49, 0.92)**	**0.68 (0.49, 0.94)**
North (ref. south)	**0.71 (0.55, 0.91)**	**0.70 (0.55, 0.90)**
Scotland (ref. south)	0.71 (0.49, 1.04)	1.25 (0.88, 1.78)
Health and Lifestyle Factors		
Overweight/Obese (ref. healthy BMI)	**0.79 (0.64, 0.98)**	**0.66 (0.54, 0.81)**
Arthritis (ref. no arthritis)	**0.60 (0.44, 0.83)**	**0.54 (0.38, 0.76)**
Bronchitis (ref. no bronchitis)	**0.74 (0.57, 0.97)**	**0.62 (0.47, 0.82)**
High blood pressure (ref. normal blood pressure)	**0.71 (0.52, 0.97)**	**0.67 (0.48, 0.92)**

	Light Stable vs. Low, decreasing[a]	**Moderate, increasing vs. Low, decreasing[a]**
	OR (95% CI)[b]	OR (95% CI)[b]
Suffers breathlessness (ref. no breathlessness)	**0.30 (0.19, 0.48)**	**0.14 (0.06, 0.29)**
Suffers chest pain (ref. no chest pain)	0.74 (0.48, 1.13)	0.64 (0.40, 1.02)
Current/ex-smoker (ref. non-smoker)	**0.42 (0.34, 0.52)**	**0.31 (0.24, 0.39)**
Alcohol consumption		
Occasional (ref. none)	1.29 (0.83, 2.02)	1.47 (0.89, 2.43)
Light (ref. none)	1.50 (0.96, 2.35)	**2.73 (1.67, 4.45)**
Moderate (ref. none)	1.27 (0.81, 1.99)	**2.15 (1.31, 3.53)**
Heavy (ref. none)	1.55 (0.92, 2.61)	**2.30 (1.30, 4.07)**
Dietary habits		
Occasional breakfast cereal (ref. none)	**2.13 (1.49, 3.05)**	**2.13 (1.50, 3.03)**

	Light Stable vs. Low, decreasing[a]	Moderate, increasing vs. Low, decreasing[a]
	OR (95% CI)[b]	OR (95% CI)[b]
Regular breakfast cereal (ref. none)	**1.57 (1.25, 1.98)**	**1.66 (1.32, 2.08)**

Analytic sample consisted of 4952 participants

[a]Low, decreasing (reference group). [b]Models adjusted for employment status and number of CVD diagnoses as time-varying covariates, and occupational class, marital status, number of children, region, BMI, arthritis, bronchitis, blood pressure, breathlessness, chest pain, smoking status, alcohol consumption and breakfast consumption at baseline. Bold indicates statistical significance ($p<0.05$).

Table 5.3. Trajectories of physical activity and the effects of time-varying predictors on trajectory shapes, by trajectory group[a]

	Parameter[b]	Estimate	SE	p value
Low, decreasing				
	Intercept	1.362	0.052	<0.001
	Linear	0.073	0.015	<0.001
	Quadratic	-0.006	0.001	<0.001
	Time-varying covariates			
	Not employed	-0.306	0.077	<0.001
	N. of CVD diagnoses	-0.408	0.050	<0.001
Light Stable				
	Intercept	2.212	0.042	<0.001
	Linear	-0.011	0.003	<0.001
	Time-varying covariates			
	Not employed	0.324	0.050	<0.001

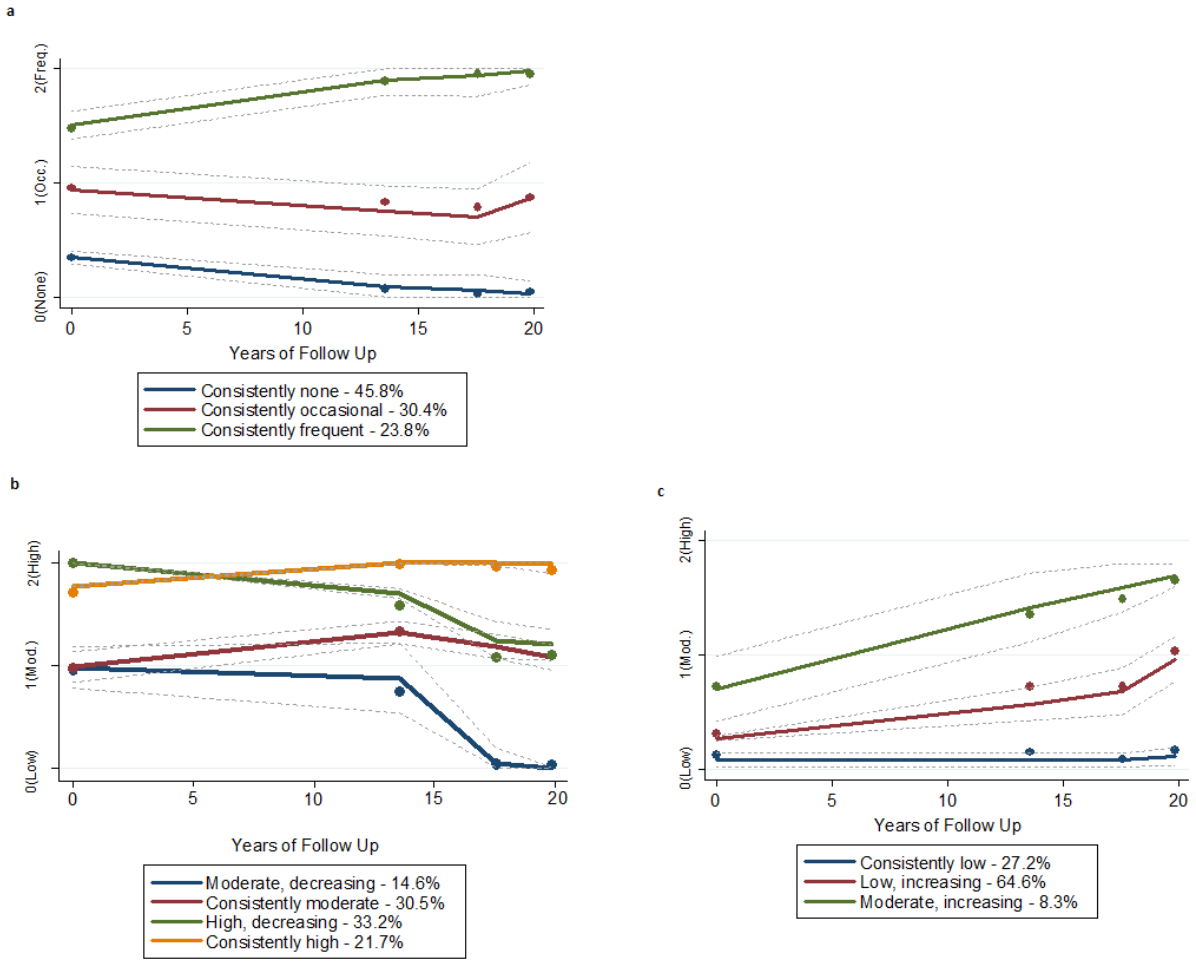
	Parameter[b]	Estimate	SE	p value
	N. of CVD diagnoses	-0.118	0.042	0.005
Moderate, increasing				
	Intercept	3.631	0.050	<0.001
	Linear	0.024	0.004	<0.001
	Time-varying covariates			
	Not employed	0.847	0.065	<0.001
	N. of CVD diagnoses	-0.060	0.060	0.313

Analytic sample consisted of 4952 participants

[a]Estimates for time-varying covariates represent the shift in physical activity trajectory per unit change in exposure variable.

[b]Models adjusted for employment status and number of CVD diagnoses as time-varying covariates, and occupational class, marital status, number of children, region, BMI, arthritis, bronchitis, blood pressure, breathlessness, chest pain, smoking status, alcohol consumption and breakfast consumption at baseline

Figure 5.2. Trajectories and 95% CIs for (a) sport participation (b) recreational activity (c) walking from midlife to old age



Analytic samples consisted of 5116 participants for sport/exercise, 5085 for recreational activity and 5106 for walking

Table 5.4. Time-stable predictors of sport/exercise participation trajectory classes

	Consistently occasional vs. Consistently none[a]	Consistently frequent vs. Consistently none[a]
	OR (95% CI)[b]	OR (95% CI)[b]
Sociodemographics		
Baseline age (per year increase)	**0.92 (0.90, 0.94)**	**0.94 (0.92, 0.95)**
Occupational class		
Manual (ref. non-manual)	**0.64 (0.53, 0.77)**	**0.48 (0.41, 0.57)**
Marital status		
Married (ref. single)	**2.18 (1.32, 3.60)**	**2.37 (1.42, 3.96)**
Widowed/Divorced (ref. single)	**3.58 (1.86, 6.89)**	**2.40 (1.20, 4.82)**
Number of children		
≥1 child (ref. no children)	1.15 (0.94, 1.40)	**1.24 (1.03, 1.51)**
Region		
Midlands (ref. south)	**0.67 (0.51, 0.89)**	0.78 (0.60, 1.01)
North (ref. south)	0.84 (0.65, 1.03)	0.84 (0.69, 1.02)
Scotland (ref. south)	1.06 (0.77, 1.46)	**1.64 (1.24, 2.18)**
Health and Lifestyle Factors		
Overweight/Obese (ref. healthy BMI)	1.11 (0.93, 1.33)	**0.80 (0.67, 0.94)**

	Consistently occasional vs. Consistently none[a]	Consistently frequent vs. Consistently none[a]
	OR (95% CI)[b]	**OR (95% CI)[b]**
Arthritis (ref. no arthritis)	1.05 (0.78, 1.42)	0.77 (0.56, 1.06)
Bronchitis (ref. no bronchitis)	0.84 (0.65, 1.07)	0.82 (0.64, 1.04)
High blood pressure (ref. normal blood pressure)	**0.71 (0.52, 0.96)**	0.83 (0.64, 1.04)
Suffers breathlessness (ref. no breathlessness)	**0.58 (0.36, 0.94)**	**0.24 (0.12, 0.48)**
Suffers chest pain (ref. no chest pain)	0.81 (0.53, 1.23)	0.82 (0.54, 1.25)
Current/ex-smoker (ref. non-smoker)	**0.59 (0.49, 0.72)**	**0.46 (0.38, 0.55)**
Alcohol consumption		
Occasional (ref. none)	1.36 (0.90, 2.04)	1.51 (0.95, 2.40)
Light (ref. none)	**1.53 (1.02, 2.28)**	**3.03 (1.94, 4.73)**
Moderate (ref. none)	1.38 (0.91, 2.08)	**2.61 (1.66, 4.12)**
Heavy (ref. none)	1.49 (0.93, 2.38)	**2.50 (1.50, 4.17)**
Dietary habits		
Occasional breakfast cereal (ref. none)	**1.42 (1.07, 1.88)**	**1.62 (1.25, 2.09)**
Regular breakfast cereal (ref. none)	**1.43 (1.17, 1.75)**	**1.55 (1.29, 1.88)**

Analytic sample consisted of 5116 participants

[a] Consistently none (reference group)

[b] Models adjusted for employment status and number of CVD diagnoses as time-varying covariates, and occupational class, marital status, number of children, region, BMI, arthritis, bronchitis, blood pressure, breathlessness, chest pain, smoking status, alcohol consumption and breakfast consumption at baseline. Bold indicates statistical significance ($p<0.05$).

Table 5.5. Trajectories of physical activity types across age and the effects of time-varying predictors on trajectory shapes, by trajectory group[a]

	Sports trajectories (n=5116)			Recreational activity trajectories (n=5085)			Walking trajectories (n=5106)		
Parameter[b]	**Estimate**	**SE**	**p**	**Estimate**	**SE**	**p**	**Estimate**	**SE**	**p**
	Consistently none			**Moderate, decreasing**			**Consistently low**		
Intercept	-3.306	0.208	<0.001	0.967	0.069	<0.001	-1.802	0.107	<0.001
Linear	-0.251	0.033	<0.001	0.488	0.050	<0.001	-	-	-
Quadratic	-	-	-	-0.037	0.004	<0.001	-	-	-
Time-varying covariates									
Leaving employment	-0.940	0.465	<0.05	-0.342	0.130	<0.05	0.234	0.148	0.115
N. of CVD diagnoses	-1.283	0.544	<0.05	-0.325	0.093	<0.001	0.007	0.101	0.946
	Consistently occasional			**Consistently moderate**			**Low, increasing**		
Intercept	0.645	0.205	0.002	0.972	0.051	<0.001	-0.767	0.060	<0.001
Linear	-0.079	0.016	<0.001	0.125	0.012	<0.001	0.063	0.005	<0.001
Quadratic	-	-	-	-0.006	0.001	<0.001	-	-	-
Time-varying covariates									
Leaving employment	1.179	0.245	<0.001	0.047	0.050	0.350	0.439	0.058	<0.001
N. of CVD diagnoses	-0.045	0.213	0.833	-0.118	0.047	<0.05	-0.017	0.043	0.683
	Consistently frequent			**High, decreasing**			**Moderate, increasing**		

	Sports trajectories (n=5116)			Recreational activity trajectories (n=5085)			Walking trajectories (n=5106)		
Parameter[b]	**Estimate**	**SE**	**p**	**Estimate**	**SE**	**p**	**Estimate**	**SE**	**p**
	Consistently none			**Moderate, decreasing**			**Consistently low**		
Intercept	4.125	0.220	<0.001	14.802	1.474	<0.001	0.386	0.1127	<0.05
Linear	0.318	0.044	<0.001	-1.427	0.178	<0.001	0.109	0.011	<0.001
Quadratic	-	-	-	0.038	0.005	<0.001	-	-	-
Time-varying covariates									
Leaving employment	1.718	0.692	<0.05	-0.057	0.072	0.430	0.085	0.160	0.597
N. of CVD diagnoses	-1.307	0.477	<0.05	-0.718	0.078	<0.001	-0.237	0.137	0.083
				Consistently high					
Intercept	-	-	-	2.658	0.069	<0.001	-	-	-
Linear	-	-	-	0.674	0.166	<0.001	-	-	-
Quadratic	-	-	-	-0.029	0.008	<0.001	-	-	-
Time-varying covariates									
Leaving employment	-	-	-	-0.079	0.373	0.833	-	-	-
N. of CVD diagnoses	-	-	-	-1.192	0.168	<0.001	-	-	-

[a]Estimates for time-varying covariates represent the shift in physical activity trajectory per unit change in exposure variable.

[b]Models adjusted for employment status and number of CVD diagnoses as time-varying covariates, and occupational class, marital status, number of children, region, BMI, arthritis, bronchitis, blood pressure, breathlessness, chest pain, smoking status, alcohol consumption and breakfast consumption at baseline

Table 5.6. Time-stable predictors of recreational activity trajectory classes

	Consistently moderate vs. Moderate, decreasing[a]	High, decreasing vs. Moderate, decreasing[a]	Consistently high vs. Moderate, decreasing[a]
	OR (95% CI)[b]	OR (95% CI) [b]	OR (95% CI) [b]
Sociodemographics			
Baseline age (per year increase)	**0.95 (0.93, 0.97)**	0.98 (0.96, 1.00)	**0.95 (0.92, 0.97)**
Occupational class			
Manual (ref. non-manual)	0.94 (0.75, 1.19)	0.97 (0.76, 1.24)	**0.76 (0.59, 0.97)**
Marital status			
Married (ref. single)	**2.23 (1.30, 3.82)**	1.66 (0.96, 2.86)	**2.94 (1.55, 5.56)**
Widowed/Divorced (ref. single)	1.76 (0.83, 3.71)	1.44 (0.67, 3.10)	**2.95 (1.27, 6.83)**
Number of children			
≥1 child (ref. no children)	1.01 (0.79, 1.29)	1.28 (0.98, 1.66)	1.09 (0.84, 1.43)
Region			
Midlands (ref. south)	0.76 (0.53, 1.08)	**0.68 (0.48, 0.98)**	**0.60 (0.42, 0.87)**
North (ref. south)	0.88 (0.67, 1.17)	**0.64 (0.49, 0.85)**	**0.52 (0.39, 0.70)**
Scotland (ref. south)	0.80 (0.55, 1.16)	**0.53 (0.35, 0.79)**	**0.47 (0.31, 0.71)**
Health and Lifestyle Factors			
Overweight/Obese (ref. healthy BMI)	0.92 (0.74, 1.16)	**0.78 (0.62, 0.99)**	**0.70 (0.55, 0.89)**

	Consistently moderate vs. Moderate, decreasing[a]	High, decreasing vs. Moderate, decreasing[a]	Consistently high vs. Moderate, decreasing[a]
	OR (95% CI)[b]	OR (95% CI)[b]	OR (95% CI)[b]
Arthritis (ref. no arthritis)	**0.65 (0.46, 0.92)**	0.81 (0.57, 1.16)	**0.55 (0.36, 0.83)**
Bronchitis (ref. no bronchitis)	**0.61 (0.46, 0.80)**	**0.62 (0.46, 0.83)**	**0.58 (0.42, 0.79)**
High blood pressure (ref. normal blood pressure)	0.75 (0.54, 1.04)	0.71 (0.49, 1.01)	**0.67 (0.46, 0.98)**
Suffers breathlessness (ref. no breathlessness)	**0.45 (0.29, 0.70)**	**0.14 (0.07, 0.31)**	**0.17 (0.08, 0.36)**
Suffers chest pain (ref. no chest pain)	0.88 (0.57, 1.36)	**0.53 (0.31, 0.90)**	0.63 (0.37, 1.06)
Current/ex-smoker (ref. non-smoker)	**0.43 (0.34, 0.54)**	**0.44 (0.34, 0.56)**	**0.29 (0.22, 0.38)**
Alcohol consumption			
Occasional (ref. none)	1.60 (0.94, 2.70)	1.22 (0.73, 2.05)	1.50 (0.86, 2.61)
Light (ref. none)	**1.79 (1.07, 3.00)**	1.35 (0.81, 2.23)	1.54 (0.89, 2.65)
Moderate (ref. none)	1.58 (0.94, 2.65)	1.05 (0.63, 1.76)	1.22 (0.70, 2.12)
Heavy (ref. none)	1.27 (0.72, 2.24)	0.80 (0.45, 1.43)	1.12 (0.61, 2.08)
Dietary habits			
Occasional breakfast cereal (ref. none)	1.06 (0.73, 1.52)	**1.45 (1.01, 2.09)**	1.16 (0.79, 1.70)

	Consistently moderate vs. Moderate, decreasing[a]	High, decreasing vs. Moderate, decreasing[a]	Consistently high vs. Moderate, decreasing[a]
	OR (95% CI)[b]	**OR (95% CI) [b]**	**OR (95% CI) [b]**
Regular breakfast cereal (ref. none)	1.18 (0.92, 1.52)	1.21 (0.93, 1.57)	1.22 (0.93, 1.60)

Analytic sample consisted of 5085 participants

[a] Moderate, decreasing (reference group)

[b] Models adjusted for employment status and number of CVD diagnoses as time-varying covariates, and occupational class, marital status, number of children, region, BMI, arthritis, bronchitis, blood pressure, breathlessness, chest pain, smoking status, alcohol consumption and breakfast consumption at baseline. Bold indicates statistical significance ($p<0.05$).

Table 5.7. Time-stable predictors of walking trajectory classes

	Low, increasing vs. Consistently low[a]	Moderate, increasing vs. Consistently low[a]
	OR (95% CI)[b]	OR (95% CI)[b]
Sociodemographics		
Baseline age (per year increase)	1.01 (0.99, 1.03)	1.02 (0.99, 1.05)
Occupational class		
Manual (ref. non-manual)	**1.24 (1.02, 1.51)**	**1.90 (1.38, 2.60)**
Marital status		
Married (ref. single)	1.36 (0.75, 2.49)	**0.38 (0.22, 0.67)**
Widowed/Divorced (ref. single)	1.21 (0.57, 2.60)	0.67 (0.32, 1.42)
Number of children		
≥1 child (ref. no children)	**1.28 (1.04, 1.58)**	0.95 (0.69, 1.32)
Region		
Midlands (ref. south)	**0.72 (0.54, 0.95)**	0.94 (0.59, 1.48)
North (ref. south)	0.92 (0.73, 1.14)	1.00 (0.70, 1.44)
Scotland (ref. south)	1.12 (0.78, 1.62)	**2.25 (1.41, 3.57)**
Health and Lifestyle Factors		
Overweight/Obese (ref. healthy BMI)	**0.80 (0.66, 0.97)**	**0.58 (0.43, 0.78)**

	Low, increasing vs. Consistently low[a]	Moderate, increasing vs. Consistently low[a]
	OR (95% CI)[b]	**OR (95% CI)[b]**
Arthritis (ref. no arthritis)	**0.61 (0.44, 0.84)**	0.79 (0.49, 1.27)
Bronchitis (ref. no bronchitis)	1.03 (0.79, 1.35)	1.08 (0.73, 1.61)
High blood pressure (ref. normal blood pressure)	0.88 (0.65, 1.20)	0.78 (0.47, 1.30)
Suffers breathlessness (ref. no breathlessness)	**0.48 (0.30, 0.76)**	**0.25 (0.09, 0.67)**
Suffers chest pain (ref. no chest pain)	1.00 (0.65, 1.54)	1.06 (0.54, 2.09)
Current/ex-smoker (ref. non-smoker)	**0.65 (0.53, 0.80)**	**0.65 (0.48, 0.89)**
Alcohol consumption		
Occasional (ref. none)	0.86 (0.55, 1.35)	1.13 (0.56, 2.30)
Light (ref. none)	1.13 (0.73, 1.75)	0.91 (0.45, 1.86)
Moderate (ref. none)	1.07 (0.68, 1.68)	1.41 (0.70, 2.86)
Heavy (ref. none)	1.37 (0.81, 2.33)	2.03 (0.93, 4.40)
Dietary habits		
Occasional breakfast cereal (ref. none)	1.22 (0.89, 1.67)	**2.01 (1.36, 2.97)**

	Low, increasing vs. Consistently low[a]	Moderate, increasing vs. Consistently low[a]
	OR (95% CI)[b]	**OR (95% CI)[b]**
Regular breakfast cereal (ref. none)	**1.26 (1.02, 1.55)**	0.95 (0.67, 1.34)

Analytic sample consisted of 5106 participants

[a] Consistently low (reference group)

[b] Models adjusted for employment status and number of CVD diagnoses as time-varying covariates, and occupational class, marital status, number of children, region, BMI, arthritis, bronchitis, blood pressure, breathlessness, chest pain, smoking status, alcohol consumption and breakfast consumption at baseline. Bold indicates statistical significance ($p<0.05$).

CHAPTER 6. TRAJECTORIES OF PHYSICAL ACTIVITY FROM MIDLIFE TO OLD AGE AND CARDIOVASCULAR DISEASE RISK FACTORS IN OLD AGE

6.1 Summary

Long-term physical activity patterns are important determinants of CVD risk factors in later life. The majority of studies exploring how changes in physical activity impact CVD risk factors have largely been based on two measurements of physical activity only, and few of these studies have focussed on more novel CVD risk factors. In this chapter, the association between trajectories of physical activity from midlife to old age and established and novel CVD risk factors in old age were examined. At the 20-year follow up, participants, aged 60-79 years, attended a physical examination and provided a fasting blood sample, which was used to derive a range of established and novel CVD biomarkers. Several other physical measurements were taken including waist circumference and lung function. First, trajectories were defined using GBTM, as described in Chapter 5, and then using a more conventional approach based on observed binary physical activity variables. The association between trajectory groups and CVD risk factors were analysed using linear and logistic regression. Compared to those following a low, decreasing trajectory, men who followed light stable and moderate, increasing trajectories had a more favourable cardiometabolic profile and lower levels of inflammation and endothelial dysfunction in old age. Linear trends were observed suggesting added benefit for more active trajectories. Similar associations were observed when trajectories were defined using a more conventional approach. It was evident that current physical activity levels were crucial but that maintenance of an active lifestyle across the adult life course was optimal. Some associations were substantially attenuated but not completely explained by waist circumference, suggesting that they were largely but not totally mediated by adiposity.

6.2 Introduction

The inverse association between physical activity and cardiovascular disease morbidity and mortality is partially explained by a range of established and novel risk factors (205, 214, 255). Numerous prospective studies have shown a dose-response relationship between physical activity and cardiometabolic risk factors. Such studies have consistently shown that higher baseline, increasing and persistently high physical activity levels are favourably associated with adiposity (209-214), lipids (209, 213-215) and diabetes risk markers (209, 216, 217) in later life.

Similar associations have been found between changes in physical activity and markers of inflammation and endothelial dysfunction in old age (119, 214, 231, 232). Much of the evidence linking longitudinal changes in physical activity and these CVD risk factors has been based on two measurements of physical activity only, meaning that important fluctuations in physical activity may have been missed. Emerging evidence has also shown an inverse association between physical activity and cardiac biomarkers (243-245). However, the majority of this evidence is based on experimental studies exploring the acute effects of exercise, and the limited number of observational studies have mainly been cross-sectional (243, 244). A previous investigation in the BRHS cohort exploring the association between changes in physical activity and cardiac markers found that becoming active and persistently higher levels of physical activity were associated with lower levels of NT-proBNP in old age, but this study only captured changes in physical activity across four years of follow up and did not adjust for other CVD risk factors (214).

Very few prospective studies have examined the associations between adult life course physical activity and these CVD risk factors in later life, when the risk of CVD is greatest. Such studies have shown that becoming active and greater accumulation of physical activity across adulthood are associated with more favourable levels of cardiometabolic, inflammatory and endothelial dysfunction biomarkers in old age (119, 221). Elhakeem et al., also showed that physical activity history provided additional information about CVD risk factor variability in old age compared to when just current physical activity was considered (119). None of these studies, however, used a GBTM approach to identify the underlying trajectories of physical activity, which could help understand the levels of physical activity that are required across the life course to reduce CVD risk factors in old age.

Recently, a handful of prospective studies have used GBTM to identify trajectories of physical activity into old age but none to my knowledge have explored associations with CVD risk factors (7, 134-138). Hence, the primary aim of this study was to examine how the total physical activity trajectories identified between midlife and old age via GBTM in Chapter 5 are associated with cardiometabolic, inflammatory, endothelial and cardiac risk factors in old age. As prior diagnosis of CVD or diabetes may have impacted subsequent physical activity trajectories, this chapter focusses on men without pre-existing CVD or diabetes at baseline, so trajectory models were re-run in this 'healthy' subsample. Associations of physical activity trajectories using binary exposure measurements were also explored.

6.3 Objectives

i. To examine the associations between 20-year GBTM-defined trajectories of total physical activity between midlife and old age with cardiometabolic, inflammatory and cardiac markers in old age.
ii. To examine the association between 20-year trajectories of total physical activity between midlife and old age based on observed binary measurements with cardiometabolic, inflammatory and cardiac markers in old age.

6.4 Methods

6.4.1 Subjects and methods of data collection

Data analysed in this chapter include information collected from the baseline, 12-, 16- and 20-year questionnaires and physical measurements, including a fasting blood sample, taken at the 20-year physical examination. Primary analyses were performed on men, aged 60-79 in 2000, without pre-existing CVD or diabetes at baseline, who had self-reported their habitual physical activity on at least three occasions across the four follow up measurements and who had complete covariate and outcome data as outlined below.

6.4.2 Physical activity measures

Habitual physical activity levels were determined using the 6-point total physical activity score, as described in detail in Chapter 3. The six-point score classified men as inactive (minimal activity across all types), occasional (regular walking or recreational activity only, or sporting activity less than once a week only), light (more frequent recreational activities plus sporting activity less than once a week, or regular walking plus some recreational activity), moderate (cycling very frequently only, or very frequent recreational activities plus regular walking, or sporting activity once a week), moderately vigorous (sporting activity 2-4 times a week, or sporting activity once a week plus regular walking/cycling and recreational activity) or vigorous (sporting activity more than 4 times a week, or less frequent sporting activity plus frequent walking/cycling and recreational activities). A binary physical activity variable was also generated classifying men as active (1) if they had at least 'light' activity or inactive (0) for inactive or occasional.

6.4.3 Cardiovascular Disease Biomarkers

At the 20-year follow up, a range of physical measurements and a fasting blood sample were collected as described in Chapter 3. Measurements were obtained for waist circumference, lung function (FEV_1), total cholesterol, HDL, LDL, triglycerides, haemoglobin A1c, factor VIII, plasma levels of tPA, d-dimer, vWF, CRP, IL-6, NT pro-BNP, hs-TnT and blood pressure, which was used to identify hypertensive individuals (systolic blood pressure of ≥160 mmHg or diastolic ≥100 mmHg or use of antihypertensive medication (276)). BMI was derived from height and weight measurements (kg/m^2).

6.4.4 Statistical methods

6.4.4.1 Identifying physical activity trajectory groups

GBTM was used to identify 20-year physical activity trajectories over the four time points in men without stroke, CHD or diabetes at baseline. The optimal number of trajectory groups and trajectory shapes were determined using the same procedures as described in Sections 3.4.5 and 5.4.4. Models were once again simultaneously adjusted for baseline age, occupational class (manual or non-manual), marital status (single, married or widowed/divorced), number of children (0 vs. ≥1), region of residence (Scotland, North, Midlands and South of England), chest pain on exertion (yes/no), breathlessness (yes/no), diagnosed health conditions (arthritis, bronchitis and high blood pressure, [yes/no]), BMI (normal weight or overweight/obese), smoking status (current/recent ex-smokers or non-smokers/long-term ex-smokers), alcohol consumption (none, occasional, light, moderate or heavy) and breakfast cereal consumption (none, occasional or regular) as well as time-varying covariates, measured at each wave, including number of CVD events (including stroke with symptoms lasting >24 hours, heart attack, myocardial infarction, coronary thrombosis or angina) and employment status (part- or full-time employment [0] or not in employment [1]). The descriptive characteristics and levels of CVD biomarkers at 20-year follow up were calculated for each trajectory group. Means and standard deviations were used to describe continuous variables, while proportions were used to summarise categorical data.

Trajectories were also defined using observed binary measurements across three time points (baseline, 12- and 20-year follow up), as described in Chapter 3. At each of the three time points, men were classified as active (1) if they had at least 'light' activity or inactive (0) for inactive or occasional. Men were allocated to one of eight possible trajectories, which are indicated by combinations of zeros and ones (1, active; 0, inactive). These groups represent a range of

possible trajectories, including persistently inactive (0-0-0), persistently active (1-1-1), increasing (0-1-1; 0-0-1), decreasing (1-0-0; 1-1-0) and inconsistent (1-0-1; 0-1-0).

6.4.4.2 Regression analyses

Multiple linear regression was used to estimate the association between physical activity trajectory groups and CVD biomarkers at the 20-year follow up. As many of the men were being treated for high blood pressure at the 20-year follow up, multiple logistic regression was used to estimate the odds of having hypertension (including taking anti-hypertensive medication) according to trajectory group membership. Regression models were adjusted for baseline variables including occupational class and region of residence and a range of factors reported or measured at the 20-year follow up, including current age, smoking status, alcohol consumption, waist circumference (except when waist circumference was the outcome) and use of lipid-lowering and anti-hypertensive medication (except when hypertension was the outcome). Models for tPA, d-dimer, vWF and Factor VIII were also adjusted for warfarin. Visual inspection of the distributions of insulin, haemoglobin A1c, IL-6, CRP, d-dimer, NT pro-BNP, Hs-TnT and glucose revealed that all these variables were positively skewed and were therefore log transformed. Regression analyses were conducted using the GBTM trajectory groups and the groupings based on the binary exposure measurements separately. Reference categories were the low, decreasing and persistently active (1-1-1) groups, respectively. Linear trends across trajectory groups were determined by fitting the trajectory group variables continuously in regression models.

Further, previous studies examining the associations between life course physical activity and subsequent CVD risk factors and other outcomes have tried to establish whether the consideration of physical activity trajectories/history provides additional clinically important information over and above what current measures of physical activity do (119, 135). To test this, models with just the current (20-year follow up) physical activity score were compared to models including the current physical activity score and the GBTM trajectory grouping variable using likelihood ratio tests. Results from regression models are also presented after adjustment for current physical activity.

6.4.4.3 Sensitivity analyses

It is possible that physical activity trajectories into old age were determined by underlying sub-clinical CVD or diabetes in midlife. To reduce the effects of this reverse causation, whereby individuals with higher but sub-clinical levels of CVD risk factors at baseline were already

predisposed to follow less active trajectories, regression models were refitted excluding men without CVD or diabetes at baseline but who went on to develop either of these conditions by the 20-year follow up.

Further, as adiposity is hypothesised to be an important mediator in the relationship between physical activity and CVD risk factors, models with and without adjustment for waist circumference were compared.

Lastly, to account for the uncertainty of trajectory group classification, regression models were refitted after applying the posterior probabilities of trajectory group membership as survey weights, giving more weight to individuals with a higher probability of belonging to a particular group and less weight to those with more uncertainty.

6.5 Results

Among the 7,735 men who were recruited at baseline, men with <3 physical activity measurements (n=2,752) or a baseline diagnosis of stroke (n=52), CHD (n=292) or diabetes (n=156) were excluded. An additional 1,465 men were excluded due to incomplete biomarker and covariate data, leaving a final sample of 3,331 men. As expected, the final sample were more active at baseline (mean physical activity score: 1.9 ± 1.3 vs. 2.4 ± 1.4, p<0.001), more likely to come from non-manual occupations (28.6% vs. 47.6%, p<0.001), be younger (52.4 vs. 48.7 years, p<0.001) and healthier (e.g. suffering from breathlessness: 12.2% vs. 2.8%, P<0.001) than those who were excluded.

6.5.1 Trajectories of physical activity

As in Chapter 5, a three-group model provided the best fit for the data. The trajectory shapes and sizes were also comparable with the results of Chapter 5, comprising of low, decreasing (21.3%), light stable (51.8%) and moderate, increasing (27.0%) trajectory groups (see figure 6.1). Results from the model selection process are also provided in appendices 6A and 6B. A similar dose-response relationship was observed across trajectory groups as shown in Chapter 5, with men in the low, decreasing trajectory groups typically being older, more likely to come from manual occupations, smoke, come from regions other than the South of England, suffer from a range of health conditions and have higher levels of cardiometabolic, inflammatory and cardiac biomarkers, see table 6.1. Using observed binary measurements of physical activity to determine trajectories, 44% (n=1345) of men were classified as persistently active (1-1-1) and 10% as persistently inactive (0-0-0), while membership of other groups ranged from 5-13%.

6.5.2 Physical activity trajectories and CVD risk factors

6.5.2.1 Associations with GBTM-derived trajectories

The association between GBTM-derived 20-year physical activity trajectories and CVD biomarkers at the 20-year follow up are shown in Table 6.2. More active trajectories were associated with more favourable levels of CVD biomarkers. Specifically, belonging to the light stable and moderate, increasing groups was associated with lower levels of insulin, glycated haemoglobin, blood glucose, inflammatory markers (IL-6 and CRP), hemostatic factors (vWF, Factor VIII, tPA and d-dimer), a smaller waist circumference, higher lung function and reduced odds of hypertension at the 20-year follow up. Belonging to the moderate, increasing group was also associated with lower triglyceride levels when compared to the low, decreasing group. In addition, belonging to the light stable group was associated with lower levels of cardiac marker Hs-TnT in comparison to the low, decreasing group. For all biomarkers except the cardiac biomarkers and total, LDL and HDL cholesterol, significant linear trends were observed across groups indicating additional benefits for more active trajectories. Indeed, the magnitude of associations were typically strongest for the moderate, increasing group.

6.5.2.2 Model comparison

Results from likelihood ratio tests comparing models with a single measurement of current physical activity in old age to models also including the GBTM-derived trajectory grouping variable are presented in Appendix 6C. Compared to models that just included the current measure of physical activity, adding the GBTM-derived trajectory improved model fit for most markers. Specifically, improved model fit was observed for triglycerides, glucose, insulin, waist circumference, glycated haemoglobin, FEV_1, Factor VIII, tPA, CRP and hs-TnT. Inclusion of the current physical activity score in the models markedly attenuated the association between trajectories of physical activity and several CVD biomarkers, as shown in Table 6.3. The greatest reductions were observed for IL-6, CRP, vWF, tPA and d-dimer. Associations with several metabolic markers were only marginally attenuated, although associations were attenuated to non-significance for insulin and hypertension.

6.5.2.3 Associations with observed binary trajectories

The associations between trajectories of physical activity defined using observed binary measurements across three time points and CVD biomarkers are presented in table 6.4. Men who were persistently active (1-1-1) across follow up had the most optimal CVD biomarker

profile, while persistent inactivity (0-0-0) had the least favourable. Compared to men who were persistently active, those who were active by the final follow up but not persistently active (i.e. those who became active [0-0-1; 0-1-1] or who were inconsistently active[(1-0-1]) had similar levels of all inflammatory, hemostatic and cardiac biomarkers and some metabolic markers. However, compared to men who were persistently active, those who became active by the 12-year follow up (0-1-1) had significantly higher triglyceride levels. Further, men who were inconsistently active (1-0-1) had higher levels of insulin and higher odds of hypertension, and men who became active by the 20-year follow up (0-0-1) had a larger waist circumference. Those who were persistently inactive, had become inactive (1-0-0; 1-1-0) and were inconsistently inactive (0-1-0) had higher levels of inflammation and markers of endothelial dysfunction than those who were persistently active. For those who had become inactive by the 20-year follow up (1-1-0), most metabolic markers were comparable with those who were persistently active, but they had higher odds of hypertension and lower levels of lung function. Associations with metabolic markers were progressively more unfavourable and more consistent for trajectories with more persistent inactivity.

6.5.3 Sensitivity analyses

To examine the mediating role of adiposity in these associations, models with and without adjustment for waist circumference were compared. Appendix 6D presents associations before adjusting for waist circumference. Although most associations persisted, many were substantially attenuated after adjusting for adiposity, as shown in Table 6.2. Notably, positive associations between more active trajectories and HDL were attenuated to non-significance after adjusting for waist circumference. Estimates were also attenuated after excluding men with stroke, CHD and diabetes at the 20-year follow up, but associations with insulin, lung function, waist circumference, IL-6, CRP, tPA and Hs-TnT persisted (see Appendix 6E). Associations were also unchanged when analyses were weighted according to trajectory group posterior probabilities.

6.6 Discussion

6.6.1 Summary of main findings

This chapter aimed to examine the association between trajectories of total physical activity between midlife and old age and established and novel CVD risk factors in old age. As in Chapter 5, three GBTM-derived trajectories were identified including low, decreasing, light stable and

moderate, increasing groups. Regression analyses revealed dose-response relationships, with more active trajectories associated with more favourable levels of CVD biomarkers. Specifically, membership of the light stable and moderate, increasing groups was associated with a more favourable cardiometabolic profile and lower levels of inflammation and endothelial dysfunction when compared to the low, decreasing group. Although following a moderate, increasing trajectory was most favourable, more modest but sustained doses of physical activity into old age may be sufficient to lower CVD risk factors. Similar associations were observed when trajectories were defined using observed binary measurements. Current physical activity levels were crucial but being persistently active proved to be optimal, particularly in relation to cardiometabolic risk factors.

6.6.2 Comparison with previous studies

To my knowledge this is the first study to explore associations between trajectories of physical activity identified using GBTM and CVD risk factors in old age. Given the novelty of using GBTM-derived trajectories of physical activity to explore associations with CVD risk factors, the findings with GBTM trajectories are not directly comparable with previous studies using more conventional approaches to classify long-term patterns of physical activity. Most previous studies exploring these associations classify physical activity patterns using a clinically meaningful cut point across two time points only (209, 214, 218, 231, 232), typically resulting in groups defined as active or inactive at both time points or with increasing or decreasing activity levels (214, 218, 231, 232). Nevertheless, some of the findings from these studies are consistent with the results presented in this chapter. For example, the finding that the moderate, increasing physical activity trajectory was associated with the most optimal CVD biomarker profile is consistent with studies that show that individuals who remain active typically have the most favourable CVD biomarker profile, including a better lipid profile and glucose tolerance, lower levels of inflammatory and hemostatic markers and NT-proBNP (119, 214, 218, 231).

Some studies suggest that those who increase their activity levels or become active have similar levels of CVD risk factors as those who remain active (119, 209, 214, 218, 230, 231). Using a GBTM approach, subjects making a clear switch from an ‘inactive’ to an ‘active’ level of physical activity and vice versa were not identified in this sample. However, similar findings were observed in this chapter when a more conventional approach for defining physical activity trajectories was used via a binary physical activity variable, with levels of CVD risk factors in those who followed increasing patterns approaching the levels of those who were persistently active.

This study is the first to my knowledge to explore associations between long-term patterns of physical activity and cardiac markers. In this chapter, a light stable trajectory was associated with lower levels of Hs-TnT trajectories when compared to the low, decreasing group, but no associations were observed with NT-proBNP. When using more conventional trajectory groupings, compared to those who were persistently active, decreasing patterns were associated with higher levels of NT-proBNP. These findings are consistent with a previous study in this cohort showing that remaining active over four years of follow up was associated with the lowest levels of NT-proBNP, while individuals who became inactive had the highest (215).

Additonal analyses suggested that although current physical activity explained a large proportion of these associations, past physical activity levels were also important, particularly for metabolic markers. That is to say there are added benefits for maintaining higher levels of physical activity for extended periods of the life course. Previous studies exploring these associations utilising more than two physical activity measurements are scarce but they also suggest that physical activity has cumulative benefits on inflammatory and endothelial markers (119, 230). Given this finding, future studies exploring these associations should consider past physical activity as well as current levels. From a clinical perspective, measuring physical activity at a single time point may not be sufficient for predicting or understanding CVD risk factor levels.

By modelling the physical activity variable continuously using GBTM, the present study extends on previous evidence by highlighting how different volumes of activity across the life course are associated with CVD markers. Indeed, it was found that persistent light volumes of activity into old age are sufficient to induce benefit. Given that most previous studies use a binary variable to define a person as active or inactive across follow up and there are large discrepancies in the cut offs used to define a person as active, the amount of physical activity required across the life course to achieve benefit has been unclear. Hamer et al., used adherence to the physical activity guidelines (i.e. ≥150 minutes/week of moderate-to-vigourous physical activity) to define a person as active and showed that sometimes or persistently meeting these guidelines was associated with lower levels of inflammatory markers when compared to those who never met these guidelines (230), while Jefferis et al., used a less stringent cut off in the BRHS cohort at different time points to the present analyses but showed similar findings (214).

Many of the observed associations were substantially attenuated by adiposity. Adjusting for waist circumference explained the observed associations between GBTM trajectories and HDL. Associations with triglycerides and insulin were also markedly attenuated, but not completely explained, by waist circumference, while other metabolic markers were only partially explained

by waist circumference. This is consistent with previous studies suggesting that adiposity is an important pathway mediating the relationship between physical activity and cardiometabolic markers but that associations typically persist after controlling for adiposity (119, 200, 201, 223). Similarly, associations with inflammatory, hemostatic and cardiac markers were partially attenuated but persisted after adjusting for waist circumference. This is comparable with other studies that have shown that adiposity mediates but does not completely explain the associations between physical activity and these novel CVD risk factors (119, 230, 231, 245), suggesting that other pathways are involved. Even though physical activity may reduce the accumulation of body fat across the life course, being overweight or obese may also prevent physical activity (118, 157, 167), and so waist circumference may also confound as well as mediate associations between physical activity and CVD risk factors.

6.6.3 Strengths and limitations

The key strengths of this study are that the data are drawn from a moderately large representative sample of British men with high follow up rates and that a wide range of established and novel CVD risk factors were measured. However, as the study includes only men predominantly of white ethnicity, findings may not be generalisable to women and non-white ethnic groups.

Another major strength is the data-driven approach to identify trajectories, giving more precise estimations of the associations between long-term patterns of physical activity and CVD risk factors in old age, and in the process identifying optimal and sub-optimal patterns of physical activity across the adult life course. GBTM-derived trajectories also incorporated time-stable and time-varying covariates in the modelling process, giving a more accurate representation of trajectory shapes. Another strength is the added use of more conventional methods to identify trajectories, providing additional insights into sensitive periods.

Although the physical activity score has been validated against heart rate, FEV_1 and device-measured physical activity (272, 274), self-reported physical activity may still be prone to recall bias. In addition, device-measured physical activity may have provided more accurate estimates of the volume of activity required across the life course to achieve benefit (339). Further, it is possible that CVD risk factors and sub-clinical levels of CVD at baseline may have already had a detrimental impact on physical activity trajectories and thus reverse causality is possible. Indeed, CVD biomarkers measured at baseline were not comparable with measurements at the 20-year follow up and so it was not possible to explore changes in CVD risk factors. Lastly, subject attrition may have biased estimates as those who dropped out of the study were generally less

healthy and active at baseline. Nevertheless, these trajectories were comparable when men with less complete physical activity data were included in the models, as shown in Chapter 5.

6.6.4 Conclusion

Trajectories of physical activity from midlife to old age were associated with established and novel CVD risk factors. GBTM-derived trajectories showed that following a moderate, increasing pattern was associated with the most favourable CVD risk factor profile in old age, including a better metabolic profile and lower levels of inflammation, endothelial dysfunction and hs-TnT. A light stable trajectory was associated with CVD risk factor levels approaching that of the moderate, increasing pattern, suggesting that fairly modest but sustained volumes of physical activity across the adult life course may be sufficient to reduce CVD risk factors in old age. Although it became apparent that current physical activity levels in old age drove the majority of these associations, physical activity history proved to be important for most CVD risk factors, particularly for metabolic markers. Associations were largely mediated but not completely explained by adiposity, suggesting other pathways are involved. The next chapter will explore how these trajectories are associated with CVD and mortality and examine the mediating role of these CVD risk factors.

Table 6.1. Characteristics of 3,331 men at 20-year follow up, by physical activity trajectory group (%, n or mean ± SD)

Characteristic	Low, decreasing (n=708)				Light Stable (n=1725)				Moderate, increasing (n=898)				Total (n=3,331)			
	No.	%	Mean (SD)	Median (IQR)	No.	%	Mean (SD)	Median (IQR)	No.	%	Mean (SD)	Median (IQR)	No.	%	Mean (SD)	Median (IQR)
Age			69.4 (5.7)				68.5 (5.5)				67.7 (5.1)				68.5 (5.5)	
Manual Occupational Class	428	60.5			966	56.0			350	39.0			1744	52.4		
Current/recent ex-smoker	276	39.0			395	22.9			158	17.6			829	24.9		
≥ mod. alcohol consumption[a]	129	18.2			340	19.7			172	19.2			641	19.2		
Resident in south England	189	26.7			608	35.3			339	37.8			1136	34.1		
Taking antihypertensive medication	298	42.1			520	30.1			215	23.9			1033	31.0		
Taking lipid-lowering medication	54	7.6			113	6.6			63	7.0			230	6.9		
Taking warfarin	26	3.7			50	2.9			18	2.0			94	2.8		
HDL , mmol/L			1.3 (0.3)				1.3 (0.3)				1.4 (0.3)				1.3 (0.3)	
LDL, mmol/L			3.8 (1.0)				4.0 (1.0)				3.9 (0.9)				3.9 (1.0)	
Total cholesterol, mmol/L,			5.9 (1.0)				6.0 (1.1)				6.0 (1.1)				6.0 (1.1)	
Triglycerides, mmol/L				1.7 (1.2)				1.6 (1.0)				1.5 (1.0)				1.6 (1.0)
Glucose, mmol/L				1.7 (0.2)				1.7 (0.1)				1.7 (0.1)				1.7 (0.2)
Insulin, µ/mL				9.6 (8.0)				8.1 (6.0)				7.5 (5.3)				

Characteristic	Low, decreasing (n=708)				Light Stable (n=1725)				Moderate, increasing (n=898)				Total (n=3,331)			
	No.	%	Mean (SD)	Median (IQR)	No.	%	Mean (SD)	Median (IQR)	No.	%	Mean (SD)	Median (IQR)	No.	%	Mean (SD)	Median (IQR)
																8.2 (6.4)
HbA1C, mmol/L				5.0 (0.8)				4.8 (0.7)				4.8 (0.7)				4.8 (0.8)
Hypertension[b]	424	59.9			865	50.1			401	44.7			1690	50.7		
FEV_1, L[c]			234.5 (67.4)				260.2 (63.4)				276.5 (61.1)				259.1 (65.3)	
Waist Circumference, cm			99.9 (10.9)				96.5 (10.0)				95.3 (9.5)				96.9 (10.2)	
IL-6, pg/mL				2.8 (2.5)				2.2 (1.8)				2.0 (1.5)				2.2 (1.9)
Factor VIII, IU/dL			138.2 (31.6)				130.8 (31.0)				127.5 (29.5)				131.5 (31.0)	
vWF, IU/dL			147.9 (48.0)				137.5 (44.5)				133.4 (43.6)				138.6 (45.3)	
tPA, ng/mL			12.3 (4.9)				10.8 (4.2)				10.2 (4.0)				11.0 (4.4)	
CRP, mg/L				2.3 (4.0)				1.4 (2.4)				1.2 (1.9)				1.5 (2.6)
d-dimer, ng/mL				86.0 (106.0)				75.0 (75.0)				68.0 (60.0)				74 (77.0)
Hs-TnT, pg/mL				12.6 (8.2)				11.3 (7.0)				11.5 (6.3)				11.6 (7.1)

Characteristic	Low, decreasing (n=708)				Light Stable (n=1725)				Moderate, increasing (n=898)				Total (n=3,331)			
	No.	%	Mean (SD)	Median (IQR)	No.	%	Mean (SD)	Median (IQR)	No.	%	Mean (SD)	Median (IQR)	No.	%	Mean (SD)	Median (IQR)
NT-proBNP, pg/mL[d]				108.0 (208.0)				87.0 (133.0)				76.5 (108.0)				88.0 (141.0)

Analytic sample consisted of 3,331 participants

Abbreviations: SD, standard deviation; IQR, interquartile range; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1C, haemoglobin A1c; FEV_1, forced expiratory volume in 1 second; IL-6, interleukin-6; CRP, c-reactive protein; vWF, von Willebrand factor; tPA, tissue plasminogen activator antigen; Hs-TnT, high-sensitivity cardiac troponin T; NT-proBNP, n-terminal pro-brain natriuretic peptide

[a] moderate alcohol consumption = 16–42 drinks/week

[b] hypertension, high systolic (≥160 mmHg) or diastolic (≥100 mmHg) blood pressure or taking anti-hypertensive medication

[c] standardised for height by multiplying FEV_1 by the square of the mean population height (metres) divided by each participants height.

[d] data were missing for an additional 194 men (n=3,137)

Table 6.2. Adjusted association[a] (OR or B coefficient, 95% CI) between 20-year physical activity trajectories and cardiovascular markers at 20-year follow up from logistic or linear regression models[b]

	PHYSICAL ACTIVITY TRAJECTORY GROUPS				
	Light Stable		Moderate, increasing		
Outcome measure	**B coefficient[c]**	**95% CI[c]**	**B coefficient[c]**	**95% CI[c]**	**p trend[c]**
Metabolic markers					
HDL, mmol/L [d]	-0.03	-0.06, 0.00	0.01	-0.02, 0.05	0.304
LDL, mmol/L [d]	**0.09**	**0.00, 0.17**	0.04	-0.06, 0.14	0.550
Total cholesterol, mmol/L [d]	0.04	-0.05, 0.13	-0.01	-0.12, 0.10	0.798
Triglycerides, mmol/L [d]	-0.03	-0.06, 0.01	**-0.06**	**-0.11, -0.02**	**0.005**
Hypertension [e]	**0.78**	**0.64, 0.94**	**0.66**	**0.53, 0.81**	-
Glucose, mmol/L [d]	**-0.02**	**-0.04, -0.01**	**-0.03**	**-0.05, -0.01**	**0.005**
Insulin, µ/mL [d]	**-0.08**	**-0.13, -0.03**	**-0.11**	**-0.17, -0.06**	**0.001**
HbA1C, mmols/l [df]	**-0.02**	**-0.03, -0.01**	**-0.02**	**-0.04, -0.01**	**0.014**
FEV_1, L [dg]	**13.92**	**8.64, 19.19**	**22.21**	**16.09, 28.33**	**<0.001**
Waist circumference (cm) [d]	**-3.25**	**-4.13, -2.36**	**-4.22**	**-5.24, -3.19**	**<0.001**
Inflammatory/hemostatic markers					
IL-6, pg/ml [df]	**-0.12**	**-0.18, -0.07**	**-0.18**	**-0.24, -0.11**	**<0.001**

	PHYSICAL ACTIVITY TRAJECTORY GROUPS				
	Light Stable		Moderate, increasing		
Outcome measure	**B coefficient[c]**	**95% CI[c]**	**B coefficient[c]**	**95% CI[c]**	**p trend[c]**
CRP, mg/L [df]	**-0.21**	**-0.30, -0.11**	**-0.27**	**-0.38, -0.17**	**<0.001**
Factor VIII, IU/dL [dh]	**-5.01**	**-7.72, -2.31**	**-5.72**	**-8.86, -2.58**	**0.001**
vWF, IU/dL [dh]	**-5.73**	**-9.65, -1.81**	**-6.42**	**-10.97, -1.88**	**0.009**
tPA, ng/mL [dh]	**-0.69**	**-1.05, -0.33**	**-1.05**	**-1.46, -0.63**	**<0.001**
d-dimer, ng/mL [dfh]	**-0.10**	**-0.16, -0.03**	**-0.11**	**-0.19, -0.03**	**0.010**
Cardiac markers					
Hs-TnT, pg/mL [df]	**-0.07**	**-0.11, -0.03**	-0.03	-0.08, 0.02	0.303
NT-proBNP, pg/mL [dfi]	-0.07	-0.17, 0.02	-0.06	-0.17, 0.06	0.381

Analytic sample consisted of 3,331 participants

Abbreviations: CI, confidence interval; OR, odds ratio; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1C, haemoglobin A1c; FEV_1, forced expiratory volume in 1 second; IL-6, interleukin-6; CRP, c-reactive protein; vWF, von Willebrand factor; tPA, tissue plasminogen activator antigen; Hs-TnT, high-sensitivity cardiac troponin T; NT-proBNP, n-terminal pro-brain natriuretic peptide

[a]All models adjusted for age, occupational class, region of residence, smoking status, alcohol consumption and waist circumference (where waist circumference was the outcome models adjusted for all other factors except waist circumference) and lipid-lowering medication

[b]Low, decreasing group served as the reference group

[c]Bold text indicates statistically significant association ($P<0.05$)

[d] additionally adjusted for blood pressure-lowering medication

[e] presented as an odds ratio and 95% confidence interval. Hypertension, high systolic (≥160 mmHg) or diastolic (≥100 mmHg) blood pressure or taking anti-hypertensive medication

[f] log transformed

[g] FEV_1 was standardised for height by multiplying FEV_1 by the square of the mean population height (metres) divided by each participant's height.

[h] additionally adjusted for warfarin

[i] Data were missing for an additional 194 men (n=3,137)

Table 6.3. Adjusted association[a] (B, 95% CI) between 20-year physical activity trajectories and cardiovascular markers at 20-year follow up from linear or logistic regression models[b], with additional adjustment for current physical activity score

	PHYSICAL ACTIVITY TRAJECTORY GROUPS				
	Light Stable		Moderate, increasing		
Outcome measure	**B coefficient**	**95% CI**	**B coefficient**	**95% CI**	**p trend**
Metabolic markers					
HDL, mmol/L [c]	-0.03	-0.07, 0.01	0.01	-0.04, 0.06	0.719
LDL, mmol/L [c]	0.06	-0.05, 0.17	0.01	-0.14, 0.16	0.917
Total cholesterol, mmol/L [c]	0.02	-0.11, 0.14	-0.07	-0.24, 0.10	0.428
Triglycerides, mmol/L [c]	-0.02	-0.08, 0.03	**-0.09**	**-0.16, -0.02**	**0.015**
Hypertension [d]	0.84	0.65, 1.07	0.73	0.52, 1.03	-
Glucose, mmol/L [c]	**-0.03**	**-0.05, -0.01**	**-0.04**	**-0.07, -0.01**	**0.008**
Insulin, µ/mL [c]	-0.06	-0.13, 0.00	-0.07	-0.16, 0.01	0.102
HbA1C, mmols/l [ce]	**-0.02**	**-0.04, -0.01**	**-0.04**	**-0.06, -0.01**	**0.002**
FEV_1, L [cf]	**10.15**	**3.27, 17.03**	**10.20**	**0.68, 19.72**	**0.039**
Waist circumference (cm) [c]	**-2.47**	**-3.64, -1.30**	**-2.18**	**-3.81, -0.56**	**0.010**
Inflammatory/hemostatic markers					
IL-6, pg/ml [ce]	-0.05	-0.12, 0.03	-0.04	-0.14, 0.07	0.504
CRP, mg/L [ce]	-0.12	-0.24, 0.00	-0.12	-0.29, 0.04	0.155
Factor VIII, IU/dL [cg]	-4.09	-7.63, -0.55	-5.28	-10.18, -0.38	0.036
vWF, IU/dL [cg]	-2.76	-7.91, 2.40	-4.77	-11.90, 2.37	0.191

	PHYSICAL ACTIVITY TRAJECTORY GROUPS				
	Light Stable		Moderate, increasing		
Outcome measure	**B coefficient**	**95% CI**	**B coefficient**	**95% CI**	**p trend**
tPA, ng/mL [cg]	-0.28	-0.75, 0.19	-0.67	**-1.32, -0.01**	**0.045**
d-dimer, ng/mL [ceg]	-0.03	-0.12, 0.06	0.03	-0.09, 0.16	0.521
Cardiac markers					
Hs-TnT, pg/mL [ce]	-0.05	-0.11, 0.00	-0.02	-0.10, 0.05	0.586
NT-proBNP, pg/mL [ceh]	0.04	-0.09, 0.17	0.13	-0.05, 0.30	0.158

Physical activity score at 20-year follow up was missing for 73 participants, resulting in a sample of 3,258

Abbreviations: CI, confidence interval; OR, odds ratio; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1C, haemoglobin A1c; FEV_1, forced expiratory volume in 1 second; IL-6, interleukin-6; CRP, c-reactive protein; vWF, von Willebrand factor; tPA, tissue plasminogen activator antigen; Hs-TnT, high-sensitivity cardiac troponin T; NT-proBNP, n-terminal pro-brain natriuretic peptide

[a]All models adjusted for age, occupational class, region of residence, smoking status, alcohol consumption and waist circumference (where waist circumference was the outcome models adjusted for all other factors except waist circumference), lipid-lowering medication and current physical activity score at 20-year follow up

[b]Low, decreasing group served as the reference group

[c] additionally adjusted for blood pressure-lowering medication

[d] presented as an odds ratio and 95% confidence interval. Hypertension, high systolic (≥160 mmHg) or diastolic (≥100 mmHg) blood pressure or taking anti-hypertensive medication

[e] log transformed

[f] FEV_1 was standardised for height by multiplying FEV_1 by the square of the mean population height (metres) divided by each participant's height.

[g] additionally adjusted for warfarin

[h] data were missing for an additional 190 men (n=3,068)

Bold indicates statistical significance ($p<0.05$)

Table 6.4. Adjusted association[a] (OR or B coefficient, 95% CI) between 20-year physical activity trajectories defined using binary exposure measurements and cardiovascular markers at 20-year follow up from logistic or linear regression models[b] in men without pre-existing CVD and diabetes

	PHYSICAL ACTIVITY TRAJECTORY GROUPS													
	0-1-1 N=394 (12.8%)		**1-0-1 N=198 (6.4%)**		**0-0-1 N=161 (5.2%)**		**1-1-0 N=270 (8.8%)**		**0-1-0 N=182 (5.9%)**		**1-0-0 N=221 (7.2%)**		**0-0-0 N=308 (10.0%)**	
Outcome measure	**B coefficient[c]**	**95% CI[c]**	**B coefficient[c]**	**95% CI[c]**	**B coefficient[c]**	**95% CI[c]**	**B coefficient[c]**	**95% CI[c]**	**B coefficient[c]**	**95% CI[c]**	**B coefficient[c]**	**95% CI[c]**	**B coefficient[c]**	**95% CI[c]**
Metabolic markers														
HDL, mmol/L [d]	-0.02	-0.06, 0.01	0.03	-0.02, 0.08	-0.01	-0.06, 0.04	-0.02	-0.06, 0.02	0.02	-0.03, 0.07	0.03	-0.01, 0.08	-0.03	-0.06, 0.01
LDL, mmol/L [d]	0.05	-0.05, 0.16	0.04	-0.10, 0.18	0.02	-0.14, 0.17	0.00	-0.13, 0.12	-0.14	-0.29, 0.01	-0.03	-0.16, 0.11	-0.06	-0.18, 0.06
Total cholesterol, mmol/L [d]	0.10	-0.02, 0.21	0.06	-0.09, 0.22	-0.01	-0.18, 0.17	0.01	-0.13, 0.14	-0.14	-0.31, 0.02	0.01	-0.14, 0.16	0.01	-0.12, 0.14
Triglycerides, mmol/L [d]	**0.07**	**0.02, 0.12**	0.00	-0.06, 0.07	-0.02	-0.09, 0.05	0.03	-0.03, 0.09	-0.02	-0.08, 0.05	-0.02	-0.08, 0.05	**0.10**	**0.05, 0.15**
Hypertension [e]	1.15	0.91, 1.46	**1.43**	**1.05, 1.95**	1.27	0.90, 1.79	**1.44**	**1.09, 1.89**	1.27	0.91, 1.76	**1.40**	**1.03, 1.89**	**1.52**	**1.17, 1.98**
Glucose, mmol/L [d]	0.01	-0.01, 0.03	0.01	-0.02, 0.04	0.03	0.00, 0.06	0.02	0.00, 0.04	**0.05**	**0.02, 0.08**	0.01	-0.02, 0.03	**0.03**	**0.01, 0.05**
Insulin, µ/mL [d]	0.06	0.00, 0.12	**0.09**	**0.01, 0.17**	0.04	-0.05, 0.13	0.07	0.00, 0.14	**0.09**	**0.01, 0.18**	0.02	-0.05, 0.09	**0.16**	**0.09, 0.22**
HbA1C, mmols/l [df]	0.00	-0.01, 0.02	0.00	-0.02, 0.02	0.01	-0.01, 0.04	0.00	-0.02, 0.02	0.02	-0.01, 0.04	0.00	-0.02, 0.03	**0.02**	**0.00, 0.04**
FEV_1, L [dg]	1.20	-5.39, 7.79	-5.15	-13.90, 3.59	-4.83	-14.47, 4.82	**-12.19**	**-19.88, -4.50**	**-15.15**	**-24.28, -6.01**	**-12.63**	**-21.05, -4.20**	**-11.72**	**-19.09, -4.36**

	PHYSICAL ACTIVITY TRAJECTORY GROUPS													
	0-1-1 N=394 (12.8%)		**1-0-1 N=198 (6.4%)**		**0-0-1 N=161 (5.2%)**		**1-1-0 N=270 (8.8%)**		**0-1-0 N=182 (5.9%)**		**1-0-0 N=221 (7.2%)**		**0-0-0 N=308 (10.0%)**	
Outcome measure	**B coefficient[c]**	**95% CI[c]**	**B coefficient[c]**	**95% CI[c]**	**B coefficient[c]**	**95% CI[c]**	**B coefficient[c]**	**95% CI[c]**	**B coefficient[c]**	**95% CI[c]**	**B coefficient[c]**	**95% CI[c]**	**B coefficient[c]**	**95% CI[c]**
Waist circumference (cm) [d]	0.55	-0.57, 1.67	1.15	-0.33, 2.64	**2.84**	**1.20, 4.47**	1.24	-0.06, 2.55	**2.07**	**0.52, 3.62**	**4.20**	**2.77, 5.62**	**3.27**	**2.03, 4.52**
Inflammatory/hemostatic markers														
IL-6, pg/ml [df]	0.03	-0.04, 0.10	-0.07	-0.17, 0.02	-0.01	-0.11, 0.10	**0.16**	**0.08, 0.24**	**0.11**	**0.01, 0.21**	**0.13**	**0.04, 0.22**	**0.13**	**0.05, 0.21**
CRP, mg/L [df]	-0.07	-0.18, 0.05	0.09	-0.07, 0.24	0.12	-0.05, 0.29	**0.15**	**0.01, 0.28**	0.08	-0.08, 0.24	**0.29**	**0.14, 0.44**	**0.15**	**0.02, 0.28**
Factor VIII, IU/dL [dh]	0.80	-2.58, 4.18	-0.94	-5.42, 3.55	1.16	-3.79, 6.11	2.85	-1.09, 6.80	3.25	-1.44, 7.94	2.37	-1.95, 6.70	3.17	-0.61, 6.95
vWF, IU/dL [dh]	2.11	-2.81, 7.02	0.22	-6.30, 6.74	2.57	-4.62, 9.76	4.71	-1.02, 10.45	4.10	-2.71, 10.92	**6.94**	**0.65, 13.22**	3.46	-2.03, 8.96
tPA, ng/mL [dh]	0.19	-0.26, 0.64	0.23	-0.37, 0.82	-0.26	-0.92, 0.40	**0.53**	**0.01, 1.06**	**0.92**	**0.30, 1.54**	0.46	-0.12, 1.03	**1.03**	**0.52, 1.53**
d-dimer, ng/mL [dfh]	-0.04	-0.13, 0.04	-0.08	-0.19, 0.04	-0.10	-0.23, 0.02	0.09	-0.01, 0.19	0.07	-0.05, 0.19	**0.12**	**0.02, 0.23**	0.08	-0.02, 0.17
Cardiac markers														
Hs-TnT, pg/mL [df]	-0.03	-0.08, 0.02	0.02	-0.04, 0.09	-0.03	-0.11, 0.04	0.02	-0.04, 0.08	0.01	-0.06, 0.08	0.02	-0.05, 0.09	0.01	-0.04, 0.07

	PHYSICAL ACTIVITY TRAJECTORY GROUPS													
	0-1-1 N=394 (12.8%)		**1-0-1 N=198 (6.4%)**		**0-0-1 N=161 (5.2%)**		**1-1-0 N=270 (8.8%)**		**0-1-0 N=182 (5.9%)**		**1-0-0 N=221 (7.2%)**		**0-0-0 N=308 (10.0%)**	
Outcome measure	**B coefficient[c]**	**95% CI[c]**	**B coefficient[c]**	**95% CI[c]**	**B coefficient[c]**	**95% CI[c]**	**B coefficient[c]**	**95% CI[c]**	**B coefficient[c]**	**95% CI[c]**	**B coefficient[c]**	**95% CI[c]**	**B coefficient[c]**	**95% CI[c]**
NT-proBNP, pg/mL [dfi]	-0.06	-0.18, 0.06	0.07	-0.10, 0.23	-0.02	-0.20, 0.16	**0.14**	**0.00, 0.28**	0.11	-0.06, 0.28	**0.18**	**0.02, 0.34**	-0.05	-0.19, 0.08

A total of 252 men were diagnosed with CVD or diabetes at the 20-year follow up, resulting in a sample 3,079 participants

Abbreviations: CI, confidence interval; OR, odds ratio; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1C, haemoglobin A1c; FEV_1, forced expiratory volume in 1 second; IL-6, interleukin-6; CRP, c-reactive protein; vWF, von Willebrand factor; tPA, tissue plasminogen activator antigen; Hs-TnT, high-sensitivity cardiac troponin T; NT-proBNP, n-terminal pro-brain natriuretic peptide

[a]All models adjusted for age, occupational class, region of residence, smoking status, alcohol consumption and waist circumference (where waist circumference was the outcome models adjusted for all other factors except waist circumference) and lipid-lowering medication

[b]The 1-1-1 group (persistently active, n=1345, 43.7%) served as the reference group

[c]Bold text indicates statistically significant association ($P<0.05$)

[d] additionally adjusted for blood pressure-lowering medication

[e] presented as an odds ratio and 95% confidence interval. Hypertension, high systolic (≥160 mmHg) or diastolic (≥100 mmHg) blood pressure or taking anti-hypertensive medication

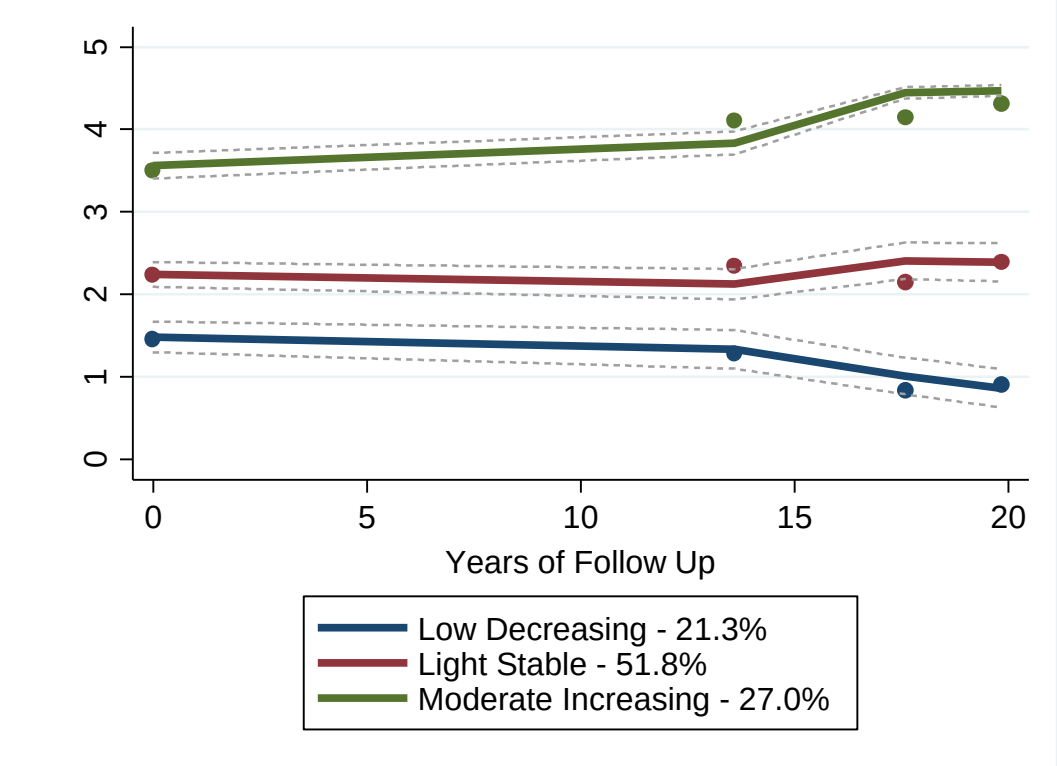
[f] log transformed

[g] FEV_1 was standardised for height by multiplying FEV_1 by the square of the mean population height (metres) divided by each participant's height.

[h] additionally adjusted for warfarin

[i] Data were missing for an additional 178 men (n=2,901)

Figure 6.1. Physical activity trajectories and 95% CIs from midlife to old age



Analytic sample consisted of 3331 participants

CHAPTER 7. TRAJECTORIES OF PHYSICAL ACTIVITY FROM MIDLIFE TO OLD AGE AND SUBSEQUENT CARDIOVASCULAR DISEASE INCIDENCE AND MORTALITY

7.1 Summary

It is well established that regular physical activity protects against CVD, but the impact of long-term physical activity patterns across the adult life course on cardiovascular disease and mortality risk remains unclear. This chapter examined how 20-year trajectories of total physical activity spanning from midlife to old age were associated with subsequent major CHD events, major stroke events, CVD mortality and all-cause mortality. Trajectories from baseline through to the 20-year follow up were first defined with GBTM, using the continuous physical activity score as described in previous chapters, and secondly using a more conventional approach, based on observed binary physical activity variables. From the 20-year follow up, in 1998/2000, men were followed up for subsequent fatal and non-fatal events until 30th June 2016. The association between trajectory groups and subsequent events were examined using cox proportional hazards models. Compared to those following a low, decreasing trajectory, membership of the light stable and moderate, increasing groups was associated with a lower risk of all-cause mortality, CVD mortality, major CHD and all CVD events. There was a significant linear trend across trajectory groups, suggesting additional benefit for more active trajectories. Associations were only partially explained by a range of established and novel CVD risk factors. No associations were observed with major stroke events. Similar associations were observed when trajectories were defined using trajectory groupings defined using binary exposure variables. These analyses suggested that survival benefits were largely driven by most recent/current physical activity.

7.2 Introduction

As discussed in Chapter 2, physical activity is an important modifiable risk factor for preventing CVD and premature mortality (66, 193-198). There is consistent evidence from prospective studies showing an inverse dose-response relationship between volume of physical activity and CVD risk (66, 193-195), some of which has been derived from studies with long-term follow up for events (247).

Most early prospective studies examining the relationship between physical activity and CVD focus on a single measurement of physical activity. However, given the accumulating evidence that physical activity changes across the life course, there has been increased attention on the impact of physical activity changes on subsequent CVD and mortality risk. The majority of studies focus on the effects of physical activity changes across two time points. The most common approach for defining changes in physical activity involve researchers subjectively grouping individuals based on a relevant cut point, resulting in groups classified as persistently active or inactive, increasers or decreasers. Persistent and increasing patterns are typically associated with around a 20-50% lower risk of CVD and mortality compared to those who are persistently inactive (256-260).

Although several studies have examined the association between long-term physical activity changes and CVD and mortality risk in old age, very little research has investigated this relationship using repeated measures of physical activity, which may give additional insight into the optimal patterns for CVD prevention. Studies using more advanced modelling strategies to accommodate for repeated measures of physical activity, such as multilevel modelling, have been largely consistent with studies using just two measurements of physical activity, suggesting that increases in physical activity can reduce mortality risk (267, 268). However, few studies utilising repeated measures of physical activity have used data-driven approaches, such as GBTM, to identify trajectories of physical activity and explore relationships with subsequent CVD and mortality (135, 137). One such study identified three declining patterns of physical activity over 9 years of follow up in older men. Following moderate- and high-activity declining patterns were associated with a reduced risk of all-cause and CVD mortality when compared to a low-activity declining pattern (135). These analyses were adjusted for a range of demographics and a few key CVD risk factors but were not adjusted for other established and novel risk factors, such as blood lipids, inflammation, endothelial dysfunction and cardiac markers. In addition, these associations were explained by the most recent measure of physical activity, suggesting that current/most recent physical activity rather than past physical activity is the most relevant indicator of risk.

Further investigation is required to explore this relationship using similar data-driven approaches to define longer-term patterns of physical activity, with additional adjustment for a range of established and novel CVD risk factors. In addition, further evidence exploring the impact of physical activity trajectories on CVD subtypes and non-fatal events is needed. Therefore, this chapter aims to examine the association between GBTM-derived 20-year physical activity trajectories into old age with subsequent major CHD and stroke events, CVD

mortality and all-cause mortality. A secondary aim was to explore the mediating role of established and novel CVD risk factors in the relationship between physical activity trajectories and the above-mentioned outcomes. This chapter also examines these associations with trajectories defined using binary exposure measurements.

7.3 Objectives

I. To examine the associations between 20-year GBTM-defined trajectories of total physical activity from midlife to old age with major CHD events, major stroke events, CVD mortality and all-cause mortality.
II. To examine the associations between 20-year trajectories of total physical activity from midlife to old age based on observed binary measurements with major CHD events, major stroke events, CVD mortality and all-cause mortality.
III. To examine the mediating role of established and novel CVD risk factors in the relationship between physical activity trajectories and major CHD events, major stroke events, CVD mortality and all-cause mortality.

7.4 Methods

7.4.1 Subjects and methods of data collection

Data analysed in this chapter were collected from the baseline, 12-, 16- and 20-year questionnaires and 20-year physical examination, including physical measurements and a fasting blood sample. Men were also followed up for major CVD events and mortality from any cause from the 20-year follow up in 1998-2000 until 30th June 2016. Information on cause of death was collected through the tagging procedures of the National Health Service Central Registers in Southport for England and Wales, and in Edinburgh for Scotland (death certificates coded using ICD-9 codes). Information on non-fatal events was obtained from General Practitioners and biennial reviews of the patients' medical records. Primary analyses were performed on men, aged 60-79 in 2000, who had at least three valid physical activity scores across the four follow up measurements from baseline and who had complete covariate data as outlined below.

7.4.2 Physical activity measures

As described in detail in Chapter 3, habitual physical activity levels were determined using the 6-point total physical activity score, classifying activity levels as inactive (minimal activity across all types), occasional (regular walking or recreational activity only, or sporting activity less than once a week only), light (more frequent recreational activities plus sporting activity less than once a week, or regular walking plus some recreational activity), moderate (cycling very frequently only, or very frequent recreational activities plus regular walking, or sporting activity once a week), moderately vigorous (sporting activity 2-4 times a week, or sporting activity once a week plus regular walking/cycling and recreational activity) or vigorous (sporting activity more than 4 times a week, or less frequent sporting activity plus frequent walking/cycling and recreational activities). A binary physical activity variable was also generated classifying men as active (1) if they had at least 'light' activity or inactive (0) for inactive or occasional.

7.4.3 Sociodemographic factors, pre-existing disease and cardiovascular disease risk factors

At the 20-year follow up, participants attending the physical examination provided a fasting blood sample, which was analysed for total, HDL and LDL cholesterol, insulin, vWF, IL-6, NT-proBNP and Hs-TnT, as described in Chapter 3. Physical measurements were also obtained including waist circumference, blood pressure and lung function (FEV_1). Men also reported whether they had ever been diagnosed with a heart attack (coronary thrombosis or myocardial infarction), stroke or diabetes. Fasting blood glucose measures of ≥7 mmol/l were used to confirm diabetes diagnosis. Men also reported marital status (single, married or widowed/divorced), smoking status (current/recent ex-smoker or non-smoker/long-term ex-smoker [>15 years]) and alcohol consumption (none, occasional, light, moderate or heavy). Current or longest held occupation (manual or non-manual) and region of residence (Scotland, North, Midlands and South) were derived from the baseline questionnaire.

7.4.4 Mortality and morbidity

Five key outcomes were examined in this analysis: major CHD events (fatal and non-fatal), major stroke events (fatal and non-fatal), CVD mortality, all CVD events (fatal and non-fatal) and all-cause mortality. For major CHD events (fatal/non-fatal), fatal MI was defined as ICD-9 codes 410–414 and non-fatal MI was defined as heart attack or coronary thrombosis in accordance with the WHO diagnostic criteria. For major stoke events (fatal/non-fatal), fatal stroke was defined as ICD-9 codes 430–438 and non-fatal stroke events included those that caused a neurological deficit for >24 hours. Fatal CVD was defined as ICD-9 codes 390–459.

7.4.5 Statistical methods

7.4.5.1 Identifying trajectories of physical activity

GBTM was used to identify 20-year physical activity trajectories over the four time points (baseline, 12-, 16- and 20-year follow up). The optimal number of trajectory groups and trajectory shapes were determined using the same procedures as described in previous chapters. As above, models were adjusted for time-stable baseline variables including age, occupational class (manual or non-manual), marital status (single, married or widowed/divorced), number of children (0 vs. ≥1), region of residence (Scotland, North, Midlands and South of England), chest pain on exertion (yes/no), breathlessness (yes/no), diagnosed health conditions (arthritis, bronchitis and high blood pressure, [yes/no]), BMI (normal weight or overweight/obese), smoking status (current/recent ex-smokers or non-smokers/long-term ex-smokers), alcohol consumption (none, occasional, light, moderate or heavy) and breakfast cereal consumption (none, occasional or regular) along with time-varying covariates, measured at each wave, including number of CVD events (including stroke with symptoms lasting >24 hours, heart attack, myocardial infarction, coronary thrombosis or angina) and employment status (part- or full-time employment [0] or not in employment [1]). Descriptive characteristics for demographic, lifestyle and CVD biomarkers at 20-year follow up were calculated for each trajectory group.

Men were also grouped based on observed trajectories using binary exposure measurements across three time points (baseline, 12- and 20-year follow ups), as described in Chapter 3 and 6. At each of the three time points, men were classified as active (1) if they had at least 'light' activity or inactive (0) for inactive or occasional, resulting in eight possible trajectories (0-0-0, 1-0-0, 1-1-0, 1-0-1, 0-1-0, 0-0-1, 0-1-1, 1-1-1).

7.4.5.2 Survival analysis

Initially, Kaplan-Meier methods were used to estimate probabilities of events and plot survival curves. Cox proportional hazards regression models were also used to calculate adjusted hazard ratios for the risk of all-cause mortality, CVD mortality, major CHD events, major stroke events and all CVD events according to trajectory groups. Linear trends were examined by entering the trajectory grouping variable continuously into the models. For participants with no events, data were censored on the 30th June 2016. The proportional hazards assumption was examined using graphical methods and Schoenfeld residuals. Model 1 adjusted for age, marital status, alcohol consumption, smoking status, and previous diagnosis of MI, stroke and diabetes (reported at

the 20-year follow up), occupational class and region (reported at baseline). To examine the mediating role of CVD risk factors, biomarkers were added sequentially to the model. Model 2 additionally adjusted for a range of cardiometabolic markers measured at the 20-year follow up, including LDL, HDL, systolic blood pressure, insulin, waist circumference and FEV_1. Model 3 additionally adjusted for the inflammatory and hemostatic markers IL-6 and vWF. Model 4 additionally adjusted for the cardiac markers Hs-TnT and NT-proBNP.

Further, to understand whether GBTM-derived physical activity trajectories provided additional information on the risk of subsequent CVD events and mortality over and above current (20-year follow up) measures of physical activity, likelihood ratio tests were performed comparing models with just the current physical activity score as the predictor variable with models that additionally included the GBTM trajectory grouping variable. Results from survival models are also presented after adjustment for current physical activity.

7.4.5.3 Sensitivity analyses

To reduce the effects of any underlying subclinical CVD at the 20-year follow up on physical activity, survival analyses were performed after excluding the first 2 years of follow up. Further, as CVD onset can impact physical activity, as shown in Chapter 5, and subsequently increase the risk of mortality, trajectories were also identified after excluding participants who developed CVD during the 20-year trajectory period using GBTM. Survival analyses were modelled again in this restricted subsample. As in Chapter 6, models were refitted after applying the posterior probabilities of trajectory group membership as survey weights to account for the uncertainty of group membership.

7.5 Results

From the 7,735 men recruited at baseline, 4252 surviving men attended the 20-year physical examination (77% of survivors). Of these, 197 men were excluded due to insufficient physical activity data (i.e. <3 physical activity measures) and a further 824 men were excluded due to missing covariate data, leaving 3231 available for analyses. As expected, men who were excluded from the analytic sample (n=4504) were significantly older at baseline (52.4 vs. 48.7 years; $p < 0.001$), were more likely to be inactive at baseline (43.3% vs. 34.9%; $p<0.001$), come from manual occupations (66.3% vs. 52.0%; $p < 0.001$) and suffer from a range of health conditions, including breathlessness (9.3% vs. 2.8%; $p < 0.001$), overweight/obesity (55.3% vs. 52.7%; $p=0.020$), arthritis (11.6% vs. 8.1%; $p < 0.001$) and bronchitis (20.8% vs. 14.2%, $p < 0.001$).

7.5.1 Trajectories of physical activity

As reported in previous chapters, a three-trajectory group model emerged as the most parsimonious description of the longitudinal data, including low, decreasing (22.7%), light stable (51.0%), and moderate, increasing (26.3%) trajectory groups (see Figure 7.1). Results from the model selection process are also provided in appendices 7A and 7B. In line with the results from previous chapters, there was a clear dose-response relationship across trajectory groups, whereby men in the most active trajectory groups presented with more favourable demographic characteristics, lifestyle behaviours, health outcomes and levels of CVD risk factors, see table 7.1. Using observed binary measurements of physical activity, 44% (n=1345) of men were classified as persistently active (1-1-1) and 11% as persistently inactive (0-0-0), while membership of other groups ranged from 5-13%.

7.5.2 Physical activity trajectories and risk of all-cause mortality, CVD mortality and major CVD events

7.5.2.1 Associations with GBTM-derived trajectories

Over a median follow up of 16.4 years, there were 1735 deaths, of which 35% (n=610) were due to CVD. During follow up, there were also 353 major CHD events and 346 major stroke events, as shown in table 7.2. Survival curves for all-cause mortality, CVD mortality, major stroke events, major CHD events and all CVD events according to trajectory groups are presented in Figures 7.2 to 7.6. Table 7.2 presents HRs for the risk of these outcomes with varying levels of adjustment. Unadjusted rates for all-cause mortality, CHD events, stroke events, CVD mortality and all CVD events were lowest for the moderate, increasing trajectory group and highest for the low, decreasing group. Cox regression analysis showed that compared to the low, decreasing group, membership of the light stable (HR 0.73, 95% CI 0.65, 0.81) and moderate, increasing trajectory (HR 0.64, 95% CI 0.55, 0.73) groups was associated with a lower risk of all-cause mortality in minimally adjusted models (adjusted for age, occupational class, marital status, alcohol consumption, smoking status, region and previous diagnosis of MI, stroke and diabetes). This association was somewhat attenuated after adjusting for cardiometabolic (LDL, HDL, systolic blood pressure, insulin, waist circumference and FEV_1 [HR 0.78, 95% CI 0.69, 0.87; HR 0.71, 95% CI 0.61, 0.81]), inflammatory and hemostatic (IL-6 and vWF [HR 0.80, 95% CI 0.71, 0.90; HR 0.74, 95% CI 0.64, 0.85]) and cardiac biomarkers (Hs-TnT and NT-proBNP [HR 0.83, 95% CI 0.74, 0.94; HR 0.76, 95% CI 0.66, 0.88) but remained statistically significant. Men in the light stable and moderate, increasing groups also had a lower risk of major CHD events, CVD mortality and all

CVD events. The association between the light stable trajectory and all CVD events was attenuated to non-significant levels after adjusting for all CVD risk factors. All other associations were slightly attenuated but remained significant after adjustments. Significant linear trends were observed for all-cause mortality, CHD events, CVD mortality and all CVD events across trajectory groups, suggesting added benefit for higher physical activity trajectories. No associations were observed between GBTM trajectories of physical activity and major stroke events.

7.5.2.2 Model comparison

P values from likelihood ratio tests comparing models with a single measurement of current physical activity in old age to models also including the GBTM-derived trajectory grouping variable are presented in Appendix 7C. Compared to fully adjusted models that just included the current measure of physical activity together with all CVD risk factors, adding the GBTM-derived trajectory group variable did not improve model fit for major CHD events, major stroke events, all CVD events and all-cause mortality. However, in the minimally adjusted models, adding the GBTM-derived trajectory did improve model fit for CVD mortality. This suggests that trajectories of physical activity are important for explaining the variability in CVD mortality but that the effects of these trajectories are mediated by CVD risk factors. Including the current physical activity score in models with GBTM-derived trajectories attenuated the associations between GBTM trajectories and risk of all-cause mortality, major CHD events and all CVD events, as shown in table 7.3. Associations with CVD mortality were partially attenuated but not completely explained by the current physical activity score.

7.5.2.3 Associations with observed binary trajectories

The association between trajectories defined using observed binary measurements and events are shown in table 7.4. Unadjusted mortality rates for all-cause mortality, CHD events, CVD mortality and all CVD events were typically lower for the most recent and most persistently active trajectories. Compared to men who were persistently active, those who were active at the final follow up but who were inactive at previous time points (i.e. those who became active (0-0-1; 0-1-1) or who were inconsistently active (1-0-1)) had a similar risk of all-cause mortality in minimally and fully adjusted models. However, compared to men who were persistently active, those who were persistently inactive (0-0-0), who had become inactive (1-0-0; 1-1-0) and who were inconsistently inactive (0-1-0) at the final follow up had a higher risk of all-cause mortality. Although associations were not as consistent, a similar pattern of association

emerged for CHD events, CVD mortality and all CVD events. Some associations were attenuated after adjusting for CVD risk factors. However, significant linear trends were observed, suggesting that more persistent higher levels of activity are beneficial. No associations were observed between these trajectory groupings and major stroke events.

7.5.3 Sensitivity analyses

In several models, the proportional hazards assumption was not met for age. When violated, age was collapsed into ten categories and centred. Models were run again with this categorised age variable, but no meaningful differences were observed and so results are presented with the untransformed age variable. All associations were similar after removing men with pre-existing CVD (see Appendix 7D) and after excluding the first two years of follow up (see Appendix 7E). Exploratory analyses showed that there was a significant risk reduction in fatal but not non-fatal stroke events in fully adjusted models in men following a light stable trajectory compared to the low, decreasing group (HR 0.58, 95% CI 0.37, 0.92) but no associations were observed for non-fatal stroke events. Lastly, there were no meaningful differences when models were weighted according to posterior probabilities so unweighted models are presented.

7.6 Discussion

7.6.1 Summary of main findings

This chapter aimed to examine the association between 20-year trajectories of total physical activity from midlife to old age and subsequent major CHD events, major stroke events, CVD mortality and all-cause mortality. The three trajectory groups were again identified as low, decreasing, light stable and moderate, increasing. Survival analyses showed that the light stable and moderate, increasing groups were at a lower risk of all-cause mortality, CVD mortality, major CHD and all CVD events when compared to the low, decreasing group. Linear trends were also observed suggesting added survival benefit for more active trajectories. Associations were attenuated, but not completely, after adjusting for established and novel CVD risk factors. No associations were observed between trajectory groups and major stroke events, although there was evidence of a reduced risk of fatal but not non-fatal stroke events for the light stable trajectory. Similar associations were observed when trajectories were defined using observed binary measurements. The majority of associations were largely driven by the most recent/current physical activity measure; however, history of physical activity may be an important determinant of CVD mortality risk.

7.6.2 Comparison with previous studies

This is one of the first studies to explore associations between GBTM-derived trajectories of physical activity and cause-specific mortality and morbidity. For this reason, comparisons with previous studies are not straightforward.

The majority of studies to date have examined the prospective association of baseline and changes in physical activity across two time points with subsequent survival and CVD. The findings presented in this chapter are consistent with the majority of these studies suggesting that there is a dose-response relationship between physical activity and risk of CVD and all-cause mortality (193, 194, 247, 256, 257, 259, 260, 263, 340). The present findings show that a moderate, increasing volume of activity is optimal but that maintenance of a 'light' level of physical activity across the adult life course can also be sufficient to reduce the risk of CVD and mortality. Previous studies have used a variety of approaches and cut points to define physical activity changes (256, 257, 260, 262) making it difficult to draw comparisons on the required level of physical activity across the adult life course that can induce benefit. In addition, most other studies use broad definitions of CVD making it difficult to compare the present findings for CVD subtypes with previous research.

The key finding of this chapter is that following more active trajectories was associated with approximately a 25-35% reduction in risk of all-cause mortality, CHD events and CVD mortality when compared to a low, decreasing trajectory. Similar risk reductions have been reported in previous studies examining changes across two time points across the adult life course for all-cause and CVD mortality (256-258, 260, 262). Previous studies in this cohort report larger associations for all-cause mortality when compared to CVD mortality (260, 341). Discrepancies may be because this study focusses on a later life period when the risks of CVD are higher, or it may be because physical activity was self-reported, while Jefferis et al use accelerometry (341). When defining trajectories using a conventional approach, this study showed that those who became active (0-0-1; 0-1-1) had a similarly reduced risk of all-cause and CVD mortality as those who were persistently active. Similar conclusions were drawn in GBTM analyses adjusting for current physical activity, which also suggested that current physical activity is predominantly driving associations with subsequent CVD and all-cause mortality. This finding suggests that current physical activity is crucial for protection against CVD and mortality. From a clinical perspective, past physical activity may not be important for predicting subsequent risk. Nonetheless, as shown throughout this thesis, physical activity at younger ages is a significant predictor of physical activity in older ages, and thus maintaining a certain physical activity level

throughout the life course might be optimal. Several previous studies assessing physical activity across two time points have also shown similar survival benefits among those who became active and those who were persistently active (257-259, 261, 263, 264). However, some previous studies suggest that persistent activity may be optimal for reducing risks of CVD mortality, albeit with much shorter follow up for physical activity changes and subsequent events (260, 262).

Studies examining these relationships with several measures of physical activity across the adult life course are scarce but have produced similar findings (135, 137, 267, 268). One such study, using GBTM methods, also identified three similar physical activity trajectories over a 7-year follow up, although in an older sample, (135) and also found that the two most active trajectories were associated with a similarly lower risk of all-cause (HR 0.78 95% CI 0.70, 0.88 and HR 0.69 95% 0.57, 0.83) and CVD mortality (HR 0.81 95% CI 0.66, 0.99 and HR 0.68 95% CI 0.49, 0.95) when compared to the least active (135). Moreover, these associations were largely explained by the most recent/current measure of physical activity and not by history of physical activity. The findings of this chapter extend on this study by capturing patterns of physical activity over a longer period of the adult life course and by examining associations with specific types of CVD as well as the mediating role of important CVD risk factors in this relationship.

When examining the role of important CVD risk factors, associations were partially attenuated after adjusting for established cardiometabolic risk factors. These associations were further attenuated after including inflammatory, hemostatic and cardiac markers, suggesting that these relationships also operate through these mechanisms, as previously suggested (68-70, 72, 80-82). Other studies in middle-aged (339-341) and older adults (215) have also shown that established and novel CVD risk factors partially attenuate these associations but do not substantially alter them.

Despite the observed associations of physical activity trajectories with all-cause mortality, CVD mortality, CHD events and all CVD events, no associations were observed with stroke events. Most previous studies do not examine associations between physical activity changes/patterns and CVD subtypes. The present findings suggest that the observed associations between physical activity patterns and CVD mortality are largely driven by CHD and not stroke. This finding contrasts two previous meta-analyses that both found a protective effect of physical activity on stroke (342, 343). Overall the evidence linking physical activity and stroke has been somewhat mixed (344), with a number of studies also reporting no association between physical activity and major stroke events (345, 346). Further, the optimal type and amount of physical activity remains unclear. However, further exploratory analyses revealed a significant risk

reduction for a light stable trajectory when only fatal stroke was considered. Few studies have differentiated between fatal and non-fatal stroke. However, one such study in a large sample of Californian women showed that the inverse association observed between physical activity and risk of stroke was largely driven by fatal stroke events (347). Parallels can also be drawn between this finding and those of other observational studies that have shown that modest levels of physical activity may provide the greatest protection from stroke as opposed to more strenuous levels (345, 347-349). However, this is in contrast to recent meta-analyses that have shown an inverse dose-response relationship between total physical activity and risk of stroke (344, 350), although they also do not differentiate between fatal and non-fatal stroke events.

7.6.3 Strengths and limitations

A major strength of this study is that the BRHS comprises of a moderately large representative sample of British men with high follow up rates. However, as the cohort comprises of predominantly white men, findings may not be generalisable to women and non-white ethnic groups. Typically, similar dose-response relationships between physical activity and mortality have been reported in both men and women (251, 253), but few have examined gender differences with life course physical activity measurement. The study also benefits from extended and regular follow up for CHD events, stroke events and cause-specific mortality, allowing the risks of CVD subtypes to be determined. In addition, measurement of a range of established and novel cardiovascular blood markers at the 20-year follow up allowed analyses to be adjusted for important mediators in the relationship between physical activity and CVD. However, as CVD biomarkers were only measured once, at the 20-year follow up, it was not possible to capture changes in CVD risk factors across follow up, which could be important as the levels of such biomarkers are known to fluctuate. Indeed, higher levels of within-person variability are associated with an increased risk of CVD and all-cause mortality (351).

As discussed in Chapter 6, the GBTM approach reveals realistic trajectories and provides increased granularity on the volume of physical activity that is required across the life course to induce benefit. Including more conventional methods to identify trajectories adds additional insights around sensitive periods and also allows comparisons with previous studies.

As previously described, the physical activity score has demonstrated validity against heart rate, FEV_1 and device-measured physical activity (272, 274), yet it may still be prone to recall bias and may not be as precise for distinguishing between intensities of physical activity as modern device-based measures (339).

Although analyses were adjusted for prevalent CVD, sub-clinical levels at baseline may impact subsequent physical activity trajectories and so reverse causation is possible. As highlighted in previous chapters, the final sample were generally healthier and more active than those excluded from the analyses. This attrition bias may limit the generalisability of the results to the least active members of the population and may underestimate the association between physical activity trajectories and survival.

In addition, these associations may in part be explained by residual confounding. Some confounding variables, such as smoking and alcohol consumption, were self-reported and thus may introduce some measurement error. There could also be other confounding factors, either known or unknown, that were not considered, which could also result in residual confounding.

7.6.4 Conclusion

Higher levels of physical activity from midlife to old age were associated with a reduced risk of major CHD events, all-cause mortality, CVD mortality and all CVD events in a dose-response manner. These associations were only partially explained by a range of established and novel CVD risk factors. Using a GBTM approach, a moderate, increasing pattern was identified as the most protective, but a light level of physical activity sustained across the adult life course also provided significant benefit. The most recent/current level of physical activity appeared to be the most important indicator of subsequent risk. Promoting modest amounts of physical activity may be more feasible for the least active adults and may result in similar survival benefits as higher volumes.

Table 7.1. Subject characteristics at 20-year follow up according to GBTM physical activity trajectories

Characteristic	Low, decreasing (n=733)	Light stable (n=1649)	Moderate, increasing (n=849)	All (n=3231)
Age, years (mean ± SD)	69.4 (5.6)	68.5 (5.6)	67.8 (5.1)	68.5 (5.5)
Manual occupation (%,n)[a]	59.8 (438)	55.6 (916)	38.5 (327)	52.0 (1681)
Alcohol consumption, ≥light[b] (%,n)	54.6 (400)	62.4 (1029)	73.5 (591)	63.5 (1178)
Current smoker (%,n)	19.5 (143)	10.6 (174)	7.4 (63)	11.8 (380)
Married (%,n)	80.5 (590)	85.0 (1402)	86.9 (738)	84.5 (2730)
Resident in southern England (%,n)[a]	26.2 (192)	36.2 (597)	38.2 (324)	34.5 (1113)
Waist circumference, cm (mean ± SD)	100.1 (11.2)	96.4 (10.0)	95.4 (9.5)	97.0 (10.3)
LDL, mmol/L (mean ± SD)	3.8 (1.0)	4.0 (1.0)	3.9 (0.9)	3.9 (1.0)
HDL, mmol/L (mean ± SD)	1.3 (0.3)	1.3 (0.3)	1.4 (0.3)	1.3 (0.3)
Insulin, μ/mL (median, IQR)	9.6 (8.1)	8.1 (5.9)	7.5 (5.4)	8.2 (6.4)
SBP, mmHg (mean ± SD)	148.6 (23.9)	149.0 (23.8)	148.0 (24.4)	148.6 (24.0)
$FEV_{1,}$ L[c] (mean ± SD)	235.2 (69.5)	259.6 (62.5)	276.1 (61.7)	258.4 (65.5)
IL-6, pg/mL (median, IQR)	2.8 (2.4)	2.2 (1.8)	2.0 (1.5)	2.2 (1.9)
von Willebrand factor, IU/dL (mean ± SD)	148.7 (48.4)	137.1 (45.0)	133.6 (43.0)	138.8 (45.6)
Hs-TnT, pg/mL (median, IQR)	12.7 (8.1)	11.4 (7.0)	11.5 (6.3)	11.7 (7.0)
NT-proBNP, pg/mL (median, IQR)	112.0 (206.0)	88.0 (136.0)	78.0 (111.0)	89.0 (144)
Previous MI (%,n)	9.1 (67)	7.3 (120)	6.0 (51)	7.4 (238)
Previous stroke (%,n)	3.3 (24)	2.4 (39)	2.2 (19)	2.5 (82)
Previous diabetes (%,n)	14.5 (106)	7.4 (122)	7.0 (59)	8.9 (287)

Analytic sample consisted of 3231 participants

Abbreviations: GBTM, group-based trajectory modelling; FEV_1, forced expiratory volume in 1 second; HDL, high-density lipoprotein; SBP, systolic blood pressure; Hs-TnT, high-sensitivity cardiac troponin T; IL-6, interleukin-6; IQR, interquartile range; LDL, low-density lipoprotein; NT-

proBNP, N-terminal pro-brain natriuretic peptide; SD, standard deviation; MI, myocardial infarction.

[a]Reported at baseline

[b]light classified as ≥1 unit per week

[c]Standardised for height by multiplying FEV1 by the square of the mean population height (meters) divided by each participant's height.

Table 7.2. Association between physical activity trajectories and subsequent risk of CVD events and all-cause and CVD mortality

Outcome	Trajectory group	N	N.o. of events	Person-years	Rate per 1000 person-years	Model 1	Model 2	Model 3	Model 4
						Hazard Ratio (95% CI)			
Deaths (all cause)	Low, decreasing	733	494	8402.2	58.8	Referent	Referent	Referent	Referent
	Light stable	1649	869	22216.5	39.1	**0.73 (0.65, 0.81)**	**0.78 (0.69, 0.87)**	**0.80 (0.71, 0.90)**	**0.83 (0.74, 0.94)**
	Moderate, increasing	849	372	12034.9	30.9	**0.64 (0.55, 0.73)**	**0.71 (0.61, 0.81)**	**0.74 (0.64, 0.85)**	**0.76 (0.66, 0.88)**
	p trend					<0.001	<0.001	<0.001	<0.001
Major CHD events (fatal + non-fatal)[a]	Low, decreasing	733	146	8190.7	17.8	Referent	Referent	Referent	Referent
	Light stable	1649	245	21531.7	11.4	**0.73 (0.59, 0.91)**	**0.75 (0.60, 0.93)**	**0.77 (0.62, 0.95)**	**0.80 (0.64, 1.00)**
	Moderate, increasing	849	98	11672.4	8.4	**0.63 (0.49, 0.83)**	**0.67 (0.51, 0.88)**	**0.70 (0.53, 0.92)**	**0.71 (0.54, 0.93)**
	p trend					0.001	0.004	0.009	0.012
Major stroke events (fatal + non-fatal)[b]	Low, decreasing	733	76	8098.6	9.4	Referent	Referent	Referent	Referent
	Light stable	1649	186	21308.6	8.7	0.99 (0.75, 1.31)	1.04 (0.79, 1.38)	1.08 (0.82, 1.43)	1.10 (0.83, 1.46)

Outcome	Trajectory group	N	N.o. of events	Person-years	Rate per 1000 person-years	Model 1	Model 2	Model 3	Model 4
						Hazard Ratio (95% CI)			
	Moderate, increasing	849	84	11687.7	7.2	0.87 (0.63, 1.20)	0.92 (0.66, 1.28)	0.96 (0.69, 1.34)	0.98 (0.70, 1.37)
	p trend					0.368	0.573	0.773	0.851
CVD mortality[c]	Low, decreasing	733	198	8402.2	23.6	Referent	Referent	Referent	Referent
	Light stable	1649	297	22216.5	13.4	**0.64 (0.53, 0.77)**	**0.67 (0.56, 0.81)**	**0.69 (0.57, 0.84)**	**0.76 (0.62, 0.91)**
	Moderate, increasing	849	115	12034.9	9.6	**0.53 (0.42, 0.67)**	**0.58 (0.45, 0.74)**	**0.61 (0.48, 0.78)**	**0.64 (0.50, 0.82)**
	p trend					<0.001	<0.001	<0.001	<0.001
All CVD events (fatal + non-fatal)[d]	Low, decreasing	733	252	7901.3	31.9	Referent	Referent	Referent	Referent
	Light stable	1649	470	20692.5	22.7	**0.80 (0.69, 0.94)**	**0.83 (0.70, 0.97)**	0.85 (0.72, 1.00)	0.89 (0.75, 1.04)
	Moderate, increasing	849	198	11338.1	17.5	**0.70 (0.57, 0.85)**	**0.74 (0.60, 0.90)**	**0.77 (0.63, 0.94)**	**0.78 (0.64, 0.95)**
	p trend					<0.001	0.002	0.009	0.015

Analytic sample consisted of 3231 participants

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CVD, stroke/MI; MI, myocardial infarction

[a] Fatal MI was defined as ICD-9 codes 410–414. Non-fatal MI was defined as heart attack or coronary thrombosis, in accordance with the World Health Organisation diagnostic criteria.

[b] Fatal stroke was defined as ICD-9 codes 430–438. Non-fatal stroke events included those that caused a neurological deficit for >24 hours.

[c] Fatal CVD was defined as ICD-9 codes 390–459.

[d] All CVD events included all fatal CVD (ICD-9 codes 390–459)and non-fatal MI and stroke as described above.

Model 1, adjusted for age, occupational class, marital status, alcohol consumption, smoking status, region, previous diagnosis of MI, stroke or diabetes. Model 2, Model 1 + LDL, HDL, systolic blood pressure, insulin, waist circumference and FEV_1. Model 3, Model 2 + IL-6 and vWF. Model 4, Model 3 + Hs-TnT and NT-proBNP. Boldface indicates statistical significance ($p<0.05$)

Table 7.3. Association between physical activity trajectories and subsequent risk of CVD events and all-cause and CVD mortality, with additional adjustment for current physical activity score

Outcome	Trajectory group	N	N.o. of events	Person-years	Rate per 1000 person-years	Model 1	Model 2	Model 3	Model 4
						Hazard Ratio (95% CI)			
Deaths (all cause)	Low, decreasing	714	484	8158.7	59.3	Referent	Referent	Referent	Referent
	Light stable	1616	851	21811.3	39.0	0.89 (0.77, 1.04)	0.94 (0.81, 1.10)	0.96 (0.82, 1.12)	0.97 (0.83, 1.13)
	Moderate, increasing	840	366	11934.6	30.7	0.92 (0.73, 1.16)	0.98 (0.78, 1.24)	1.00 (0.80, 1.26)	1.00 (0.79, 1.26)
	p trend					0.302	0.714	0.863	0.855
Major CHD events (fatal + non-fatal)[a]	Low, decreasing	714	144	7947.1	18.1	Referent	Referent	Referent	Referent
	Light stable	1616	238	21147.4	11.3	0.81 (0.61, 1.08)	0.82 (0.61, 1.09)	0.83 (0.62, 1.11)	0.83 (0.62, 1.10)
	Moderate, increasing	840	98	11572.0	8.5	0.78 (0.50, 1.20)	0.80 (0.52, 1.25)	0.82 (0.53, 1.28)	0.79 (0.51, 1.23)
	p trend					0.172	0.226	0.276	0.211
Major stroke events (fatal + non-fatal)[b]	Low, decreasing	714	71	7889.3	9.0	Referent	Referent	Referent	Referent
	Light stable	1616	181	20914.7	8.7	1.21 (0.84, 1.74)	1.28 (0.88, 1.84)	1.30 (0.90, 1.88)	1.31 (0.91, 1.89)

Outcome	Trajectory group	N	N.o. of events	Person-years	Rate per 1000 person-years	Model 1	Model 2	Model 3	Model 4
						Hazard Ratio (95% CI)			
	Moderate, increasing	840	83	11595.9	7.2	1.23 (0.74, 2.06)	1.29 (0.77, 2.16)	1.32 (0.79, 2.20)	1.31 (0.78, 2.20)
	p trend					0.352	0.271	0.237	0.232
CVD mortality[c]	Low, decreasing	714	193	8158.7	23.7	Referent	Referent	Referent	Referent
	Light stable	1616	288	21811.3	13.2	**0.73 (0.57, 0.93)**	**0.76 (0.59, 0.98)**	**0.77 (0.60, 1.00)**	0.80 (0.62, 1.03)
	Moderate, increasing	840	114	11934.6	9.6	0.72 (0.49, 1.06)	0.76 (0.52, 1.12)	0.79 (0.54, 1.16)	0.79 (0.54, 1.17)
	p trend					0.027	0.066	0.097	0.112
All CVD events (fatal + non-fatal)[d]	Low, decreasing	714	244	7692.0	31.7	Referent	Referent	Referent	Referent
	Light stable	1616	457	20319.6	22.5	0.94 (0.76, 1.16)	0.96 (0.78, 1.19)	0.98 (0.79, 1.21)	0.98 (0.79, 1.22)
	Moderate, increasing	840	196	11246.3	17.4	0.93 (0.68, 1.28)	0.97 (0.71, 1.33)	0.99 (0.72, 1.35)	0.96 (0.70, 1.32)
	p trend					0.596	0.775	0.889	0.795

Physical activity score at the 20-year follow up was missing for 61 participants, resulting in a sample of 3170

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CVD, stroke/MI; MI, myocardial infarction

[a] Fatal MI was defined as ICD-9 codes 410–414. Non-fatal MI was defined as heart attack or coronary thrombosis, in accordance with the World Health Organisation diagnostic criteria.

[b] Fatal stroke was defined as ICD-9 codes 430–438. Non-fatal stroke events included those that caused a neurological deficit for >24 hours.

[c] Fatal CVD was defined as ICD-9 codes 390–459.

[d] All CVD events included all fatal CVD (ICD-9 codes 390–459) and non-fatal MI and stroke as described above.

Model 1, adjusted for age, occupational class, marital status, alcohol consumption, smoking status, region, and previous diagnosis of MI, stroke or diabetes. Model 2, Model 1 + LDL, HDL, systolic blood pressure, insulin, waist circumference and FEV_1. Model 3, Model 2 + IL-6 and vWF. Model 4, Model 3 + Hs-TnT and NT-proBNP. Boldface indicates statistical significance ($p<0.05$)

Table 7.4. Prospective association between physical activity trajectories defined using binary exposure measurements (from baseline [1978/80] to 20-year follow up [1998/2000]) and all-cause/cause-specific mortality and CVD events from 1998/2000 to 2016

Outcome	Trajectory group*	N	N.o. of events	Person-years	Mortality/1000 person-years	Model 1	Model 2	Model 3	Model 4
						Hazard Ratio (95% CI)			
Deaths (all cause)	0-0-0	315	197	3829.2	51.5	**1.40 (1.19, 1.65)**	**1.31 (1.11, 1.54)**	**1.28 (1.08, 1.51)**	**1.27 (1.08, 1.51)**
	1-0-0	207	122	2555.2	47.8	**1.44 (1.18, 1.75)**	**1.35 (1.11, 1.64)**	**1.31 (1.07, 1.60)**	**1.26 (1.03, 1.54)**
	0-1-0	185	115	2118.5	54.3	**1.36 (1.11, 1.66)**	**1.25 (1.02, 1.54)**	**1.24 (1.01, 1.52)**	1.22 (1.00, 1.50)
	1-1-0	265	173	3104.1	55.7	**1.57 (1.33, 1.89)**	**1.52 (1.28, 1.80)**	**1.47 (1.24, 1.75)**	**1.39 (1.17, 1.65)**
	0-0-1	151	75	2089.5	35.9	0.96 (0.76, 1.23)	0.93 (0.73, 1.19)	0.93 (0.73, 1.19)	0.91 (0.71, 1.16)
	1-0-1	180	78	2537.8	30.7	1.10 (0.87, 1.40)	1.04 (0.82, 1.32)	1.08 (0.85, 1.37)	1.04 (0.82, 1.32)
	0-1-1	380	205	5165.6	39.7	1.01 (0.89, 1.18)	1.01 (0.86, 1.19)	1.00 (0.85, 1.18)	1.01 (0.86, 1.18)
	1-1-1	1315	615	18469.8	33.3	Referent	Referent	Referent	Referent
	p trend					<0.001	<0.001	<0.001	<0.001

Outcome	Trajectory group*	N	N.o. of events	Person-years	Mortality/1000 person-years	Model 1	Model 2	Model 3	Model 4
						Hazard Ratio (95% CI)			
Major CHD events (fatal + non-fatal)[a]	0-0-0	315	58	3722.6	15.6	1.33 (0.98, 1.81)	1.24 (0.91, 1.69)	1.23 (0.90, 1.67)	1.27 (0.93, 1.72)
	1-0-0	207	38	2452.6	15.5	**1.53 (1.07, 2.18)**	**1.46 (1.02, 2.09)**	1.43 (1.00, 2.06	1.37 (0.95, 1.97)
	0-1-0	185	34	2074.6	16.4	1.37 (0.94, 1.98)	1.37 (0.94, 1.99)	1.36 (0.93, 1.97)	1.36 (0.94, 1.98)
	1-1-0	265	49	2999.6	16.3	**1.49 (1.08, 2.05)**	**1.44 (1.04, 1.99)**	**1.40 (1.01, 1.93)**	1.30 (0.94, 1.80)
	0-0-1	151	26	2035.4	12.8	1.19 (0.78, 1.81)	1.16 (0.76, 1.76)	1.16 (0.76, 1.76)	1.16 (0.76, 1.77)
	1-0-1	180	28	2396.4	11.7	1.43 (0.96, 2.14)	1.30 (0.87, 1.95)	1.33 (0.89, 1.2.00)	1.27 (0.84, 1.90)
	0-1-1	380	59	5002.5	11.8	1.07 (0.80, 1.45)	1.05 (0.77, 1.41)	1.04 (0.77, 1.40)	1.07 (0.79, 1.44)
	1-1-1	1315	167	17963.1	9.3	Referent	Referent	Referent	Referent
	p trend					0.003	0.012	0.017	0.020
Major stroke events (fatal + non-fatal)[b]	0-0-0	315	34	3721.6	9.1	1.14 (0.78, 1.68)	1.09 (0.73, 1.60)	1.06 (0.72, 1.57)	1.08 (0.73, 1.59)

Outcome	Trajectory group*	N	N.o. of events	Person-years	Mortality/1000 person-years	Model 1	Model 2	Model 3	Model 4
						Hazard Ratio (95% CI)			
	1-0-0	207	18	2454.1	7.3	1.04 (0.63, 1.72)	1.03 (0.62, 1.70)	1.00 (0.61, 1.65)	0.99 (0.60, 1.63)
	0-1-0	185	20	2032.8	9.8	1.19 (0.74, 1.92)	1.15 (0.71, 1.85)	1.13 (0.70, 1.82)	1.12 (0.69, 1.81)
	1-1-0	265	33	2961.2	11.1	1.36 (0.92, 2.00)	1.35 (0.92, 1.99)	1.31 (0.89, 1.92)	1.25 (0.85, 1.84)
	0-0-1	151	17	1994.7	8.5	1.10 (0.66, 1.84)	1.09 (0.65, 1.82)	1.08 (0.65, 1.81)	1.08 (0.64, 1.80)
	1-0-1	180	20	2404.3	8.3	1.23 (0.76, 1.98)	1.17 (0.73, 1.89)	1.22 (0.76, 1.97)	1.19 (0.74, 1.91)
	0-1-1	380	39	4996.9	7.8	0.93 (0.65, 1.34)	0.93 (0.64, 1.33)	0.91 (0.63, 1.31)	0.92 (0.64, 1.32)
	1-1-1	1315	130	17901.4	7.3	Referent	Referent	Referent	Referent
	p trend					0.229	0.344	0.431	0.465
CVD mortality[c]	0-0-0	315	84	3829.2	21.9	**1.68 (1.30, 2.19)**	**1.56 (1.20, 2.03)**	**1.54 (1.18, 2.01)**	**1.54 (1.18, 2.00)**

Outcome	Trajectory group*	N	N.o. of events	Person-years	Mortality/1000 person-years	Model 1	Model 2	Model 3	Model 4
						Hazard Ratio (95% CI)			
	1-0-0	207	42	2555.2	16.4	**1.41 (1.01, 1.98)**	1.34 (0.95, 1.88)	1.30 (0.92, 1.82)	1.19 (0.84, 1.68)
	0-1-0	185	48	2118.5	22.7	**1.59 (1.16, 2.19)**	**1.52 (1.10, 2.09)**	**1.51 (1.10, 2.08)**	**1.52 (1.10, 2.09)**
	1-1-0	265	57	3104.1	18.4	**1.40 (1.04, 1.88)**	**1.35 (1.00, 1.82)**	1.29 (0.96, 1.74)	1.16 (0.86, 1.56)
	0-0-1	151	31	2089.5	14.8	1.16 (0.79, 1.70)	1.10 (0.75, 1.62)	1.09 (0.74, 1.60)	1.03 (0.70, 1.51)
	1-0-1	180	27	2537.8	10.6	1.19 (0.79, 1.78)	1.09 (0.73, 1.64)	1.14 (0.76, 1.71)	1.08 (0.72, 1.63)
	0-1-1	380	65	5165.6	12.6	0.91 (0.68, 1.20)	0.89 (0.67, 1.18)	0.88 (0.66, 1.16)	0.90 (0.68, 1.20)
	1-1-1	1315	205	18469.8	11.1	Referent	Referent	Referent	Referent
	p trend					<0.001	<0.001	<0.001	<0.001
All CVD events (fatal + non-fatal)[d]	0-0-0	315	104	3629.2	28.7	**1.27 (1.01, 1.59)**	1.20 (0.96, 1.51)	1.18 (0.94, 1.48)	1.22 (0.97, 1.53)
	1-0-0	207	64	2363.2	27.1	**1.39 (1.06, 1.83)**	**1.35 (1.03, 1.78)**	**1.32 (1.00, 1.73)**	1.27 (0.96, 1.67)
	0-1-0	185	66	1988.8	33.2	**1.42 (1.08, 1.85)**	**1.40 (1.07, 1.83)**	**1.39 (1.06, 1.81)**	**1.40 (1.07, 1.84)**

Outcome	Trajectory group*	N	N.o. of events	Person-years	Mortality/1000 person-years	Model 1	Model 2	Model 3	Model 4
						Hazard Ratio (95% CI)			
	1-1-0	265	88	2856.7	30.8	**1.40 (1.11, 1.78)**	**1.38 (1.08, 1.75)**	**1.32 (1.04, 1.68)**	1.23 (0.97, 1.57)
	0-0-1	151	46	1940.6	23.7	1.13 (0.82, 1.54)	1.11 (0.81, 1.51)	1.10 (0.80, 1.51)	1.10 (0.80, 1.51)
	1-0-1	180	50	2294.3	21.8	1.32 (0.98, 1.78)	1.26 (0.93, 1.70)	1.29 (0.96, 1.75)	1.24 (0.92, 1.67)
	0-1-1	380	103	4840.8	21.3	0.96 (0.77, 1.21)	0.94 (0.75, 1.17)	0.93 (0.74, 1.16)	0.94 (0.75, 1.18)
	1-1-1	1315	326	17421.3	18.7	Referent	Referent	Referent	Referent
	p trend					<0.001	0.001	0.003	0.004

Analytic sample consisted of 2998 participants

Abbreviations: MI, myocardial infarction; CVD, stroke/MI

* Physical activity trajectories correspond to levels of physical activity from baseline through 12 and 20 year follow ups. 1 indicates at least 'light' physical activity levels and 0 denotes 'inactive' or 'occasional' activity levels. For example, (0-0-0) represents low physical activity at all periods, whilst (1-0-0) indicates high physical activity at baseline only.

[a] Fatal myocardial infarction (MI) was defined as ICD-9 codes 410–414. Non-fatal MI was defined as heart attack or coronary thrombosis, in accordance with the World Health Organisation diagnostic criteria.

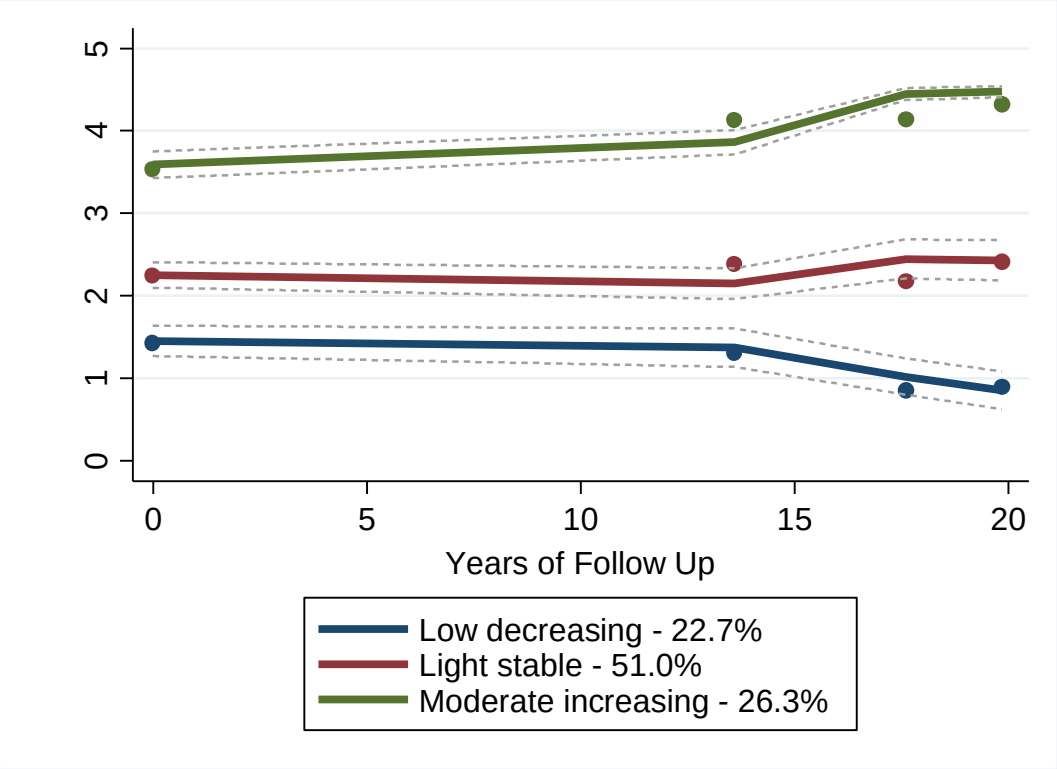
[b] Fatal stroke was defined as ICD-9 codes 430–438. Non-fatal stroke events included those that caused a neurological deficit for >24 hours.

[c] Fatal CVD was defined as ICD-9 codes 390–459.

[d] All CVD events included all fatal CVD (ICD-9 codes 390–459) and non-fatal MI and stroke events.

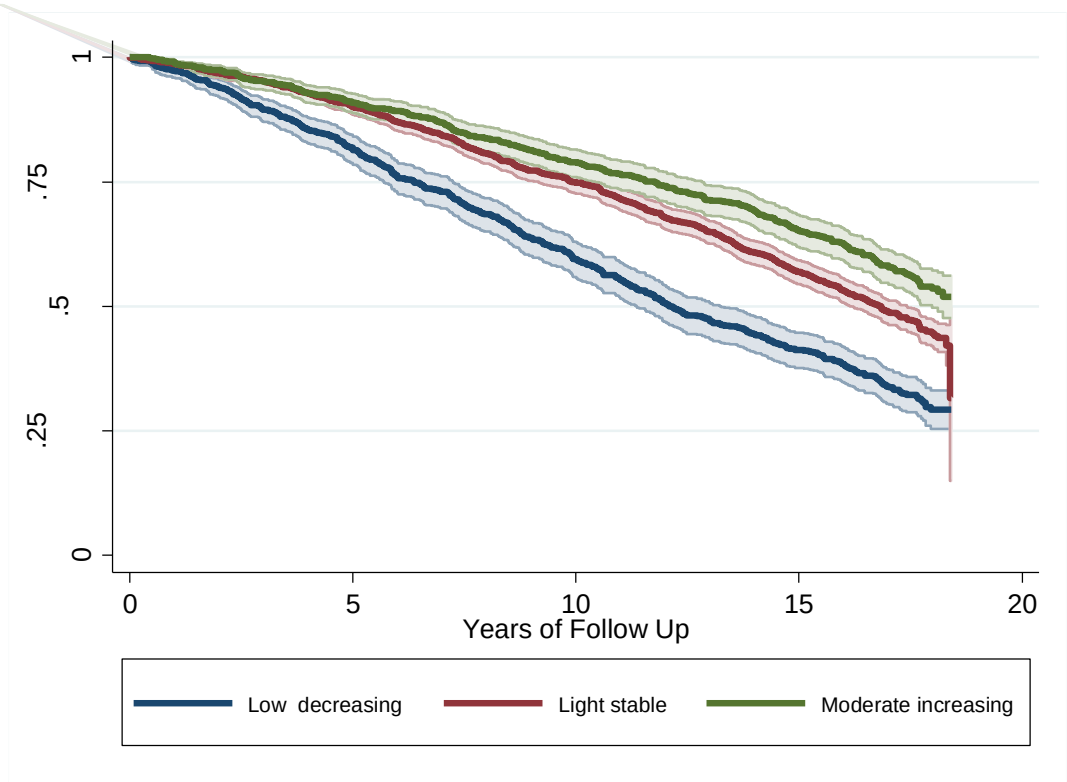
Model 1, adjusted for age, occupational class, marital status, alcohol consumption, smoking status, region, previous diagnosis of MI, stroke or diabetes. Model 2, Model 1 + LDL, HDL, systolic blood pressure, insulin, waist circumference and FEV_1. Model 3, Model 2 + IL-6 and vWF. Model 4, Model 3 + Hs-TnT and NT-proBNP. Boldface indicates statistical significance ($p<0.05$)

Figure 7.1. GBTM-derived physical activity trajectories and 95% CI from midlife to old age



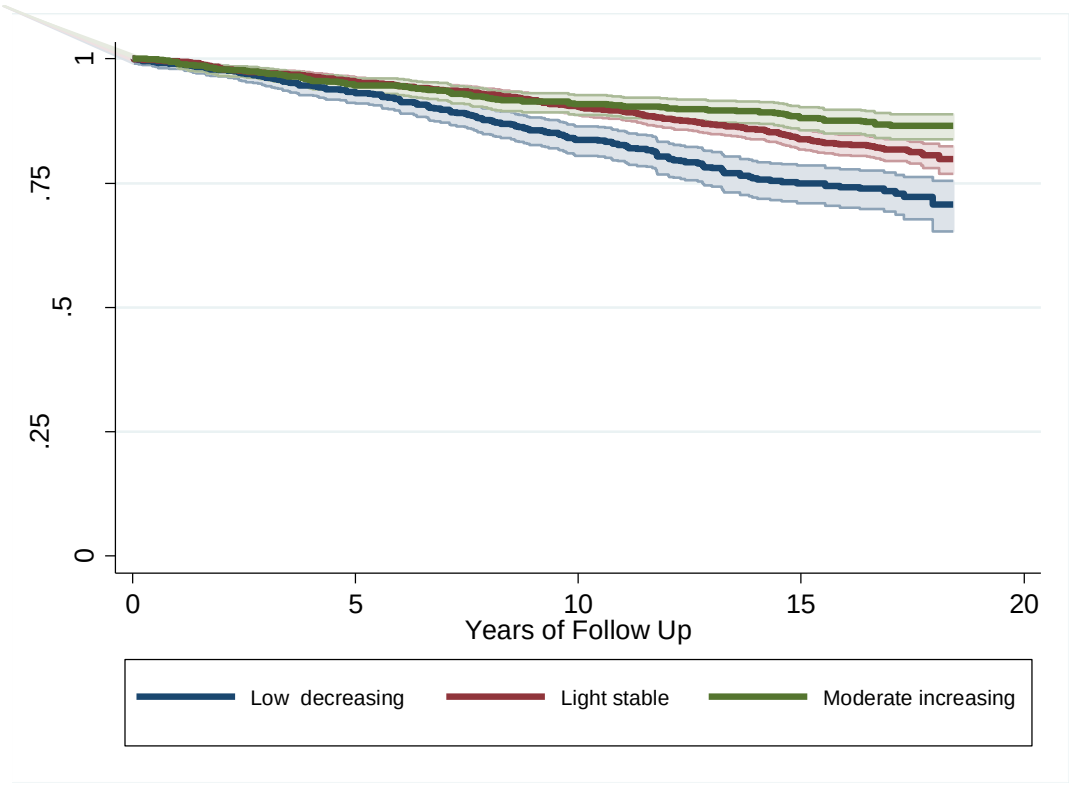
Analytic sample consisted of 3231 participants

Figure 7.2. Kaplan-Meier survival curves and 95% CIs comparing all-cause mortality according to trajectory groups in men aged 60-79 years



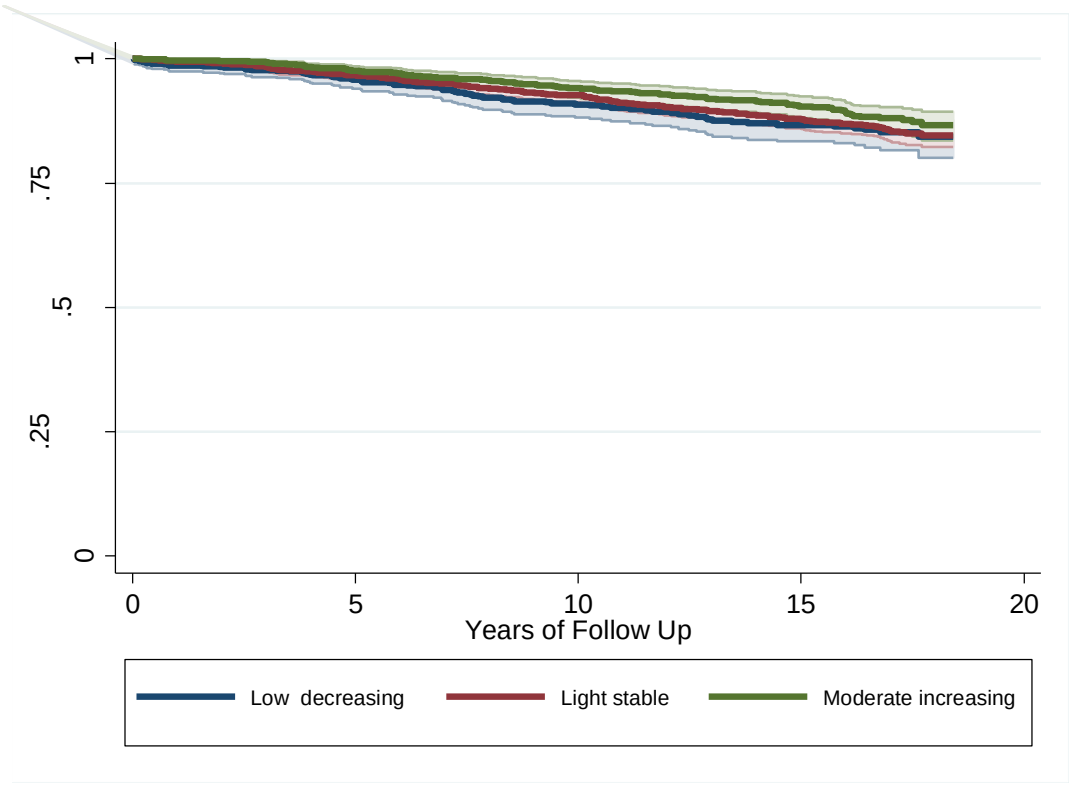
Analytic sample consisted of 3231 participants

Figure 7.3. Kaplan-Meier survival curves and 95% CIs comparing all major CHD events according to trajectory groups in men aged 60-79 years



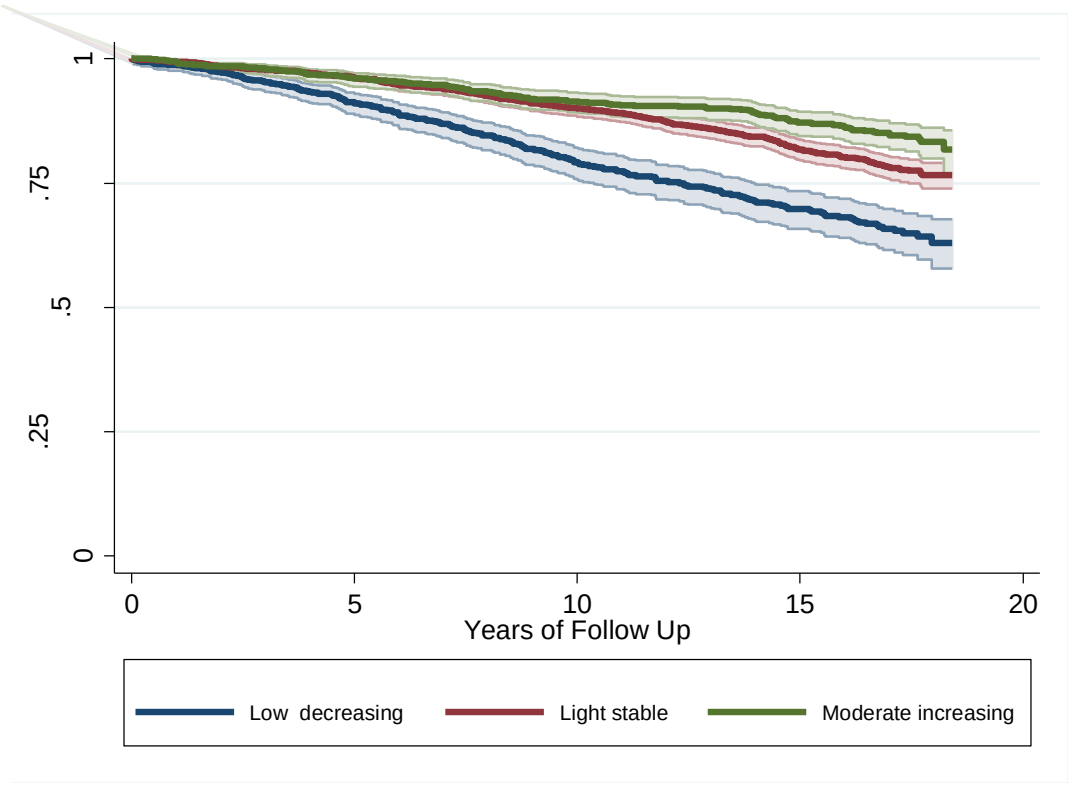
Analytic sample consisted of 3231 participants

Figure 7.4. Kaplan-Meier survival curves and 95% CIs comparing all stroke events according to trajectory groups in men aged 60-79 years



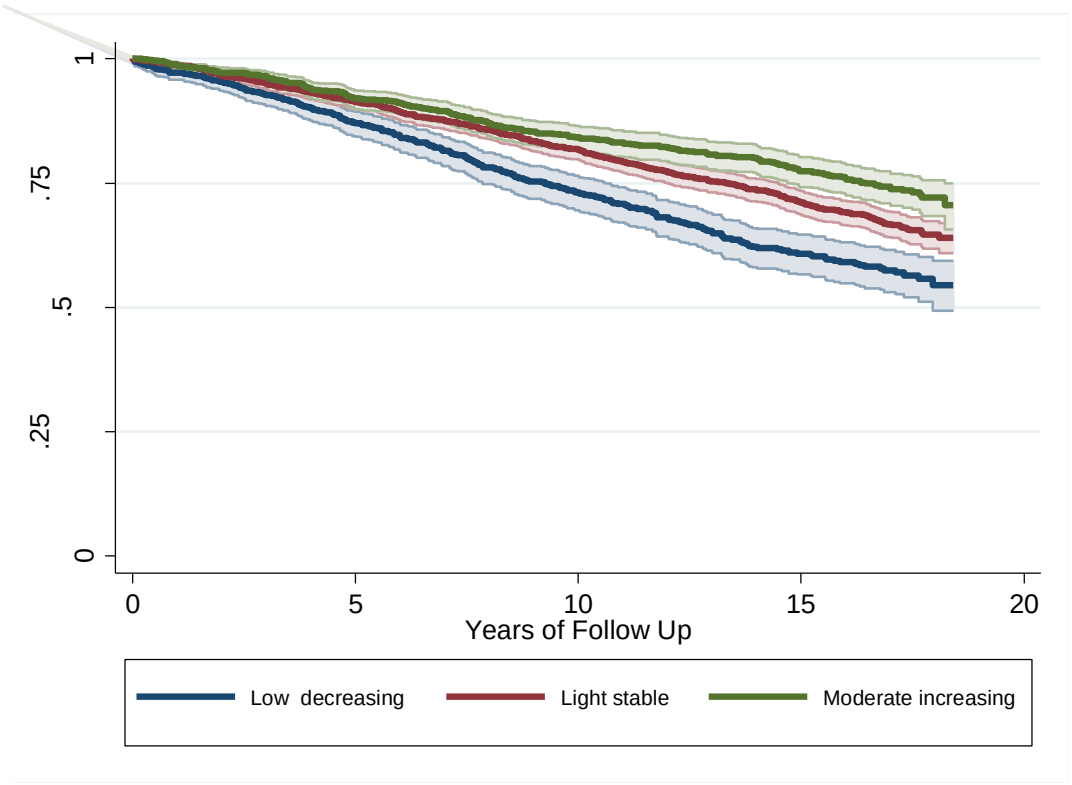
Analytic sample consisted of 3231 participants

Figure 7.5. Kaplan-Meier survival curves and 95% CIs comparing CVD mortality according to trajectory groups in men aged 60-79 years



Analytic sample consisted of 3231 participants

Figure 7.6. Kaplan-Meier survival curves and 95% CIs comparing all CVD events according to trajectory groups in men aged 60-79 years



Analytic sample consisted of 3231 participants

CHAPTER 8. IMPLICATIONS AND CONCLUSIONS

8.1 Summary

This chapter summarises the key findings of this thesis and how they can inform public health policy and future epidemiological studies. This thesis set out to identify the patterns of physical activity behaviour from midlife to old age and understand the predictors of these trajectories and how they impact on subsequent CVD and mortality risk.

Physical activity habits in old age were largely determined by physical activity in midlife, but there were a number of factors identified that were associated with these patterns that could inform strategies aiming to promote physical activity in later life. Physical activity trajectories across the adult life course were associated with subsequent risk of CVD and mortality in later life, but a substantial proportion of this risk can be explained by most recent/current physical activity levels in old age. From a public health policy perspective important implications include: i) physical activity needs to be a regular habit by midlife to increase the prospects of living an active later life; ii) efforts need to be made to promote physical activities in early life that can be maintained across the life course or at least establish a habit for physical activity; iii) a range of sociodemographic, health and behavioural factors could be used to identify those most at risk of long-term inactivity; iv) tailored approaches are required to modify physical activity around major life events and v) current activity level in old age is the most important indicator of subsequent risk of CVD and mortality. Considerations for future research include: i) the need for additional prospective studies using GBTM to identify trajectories of physical activity; ii) the need to identify trajectories of physical activity across the entire life course; iii) the need to use device-based measures for physical activity measurement across the life course; iv) the need to explore how trajectories of specific types of physical activity are associated with CVD and mortality and v) the need for qualitative studies to gain a deeper understanding of determinants of life course physical activity patterns.

8.2 Key findings

This thesis uses nearly 40 years of follow up data from the BRHS to explore the longitudinal patterns of physical activity and how they are associated with subsequent CVD risk factors, CVD events and mortality in British men transitioning from midlife to old age.

Chapter 4 found that physical activity tracks moderately from midlife to old age. Sport/exercise tracked stronger than other physical activity types and was a stronger predictor of physical activity in later life. Golf was the most common sport and tracked stronger than other sports/exercises. Bowls, walking/hiking and dancing were the most frequently adopted sports/exercises. Persistent activity across adulthood, early uptake of sport/exercise and sampling a diverse range of sport/exercises further increased the odds of being active in old age.

Chapter 5 identified the trajectories of physical activity and physical activity types from midlife to old age. Three distinct trajectories of total physical activity were identified. Although the identified trajectories suggested some within-person variability over time, they also largely confirmed the findings of chapter 4 that activity levels in old age were largely determined by midlife activity. Three trajectories were also identified for sport/exercise, highlighting that participation was fairly stable. Trajectories of walking and recreational activity were more variable, showing increasing and decreasing patterns, respectively. Not smoking, a healthy weight and good overall health were consistently associated with more favourable trajectories. Relationships with other predictors were specific to physical activity type. Retirement and CVD onset could alter trajectories but the effects of these events were modified by an individual's history of physical activity. In fact, the common perception that CVD events initiate long-term declines in physical activity does not necessarily apply to the most active older adults.

Chapters 6 and 7 showed that compared to those following a low, decreasing trajectory, following a light stable or moderate, increasing trajectory was associated with more favourable levels of CVD risk factors and a lower risk of all-cause mortality, CVD mortality and major CHD. Although prior physical activity may be relevant for determining levels of CVD risk factors, the most recent/current measurement of physical activity may be the most important measure for determining subsequent risk of CVD and all-cause mortality. Nevertheless, encouraging physical activity across the adult life course may be important for establishing a lasting physical activity habit and thus reducing the burden of CVD in later life.

8.3 Strengths and limitations of this thesis

8.3.1 General methodological considerations

The BRHS is highly suitable for addressing the objectives of this thesis. The BRHS is comprised of a large and geographically representative sample of community dwelling middle-aged British men in 1978-80. Further, the extended prospective follow up with repeated measures of self-

reported physical activity allows the long-term tracking and trajectories of physical activity and physical activity types to be determined across 20-years of follow up. Data collected also included a range of confounding and mediating factors, which could be accounted for in analyses. In addition, data collection and recording have been sustained to a high level since baseline, achieving near complete follow up (>98%) for morbidity and mortality (280). Other key strengths of this thesis include detailed information on cardiovascular blood markers measured at the 20-year follow up and regular follow up using standard definitions of CHD events, CVD events and mortality. These data allow the association of physical activity trajectories with CVD risk factors and distal CVD events and mortality to be investigated. A key limitation of the BRHS is that the sample is restricted to men only and there is limited representation of black and minority ethnic groups, reducing the generalisability of the findings. The BRHS also excluded towns with high mobility, so highly mobile people may also be underrepresented. Another important consideration is the possibility that cohort effects may influence the findings of this thesis. The experiences of this cohort will be very different to those who are currently transitioning from adulthood into old age. For example, manual professions in the 1950s and 1960s would have been more demanding than manual occupations today and may impact physical activity differently.

8.3.2 Physical activity measurement

The self-report physical activity measure used in this thesis benefits from validation against a range of measures. Results from validation studies showed a strong inverse relationship between the physical activity score and electrocardiograph measured resting heart rate ($p<0.001$) and a strong positive association with accelerometer-measured moderate-to-vigorous physical activity ($r=0.49$, $p<0.001$), providing evidence of construct and content validity (272, 274). In addition, comparability between waves has been enhanced by retaining the same questions and scoring mechanisms across follow up. The physical activity score used in this thesis could be criticised as the association with device-based measures is not perfect and there is evidence to suggest that light intensity activity can be misclassified (274). Recall bias may also impact the validity of the findings, particularly as the cohort ages when recall issues may be exacerbated due to memory loss. Further, although the self-reported physical activity score has been validated, objective measures of physical activity, which may be more accurate for estimating the quantity and intensity of physical activity, were not available when the study was initiated. Another potential problem with this score is that intensity weights remain constant over time, but we know that the energy requirements of physical activity increase with age. For

instance, a 3 MET activity may be considered light to moderate activity for a 40 year old but could be a vigorous activity for an 80 year old. Consequently, physical activity levels may be underestimated as the cohort ages. Also, as the first follow up questionnaire after 5 years did not include the physical activity items, it is possible that important fluctuations in physical activity may have been missed in the 12-year interval between baseline and the next follow up measurement.

8.3.3 Trajectory modelling approach

In this thesis, GBTM was selected as the most appropriate approach for identifying physical activity trajectories. GBTM revealed the most prominent underlying trajectories that may not have been identified using alternative approaches. Traditional growth curve modelling could have been applied to the data. However, this modelling approach only produces one set of growth parameters for the entire sample (i.e. an average trajectory), which may not have represented individuals who followed different trajectories. Other traditional approaches, which have previously been used with BRHS data, could have been applied to manually create more clinically relevant trajectory groups, such as those who 'increase' or 'decrease' physically activity levels. However, the GBTM trajectories identified in this thesis question whether these groupings truly exist. GBTM can also include time-stable and time-varying predictors and can accommodate missing data, using the maximum likelihood method.

8.3.4 Missing data

As shown in Figure 3.3, there was considerable loss to follow up, which is expected in cohort studies. It is possible that subject attrition in the BRHS may have led to a biased sample, possibly leading to biased estimates between exposure and outcome. When the study was initiated (1978-80), the characteristics of non-responders (i.e. men who were sent an invitation but declined or did not respond after one reminder) were collected and compared to study participants. Compared to men recruited into the study, non-responders were younger, more likely to be unmarried, and more likely to be less skilled workers (281). Mortality rates in the first three years of follow up were higher in non-responders, but were similar thereafter. CVD mortality rates were also similar, indicating that analyses of CVD mortality are representative and not biased by non-responders. Men who were recruited to the study but who did not attend the 20-year re-examination were more likely to be older, smoke, report disabling conditions, take medications, engage in unhealthy behaviours and be more deprived at baseline than those who attended the examination (282). By including such variables in analyses, the impact of

selection bias and attrition on exposure-outcome associations can be reduced or eliminated (352). Furthermore, selection bias is not considered an issue when exploring exposure-outcome associations if there is sufficient variation in the exposure (353). Importantly most of the missingness during the 20-year trajectory period was due to death (~70%), suggesting that a survival selection bias may have biased the findings. The GBTM models used in this thesis can accommodate for this by including participants with at least one physical activity measure under the assumption that missingness is at random. It is difficult to check this assumption, but previous research in this cohort suggests that missing physical activity data is likely explained by the observed data (i.e. health status, socioeconomic status etc). Incorporating all available data in the models maximises the sample size and increases the precision of the estimated trajectories and associations with predictor variables. Nevertheless, as questionnaires were less likely to be completed by the least healthy participants, it is possible that declines in physical activity preceding death may not have been adequately captured.

8.3.5 Residual confounding

Although this thesis controls for a range of confounding and mediating factors, it may be that some important confounders were not captured or measured with sufficient granularity to eliminate the possibility of residual confounding. For example, dietary factors, such as salt intake, may confound the association between physical activity and CVD events, but such dietary factors were not consistently reported in the BRHS and thus were not included in survival models. Although the possibility of residual confounding cannot be excluded, adjustment for blood markers such as LDL cholesterol which reflect dietary intake did not eliminate the associations, Moreover, other studies with more accurate measurement of diet have shown that physical activity is protective against CVD even after adjusting for diet (354). Another potential issue is that certain confounding variables were categorised rather crudely into binary variables, such as smoking status (smoker vs. non-smoker/long-term ex-smoker), which may not have accurately captured associations with outcome variables. Further, unmeasured confounders such as psychological factors were not captured in the BRHS, which may have biased associations between physical activity and CVD.

8.3.6 Reverse causality

Reverse causality is an important consideration when studying associations between physical activity and health. It could be argued that health status drives physical activity levels rather than the other way round, particularly in older populations when morbidity risks are at their

highest. Indeed, chapter 5 showed that health status in midlife is an important predictor of subsequent physical activity trajectories into later life. It is likely then that the associations between physical activity and health in later life are bidirectional. This thesis attempts to control for existing and underlying health conditions to separate the effects that physical activity trajectories have on subsequent risk factory levels, CVD events and mortality. In chapter 6, individuals with existing CVD at baseline were excluded from analyses, thereby reducing the extent to which the associations reflect the influence of existing CVD risk factor levels on physical activity trajectories. However, it is possible that physical activity levels may be influenced by health status in individuals who are already on the disease pathway but are yet to experience a CVD event. Hence, chapter 6 makes further attempts to control for underlying CVD by removing individuals who went on to develop CVD in the 20-year trajectory period. Nevertheless, it is still possible that individuals who are in the very early stages of disease may not have been accounted for and so the captured associations may still to some extent reflect the influence that health status has on physical activity. By contrast, chapter 7 includes individuals with pre-existing CVD, alternatively adjusting for CVD diagnosis in the models, and thus maximising sample size.

8.4 Novelty of findings

As discussed in Chapter 2, previous cohort studies have suggested that physical activity tracks moderately across the life course (17, 89, 93). However, most previous studies have focussed on early life periods, particularly around the transition to adulthood, or have covered only a short period of adult life. Chapter 4 provides evidence that physical activity also tracks moderately over a significant period of the adult life course including the transition to old age. It also extends on previous tracking studies by exploring how specific types of physical activity track into old age. Indeed, very few studies have explored how specific physical activity types track at any stage of the life course not to mention in later life periods. Moreover, this is the first study to my knowledge to prospectively examine how specific types of sport/exercise track during the transition to old age, highlighting specific types of sport/exercise that can be sustained and adopted into old age.

Chapter 2 highlighted several studies that have attempted to understand how and why physical activity changes across the life course (112); however, very few have used data-driven methods, such as GBTM, to identify physical activity patterns. The majority of studies use conventional approaches to classify physical activity patterns, frequently resulting in loss of information. Using GBTM, this thesis revealed trajectories that are not typically identified using conventional

approaches. Indeed, in this sample of British men, the traditional trajectory classifications (i.e. increasing, decreasing, and persistently active/inactive) may not accurately represent the true underlying trajectories of physical activity. Further, to my knowledge no previous studies have used data-driven methods to examine trajectories of specific types of physical activity. The findings in Chapter 5 show that trajectories of physical activity types are distinct. Walking emerged as the most likely activity to increase in old age and thus may be the most feasible intervention target. Although there are some common predictors across all physical activity types, some predictors were also specific to physical activity type trajectories. Another novel aspect of the analyses in chapter 5 is that GBTM has the ability to incorporate time-varying covariates. This chapter was therefore able to explore the impacts of retirement and CVD diagnosis on physical activity trajectories, providing additional evidence that these events can initiate change in physical activity but that the direction and magnitude of these changes vary according to prior physical activity trajectories. Indeed, retirement may result in an upturn in activity but only in those who are already active, and CVD onset may not necessarily initiate a lasting decline in physical activity for everyone, with the most active seeming to maintain total physical activity levels after a CVD event.

The main novelty of the results presented in chapters 6 and 7 is that they showed that a light stable level of physical activity across the adult life course is sufficient to reduce a range of established and novel CVD risk factor levels and reduce the risk of CVD events and all-cause mortality. Previous studies using more conventional approaches to define trajectories via binary exposure measurements provide less precise estimates about the level of physical activity that is required to achieve such benefits. Chapter 7 also highlighted the importance of current physical activity levels in determining future CVD and mortality risks. However, as the trajectories identified show that past physical activity levels are fundamental for determining current levels, by definition they also highlight the importance of past physical activity for preventing these outcomes. Chapter 7 also adds to the limited evidence demonstrating the mediating role of novel CVD risk factors in the relationship between physical activity trajectories, CVD and mortality. Most previous studies using GBTM to explore associations with similar outcomes do not adjust for these disease biomarkers (135, 137, 355).

8.5 Implications for policy and public health

8.5.1 The importance of physical activity trajectories for determining CVD and mortality risks in older age

In this thesis, 20-year trajectories of physical activity from midlife to old age have been shown to be associated with CVD risk factors, major CVD events, CVD mortality and all-cause mortality in later life. Few cohort studies have been able to consider long-term patterns of physical activity with repeated measures in relation to these outcomes (119, 135, 137, 213, 221, 230, 266-268), as many do not have sufficient follow up to explore such relationships. Even fewer have used GBTM to identify trajectories of physical activity to explore these associations (135, 137, 222). Although the findings from Chapter 7 suggest that current/most recent physical activity levels are the most clinically relevant indicator of future CVD and mortality risk, past physical activity behaviour is crucial for determining current physical activity levels and also plays an important role in determining the levels of some CVD risk factors in later life that mediate associations with CVD mortality risk.

Some previous studies have suggested that persistent physical activity across the life course is optimal for reducing CVD risk (260, 262), while others find that becoming active in later life is associated with a similar risk as those who are persistently active (257, 261, 263, 264). This thesis is in line with studies that suggest current physical activity in old age is the most critical period for CVD and mortality risk. Clinically, therefore, current physical activity should be viewed as the most valuable measurement for risk prediction. However, past physical activity should still be considered, when possible, given that it has cumulative effects on cardiometabolic risk factors.

Furthermore, the very shape of the trajectories identified in this thesis, highlights the importance of prior activity levels for determining current physical activity levels and subsequently the risk of CVD and mortality. Encouraging lifelong physical activity should, therefore, still be a high priority for policy makers. The GBTM-defined trajectories also provide more insight into the volume of physical activity that is required across the adult life course to reduce the risk of CVD and mortality. Over recent years there has been considerable debate about how physical activity should be accumulated to achieve benefit, including the type, amount and intensity of physical activity (67). This thesis suggests that a moderate, increasing trajectory was the most optimal naturally occurring trajectory, but it also highlights that a sustained light volume of activity, a previously unobserved trajectory, could be sufficient to

induce benefit. In this thesis, a light volume of activity translates to occasional sporting exercise or moderate amounts of walking combined with some gardening/do-it-yourself projects.

8.5.2 Strategies to promote life-long physical activity

'It's never too late' is a common phrase used in scholarly literature and the media to highlight that the benefits of physical activity can be acquired late in life (356, 357). While this may be true in those that are able to increase their activity levels, this thesis suggests that in real-world settings older adults who become active from a very inactive state are rare, at least without intervention. Subsequently the importance of lifelong physical activity needs to be stressed in public health recommendations and strategies.

A key finding from this thesis was that total physical activity tracked from midlife to old age. However, sport and exercise tracked stronger than other forms of physical activity. Efforts to encourage early engagement in sport/exercise is one clear approach that could help promote sustained physical activity across the life course. Promoting early life participation in golf could be particularly fruitful as it was the most common sport/exercise and the most likely to be sustained. The health benefits of golf are now being increasingly recognised. In October 2018, the first International Congress on Golf and Health was held at the International Society for Physical Activity and Health Conference (358), raising awareness on the health benefits of golf to policy makers and leaders in public health. A wide range of evidence was presented relating to the health benefits of golf, including the benefits to cardiovascular, respiratory and mental health (359-361). Although promoting golf may be a successful strategy alone, a wide range of sports/exercises should be offered for all age groups to optimise physical activity readiness in later life. Adapting popular sports/exercises to make them age appropriate may also keep older adults in sporting activities that they enjoy for longer (362, 363). Walking football, an adaptation of association football that does not permit running or slide tackles, has recently emerged as a feasible and cost effective sport/exercise in adults over 50 (362). Other governing bodies could be doing more to explore ways that sport can be adapted for older players. Further, strategies to tackle the large social inequalities in sport/exercise participation should also be prioritised, particularly for golf, racquet sports and swimming where large inequalities were observed. Future research should explore barriers to these sports/exercises in disadvantaged groups and sports providers should seek to minimise them.

Although participating in sports/exercise may be optimal for lifelong activity, many people prefer alternative forms of activity and so other initiatives are required. Interestingly, this thesis showed that those who sustain light levels of physical activity into old age generally do not

participate in sport/exercise frequently, but they do increase their walking. Hence, strategies to encourage walking and other less structured forms of physical activity may be crucial for maintaining activity in those with a history of modest levels of physical activity. There has been extensive research on the health benefits of walking (364) and the effectiveness of walking interventions in older adults (365, 366). Some walking interventions have been shown to have lasting benefits to physical activity levels up to four years post intervention (365). Promoting walking may be particularly effective as it seems to be accessible across all social classes and in adults with health conditions. The current guidelines recommend at least 150 minutes of moderate-to-vigorous intensity physical activity per week or at least 75 minutes of vigorous intensity physical activity per week, as well as muscle-strengthening activities on 2 or more days a week (7). However, a recent report from the Physical Activity Guidelines Advisory Committee has now acknowledged the emerging evidence around the benefits of lower volumes and of light intensity physical activity in the least active members of the population (272). A light volume of physical activity could be recommended in the least active middle-aged adults as it may be more feasible and sustainable than higher volumes of activity and still brings some health benefits.

Chapter 5 of this thesis highlighted a number of factors that were associated with activity across the adult life course. This information could be used to inform intervention strategies to reduce the risk of lifelong inactivity. Individuals exposed to risk factors associated with continuous inactivity could be prioritised for referral to physical activity interventions. Individuals suffering from health conditions, such as breathlessness, obesity, CVD and arthritis, might have limited physical capabilities and would probably need to be referred to specialist services. There has been some work on promoting physical activity in patients with chronic conditions, such as obesity, CVD, COPD and arthritis, but further research is required to optimise initiatives in these patient groups (367, 368). Contrary to common perceptions, this thesis also showed that physical activity can be maintained following CVD events but only in the most active individuals. Plausibly, those who are already active have a higher tolerance to such events and are more motivated to sustain activity levels than their inactive peers. However, this finding may also be explained by the inequalities in referral to cardiac rehabilitation services, which have been observed among women, ethnic minorities and those from disadvantaged backgrounds (369). There is evidence from recent systematic reviews and meta-analyses that cardiac rehabilitation programmes can reduce the risk of mortality and hospitalisation as well as improve aspects of mental wellbeing (369), so efforts to promote uptake and adherence to these services in underrepresented groups should be prioritised. In addition, prevention and early detection of

chronic conditions as well as development of new treatments to better manage them could also have a wider impact.

As well as specialist services for those with chronic conditions, inactive older adults without physical limiting conditions could be targeted with population level approaches. Given that men from the north and midlands of England were at an increased risk of continuous inactivity, interventions targeting environmental factors in these regions may be effective. A range of environmental factors that are known correlates of physical activity should be considered in urban planning and development, such as proximity to green spaces, street connectivity and land-use mix (112, 146, 182). There is some evidence that adaptions to the physical environment, such as renovating parks, building/repairing new footpaths and outdoor gyms/playgrounds, can on their own increase physical activity (370, 371). However, more promising results have been observed for interventions combining environmental changes with promotional campaigns to raise awareness of the facilities, including media coverage and maps of trails/paths for example (371).

Given that being married and having children were strongly associated with more favourable trajectories, those who are socially isolated may be particularly vulnerable to long-term inactivity. Tackling social isolation is therefore an important approach for increasing physical activity levels in later life. Recent research highlighting the negative health consequences of social isolation and the high prevalence of older adults in the UK who rarely speak to a friend or family member (372) has increased the awareness of loneliness and social isolation over recent years, resulting in a number of initiatives to combat this issue. Notably, the National Lottery has given £78 million in funding to the Ageing Better programme, which aims to develop ways for older adults to connect with their communities and increase social networks (373). To date, interventions have largely focussed on modifying physical activity behaviour to reduce social isolation (374), but equally interventions aimed at reducing social isolation, such as the Ageing Better programme, may initiate increases in physical activity levels.

This thesis also highlights periods of the adult life course where physical activity may be modifiable, which could inform the timing of interventions. Retirement emerged as an important life event where those who are already active tended to take up more physical activity, predominantly through sport/exercise and walking. Thus, retirement may be a window of opportunity to encourage uptake of activities that can be maintained into later life. Despite this window of opportunity, many recently retired adults feel like '*a forgotten group*' with limited tailored opportunities available for them (375). Further, given the finding that retirement

can initiate a decrease in physical activity in the least active, strategies to promote physical activity in the least active and disadvantaged groups need to be explored. The workplace could be an ideal setting to maximise the exposure of interventions aimed at retirees. Workplaces could be used to introduce the least active employees to physical activities that can be adopted and maintained into later life and signpost them to relevant services in the community for ongoing participation post-retirement. Even though retirement appears to be an important life period, interventions focussing on this transition are scarce (376). There is, however, emerging evidence that recruiting retirees via employers is feasible (377) and that interventions focussed on recently retired adults are effective (378).

8.6 Implications for future research

This thesis is one of the first studies to use GBTM to identify the trajectories of physical activity over an extended period of the adult life course and to examine their predictors and consequences for later health. However, additional research questions have emerged as a result of the findings and the limitations of this thesis. Specifically, there is a need to examine physical activity trajectories across the entire life course and to replicate these studies in women and underrepresented groups. Further research to translate these findings into interventions is also required. This section discusses the implications and recommendations for future epidemiological research arising from this thesis.

8.6.1 Investigating physical activity trajectories and understanding their determinants and consequences for health in women and minority ethnic groups

One of the key limitations of the BRHS is that the sample comprises of only men, predominantly of white ethnicity. Therefore, the findings cannot be generalised to women and black and minority ethnic groups. Future studies should seek to replicate these analyses in cohorts that include these groups. This could be important as we know that physical activity levels and CVD risks vary according to gender and ethnicity (304, 379, 380). Not only are women generally less active than men but their physical activity is accumulated differently (304). Men tend to participate less in physical activity in the home and more in leisure-based activities when compared to women (379, 380). Preferences for specific sports/exercises are also specific to gender. For example, in older adults more men play golf than women, while more women swim regularly than men (304). Participation rates in specific sports and activities also differ in older adults according to ethnicity (304). When compared to older white British adults, golf and bowls participation is less frequent among older adults from black and minority ethnic groups, whereas

conditioning exercises and fitness classes are equally if not more common. Women also typically develop CVD later than men (381) and black and minority groups have higher rates of CVD than those from white backgrounds (382). As mentioned in Chapter 4, the popularity of specific sports/exercises varies in different regions and cultures and so these findings could also be country specific. Studies in specific populations could demonstrate whether trajectories of physical activity differ according to location and if tailored intervention strategies are required.

8.6.2 Investigating physical activity trajectories and their determinants and consequences for health across the entire life course

Another limitation of the BRHS is that participants were recruited in midlife and not earlier. Subsequently this thesis only focusses on the adult life course. Physical activity habits could be deeply ingrained before midlife and thus may be less modifiable during later life stages. It is well established that physical activity levels in childhood predict physical activity levels in early adulthood (17, 383), yet how physical activity develops from birth to old age remains unclear. It is also possible that certain early life exposures are critical for lifelong physical activity.

Existing birth cohort studies, such as the Millennium Cohort study, may be suitable in the future to explore the origins of physical activity across the entire life course and provide more up-to-date evidence. However, there may be significant time lag before such studies will be sufficiently powered to link with disease endpoints. Issues regarding the comparability of physical activity measures across waves could also make life course analysis problematic. Current and future cohort studies should retain the same measurement tools over time where possible or use comparable measures to facilitate life course analysis. Future studies would also benefit from more frequent and equally spaced follow ups. As mentioned in previous chapters, important fluctuations in physical activity could have been missed in the gaps between follow ups. New technologies, such as smart phone apps, may facilitate and offer additional opportunities for routine collection of physical activity data across the life course, providing rich real-time contextual information.

8.6.3 Investigating physical activity trajectories using device-based measures

While a key strength of this thesis is that the self-reported measure of physical activity has been validated against device-based measures and provides contextual information, wearable devices may provide more accurate information on the volume and intensity of physical activity (384). The recall, social desirability and misclassification biases associated with self-report measures may be reduced with modern measurement approaches. Recent technological

advancements have made wearable devices more user friendly, improving compliance and feasibility for use in large cohort studies (385). Further prospective studies using device-based measures are required to see whether similar trajectories emerge and to provide more precise estimates on the volume of physical activity that is required across the life course to achieve health benefits. This may be particularly useful for informing physical activity recommendations, which emphasise attaining a specific amount of physical activity.

8.6.4 Health consequences of physical activity and sport type trajectories

This thesis explored the associations between total physical activity trajectories and health outcomes. It may also be possible to use BRHS data to explore associations between major physical activity types (i.e. walking, recreational activity and sport/exercise) and health outcomes, but the BRHS is insufficiently powered to explore associations between very specific types of sport/exercise and health outcomes. Several studies have attempted to understand the health benefits of specific types of physical activity and sport, but they have typically only measured participation at one or two time points (221, 253, 359-361). For example, racquet sports participation has been shown to be one of the most favourable activities in midlife for reducing mortality risk (253), yet it is rarely sustained into old age, as shown in chapter 4 of this thesis. Further cohort studies are required to understand the predictors and health benefits of long-term participation in specific physical activities, but they would need to be very large to be sufficiently powered to explore these associations. Of particular interest may be activities that are regularly maintained and adopted in later life, such as golf, bowls and walking. As mentioned above, there has been significant attention on the health benefits of walking and golf, but no research has been conducted on the benefits of bowling games to my knowledge. Such research could inform strategies to target the most beneficial and feasible sport types, particularly in the least active. Notably, future research should consider that isolating the effects of specific physical activities requires some means of adjusting for participation in all other types of physical activity.

8.6.5 Qualitative investigations of life course physical activity

The emerging body of evidence on the determinants of changes and trajectories of physical activity over the life course has been acquired primarily from quantitative research. However, qualitative or mixed research methods could be used in this context to gain a more in-depth understanding of what drives long-term engagement, change or maintenance of physical activity across the life course. They may also help explain why some older adults' activity levels change

following major life events and others do not, which may not be possible using quantitative data alone. For example, it would be informative to explore further why the effects of retirement differ between active and inactive retirees. Further, it might help explain why golf and bowls track strongly during old age, while racquet sports track much weaker. Previous studies interviewing older adults have helped to gain a more in-depth understanding about key barriers, motivators and life events that influence physical activity across the life course (386-388). Qualitative approaches to facilitate recall across the life course, such as lifeline interviews, are increasingly being used in this field (389). Such research has only been conducted in individuals who are continually active across the life course (386, 387) but, as identified in this thesis, there are other individuals who follow different trajectories of physical activity that may offer additional insights. Involving individuals with lived experiences are important for highlighting opportunities for intervention that are valid and reflect the needs of the target group (390).

8.7 Concluding statement

As the proportion of older adults in the UK population continues to grow, prevention of CVD, a major cause of mortality and morbidity, is an increasingly important goal. Physical activity is one of the most beneficial modifiable risk factors that can help prevent CVD. As physical activity is potentially modifiable, it is important to understand how it develops across the life course and how lifelong participation impacts health outcomes in old age.

This thesis has shown that physical activity levels in midlife, or prior, largely determine subsequent activity levels throughout adulthood and into old age. Generally, the most active tend to remain the most active and the least active tend to remain the least active. Age-related changes in participation and predictors of these changes are specific to physical activity type, highlighting important opportunities for intervention.

Higher sustained levels of physical activity from midlife to old age were associated with the lowest risk of CVD and mortality. However, maintaining a light level of physical activity across the adult life course also provided significant benefit. Physical activity history proved to be important in determining CVD risk factor levels but measures of current activity may be the most convenient and efficient means for determining subsequent risk of CVD and mortality.

Overall, the results highlight the importance of promoting early engagement in a range of physical activities to support lifelong participation and reduce the risk of CVD and all-cause mortality in old age.

APPENDICES

Appendix 1A. Conference oral presentations

Aggio D, Papachristou E, Papacosta O, Lennon LT, Ash S, Whincup PH, Wannamethee SG, Jefferis BJ. Physical activity trajectories and predictors during the transition to old age. J Epidemiol Community Health 2017;71:A34. Presented at Society for Social Medicine annual scientific meeting, Manchester, 7th September, 2017

Aggio D, Papachristou E, Papacosta O, Lennon LT, Ash S, Whincup PH, Wannamethee SG, Jefferis BJ. Trajectories of physical activity types and their predictors during the transition to old age: a 20-year cohort study of British men. J Phys Act Health 2018;15(10) Suppl:S1-S249. Presented at the 7th International Society for Physical Activity and Health Congress, London, 15th October, 2018

Appendix 1B. Conference poster presentations

Aggio D, Papachristou E, Papacosta O, Lennon LT, Ash S, Whincup PH, Wannamethee SG, Jefferis BJ. Trajectories of Physical Activity from Midlife to Old Age and Associations with Subsequent Cardiovascular Disease and All-Cause Mortality in British Men. Presented at the UCL Populations & Lifelong Health Domain Symposium on Tuesday 26 March, 2019.

Aggio D, Papachristou E, Papacosta O, Lennon LT, Ash S, Whincup PH, Wannamethee SG, Jefferis BJ. Association Between Twenty-year Trajectories of Physical Activity From Midlife to Old Age and Cardiovascular Disease Risk Factors: A 20-Year Cohort Study of British Men. Circulation. 2018;137:AMP33. Presented at the EPI/Lifestyle 2018 Scientific Sessions, New Orleans, 21st March, 2018 and at the UCL Faculty of Population Health Sciences Postgraduate Research Symposium, 2018.

Appendix 2A. Search terms for relevant literature

Population:

Old* adult*; Old* age; Ageing/aging; Elder*; Geriatric*

Physical activity measures:

Physical activ*; Exercise; Sport; Walk*; Strengthening; Resistance training; Weight training

Study design:

Track*; Longitudinal*; Stability; Change*; Trajector*; Patterns

Key outcomes:

Cardiovascular disease; Coronary heart disease ; Heart disease; Myocardial infarction; Heart attack; Stroke; Cerebrovascular; Mortality; Death; Morbidity

Appendix 3A. Standard medical record review form

Serial No: <SERNO>

Name: <FIRST NAME> <SECOND NAME> <SURNAME>

Address: <ADDR1>
<ADDR2>
<ADDR3>
<ADDR4> <POSTCODE>

Please tick if address is correct ☐

New address:

DOB: <DOB>

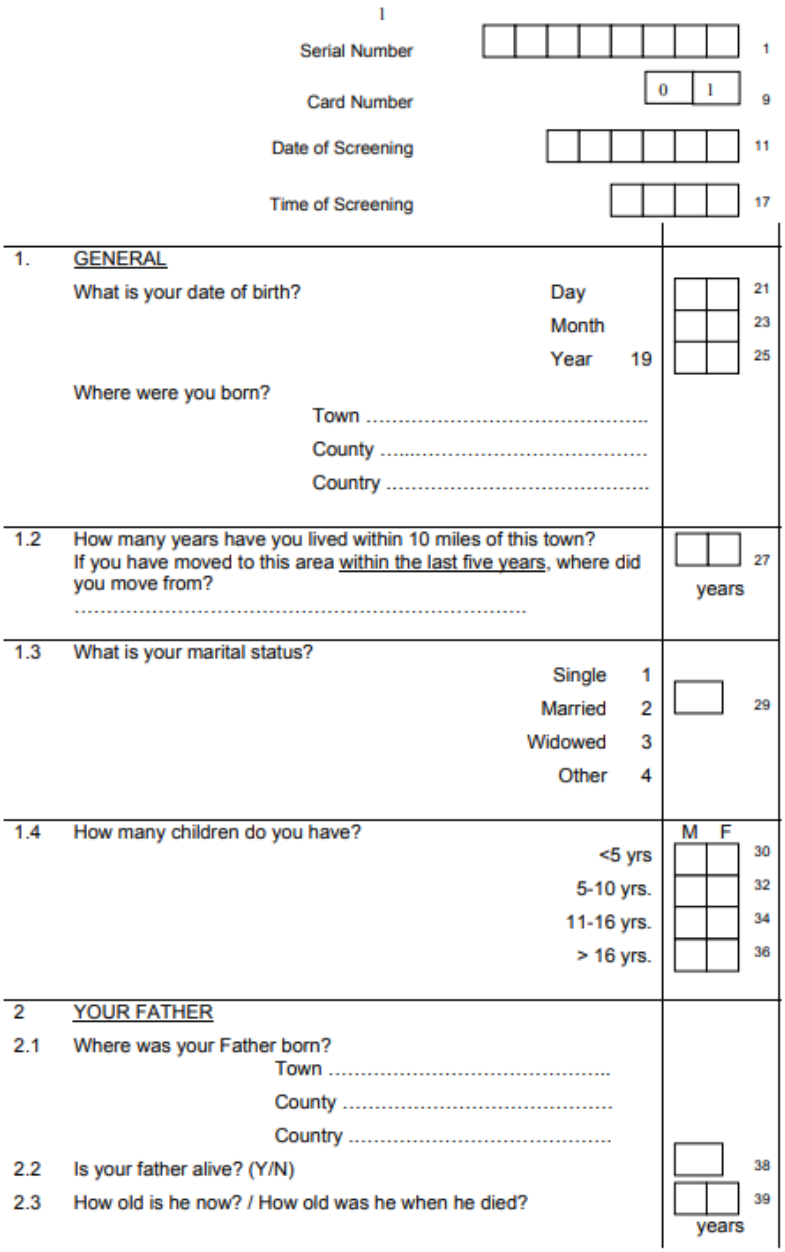
NHS No: <NHS>

THE QUESTIONS ON THIS PAGE (1-6) RELATE TO THE PERIOD FROM 1ST JANUARY 2000 TO DATE

		YES	NO	
1	Is the above patient still registered with you ?	☐	☐	
2	Has he **consulted** you since 1st January 2000?	☐	☐	
3	Was any consultation for a **new episode** of:	YES	NO	(day, month, year)
	Myocardial Infarction (MI) Heart attack, Coronary thrombosis	☐	☐	Date: .....
	Angina Exertional or stress related chest pain	☐	☐	Date: .....
	Stroke Cerebrovascular accident (CVA), cerebral thrombosis, haemorrhage, embolism	☐	☐	Date: .....
	Transient Ischaemic Attack (TIA) Cerebrovascular disturbance (<24 hours); leaving no residual damage	☐	☐	Date: .....
	Diabetes (NIDDM Type 2 / IDDM Type 1)	☐	☐	Date: .....
	Heart Failure Congestive Cardiac Failure - (CCF) or Left Ventricular Failure - (LVF)	☐	☐	Date: .....
	Other Cardiovascular disease:			
	Peripheral Arterial Disease (PAD,PVD) Intermittent claudication, lower limb ischaemia	☐	☐	Date: .....
	Aortic Aneurysm rupture, dissection	☐	☐	Date: .....
	Deep Vein Thrombosis (DVT) blood clot in the leg	☐	☐	Date: .....
	Pulmonary Embolism (PE) blood clot in the lung	☐	☐	Date: .....
4	Has he been referred to a Consultant for any new cardiovascular condition?	YES ☐	NO ☐	Date: .....
	Diagnosis :			
5	Have any of the following procedures taken place:	YES	NO	
	Coronary Artery Bypass Graft (CABG)	☐	☐	Date: .....
	Coronary Angioplasty (PTCA) Percutaneous coronary angioplasty, balloon treatment. Insertion of stents ☐	☐	☐	Date: .....
6	Has he had a Cancer diagnosis?	YES ☐	NO ☐	Date: .....
	Site:			

1.

Appendix 3B. Baseline questionnaire in 1978-80



1

Serial Number [ ][ ][ ][ ][ ][ ][ ] 1

Card Number [0][1] 9

Date of Screening [ ][ ][ ][ ][ ][ ] 11

Time of Screening [ ][ ][ ][ ] 17

1. GENERAL

What is your date of birth? Day [ ][ ] 21

Month [ ][ ] 23

Year 19 [ ][ ] 25

Where were you born?

Town .....

County .....

Country .....

1.2 How many years have you lived within 10 miles of this town? If you have moved to this area within the last five years, where did you move from? [ ][ ] 27 years

.....

1.3 What is your marital status? [ ] 29

Single 1

Married 2

Widowed 3

Other 4

1.4 How many children do you have?

	M	F	
<5 yrs	[ ]	[ ]	30
5-10 yrs.	[ ]	[ ]	32
11-16 yrs.	[ ]	[ ]	34
> 16 yrs.	[ ]	[ ]	36

2 YOUR FATHER

2.1 Where was your Father born?

Town .....

County .....

Country .....

2.2 Is your father alive? (Y/N) [ ] 38

2.3 How old is he now? / How old was he when he died? [ ][ ] 39 years

2.4 If your father has died, what were you told was the cause of his death?

Heart trouble	1	
High blood pressure	2	
Stroke	3	☐ 41
Respiratory disease	4	
Cancer of lung	5	
Other cancer	6	
Accident or injury	7	
Other	8	
Don't know	9	

3 YOUR MOTHER

3.1 Where was your mother born?

Town .....

County .....

Country .....

3.2 Is your mother alive? (Y/N) ☐ 42

3.3 How old is she now? / How old was she when she died? ☐☐ years 43

3.4 If your mother has died, what were you told was the cause of her death?

Heart trouble	1	
High blood pressure	2	
Stroke	3	☐ 45
Respiratory disease	4	
Cancer of breast	5	
Other cancer	6	
Accident or injury	7	
Other	8	
Don't know	9	

4. OCCUPATION

4.1 What is your present job? .....

If employed go to question 4.4

4.2 If you are unemployed, for how long has this been?

<6weeks	1	
6wk.-5mo.	2	
6mo. –1yr.	3	☐ 46
> 1 year	4	

4.3 Is this because of ill health? (Y/N) ☐ 47

.....

4.4 What kind of work have you done for the longest period of time?

.....

4.5 What business or industry is this?

.....

4.6 How many years have you done this kind of work? ☐☐ years 48

4.7 Are / were you:

SELF-EMPLOYED	with 25 or more employees	1	☐ 50
	with less than 25 employees	2	
	without employees	3	
MANAGER	of 25 or more people	4	
	of less than 25 people	5	
FOREMAN	.....	6	
ORDINARY EMPLOYEE	.....	7	
ARMED SERVICES	.....	8	

5 SEVERE CHEST PAIN

5.1 Have you ever had a severe pain in your chest lasting for half an hour or more? (Y/N) ☐ 51

If NO, go to question 6.

5.2 Where did you get this severe pain? ☐ 52

(Show chart.)

5.3 Did you see a doctor because of this pain? (Y/N) ☐ 55

6 CHEST PAIN

6.1 Do you ever have any pain or discomfort in your chest? (Y/N) ☐ 56

If NO, go to question 7.

6.2 When last did you get the pain?

		☐ 57
Within 1 month	1	
1-5 months ago	2	
6-12 months ago	3	
Over 1 year ago	4	
Occasionally	5	

6.3 How often do you get it?

Daily	1
Weekly	2
Monthly	3
Once only	4
Occasionally	5

58

6.4 Where do you get this pain or discomfort?

(Show chart.)

59

6.5 When you walk at an ordinary pace on the level, does this produce the pain? (Y/N) 62

6.6 When you walk uphill or hurry, does this produce the pain? (Y/N) 63

6.7 When you get any pain or discomfort in your chest on walking, what do you do?

Stop	1
Slow down	2
Continue at the same pace	3

64

6.8 Does the pain or discomfort in your chest go away if you stand still? (Y/N) 65

6.9 How long does it take to go away?

10 minutes or less	1
more than 10 minutes	2

66

7.0 PHLEGM, COUGH AND BREATHING

7.1 Do you usually bring up phlegm (spit) from your chest first thing in the morning in the winter? (Y/N) 67

If NO, go to question 7.4

7.2 Do you bring up phlegm like this on most days for as much as 3 months in the winter each year? (Y/N) 68

7.3 In the past 3 years have you ever had a period of increased cough and phlegm lasting 3 weeks or more?

Yes, once	1
Yes, twice or more	2
Never	3

66

7.4 Does your chest sound wheezy or whistling on most days (or nights)? (Y/N) 70

7.5	Does the weather affect your breathing? And if so, at what season of the year is it most affected? Not affected 1 Winter 2 Summer 3 Both 4	☐ 71
8	BREATHLESSNESS	
8.1	Do you get short of breath walking with people your own age on level ground? (Y/N)	☐ 72
8.2	On walking up hills or stairs, do you get more breathless than people you on age? (Y/N)	☐ 73
8.3	Do you ever have to stop walking because of breathlessness? (Y/N)	☐ 74
	S.E.G.	☐☐ 75
	Social class	☐ 77
	Activity score	☐ 78

Serial Number | | | | | | | | |

Card Number | 0 | 2 |

9	**LEG PAIN**		
9.1	Do you ever get pain in your calf muscles on walking at an ordinary pace, on the level? (Y/N)		11
9.2	Do you get pain in your calf muscles when you walk uphill or hurry? (Y/N)		12
10	**MEDICAL HISTORY**		
10.1	Have you ever been told by a doctor that you have, or have had, any of the following?		
	Angina (Y/N)		13
	Heart attack (Y/N)		14
	Coronary thrombosis (Y/N)		15
	Myocardial infarction (Y/N)		16
	Other heart trouble (Y/N)		17
	High blood pressure (Y/N)		18
	Stroke (Y/N)		19
	Diabetes (Y/N)		20
	Peptic ulcer (Y/N)		21
	Gout (Y/N)		22
	Gall bladder disease (Y/N)		23
	Thyroid disease (Y/N)		24
	Arthritis (Y/N)		25
	Bronchitis (Y/N)		26
	Asthma (Y/N)		27
	Other condition (s) including surgery..... (Y/N)		28
10.2	Are you on any regular medical treatment from a doctor for any condition? (Y/N)		29
	If NO, go to question 10.3		
	Do you know if the pills / medicines /injections are:-		
	Tranquillizers Y/N		30
	Pain killers Y/N		31
	Antihypertensive drugs Y/N		32
	Anti coagulants Y/N		33
	Lipid lowering drugs Y/N		34

Oral antidiabetics	Y/N		35
Injection of insulin	Y/N		36
Any others	Y/N		37
Don't know	Y/N		38

10.3 Have you taken any of these in the last 48 hours?

Tranquillizers	Y/N		39
Pain killers	Y/N		40
Antihypertensive drugs	Y/N		41
Anti coagulants	Y/N		42
Lipid lowering drugs	Y/N		43
Oral antidiabetics	Y/N		44
Injection of insulin	Y/N		45
Any others	Y/N		46
Don't know	Y/N		47

11 DIET & ALCOHOL

11.1 How many times during an average week would you have the following foods?

Meat (including beef, lamb, pork, bacon in any form)		48
Chicken		50
Fish		52
Eggs - how many eggs do you eat in a week		54
Cheese – how often do you eat cheese, including cheese dishes?		56
Breakfast cereals – how often do you eat these (porridge included)? State kind		58

11.2 What kinds of bread do you eat ?

White	Y/N		60
Brown	Y/N		61
Wholemeal	Y/N		62
Other	Y/N		63

11.3 Spreading fats: What kinds do you use at home?

Butter	Y/N		64
Margarine	Y/N		65

(State kind or brand name.)

11.4 Do you take sugar?

In tea	Y/N		66
In coffee	Y/N		67
In other drinks	Y/N		68

11.5 Do you use milk?

On cereals	Y/N		69
In tea	Y/N		70
In coffee	Y/N		71
As a milk drink	Y/N		72

11.6 (i) Would you describe your present alcohol intake as:

None	1		
On special occasions only	2		
Once or twice a month	3		73
Weekends	4		
Daily / most days	5		

<u>If NONE, go to question 12</u>

(ii) What type of drink do you usually take?

Beer	1		
Spirits	2		
Wine/sherry	3		74
Mixed beer & spirits	4		
Mixed beer, spirits, wine and sherry	5		

(iii) How much do you usually take?

2 drinks a day or less	1		
3-6 drinks a day	2		
more than 6 drinks a day	3		75

(One drink is a single whisky, gin or brandy, a glass of wine, sherry or port or half a pint of beer.)

Serial Number

Card Number 0 3

12 SMOKING

12.1 (i) Do you smoke at present?

Yes, regularly	1	
No	2	11
Occasionally	3	

If NO, go to question 12.6

(ii) How old were you when you started? years 12

(iii) Have you ever given up smoking? (Y/N) 14

(iv) If yes, what is the maximum time for which you have given up smoking? years 15

12.2 (i) Do you smoke cigarettes now?

Yes regularly	1	
No	2	17
Occasionally (<1 day)	3	

If NO, or OCCASIONALLY go to question 12.3

(ii) How many cigarettes do you usually smoke a day? 18

(iii) If hand rolled, how much tabacco do you use a week? (ozs.) ozs. 20

Now proceed to 12.4

12.3 (i) Were you previously a regular cigarette smoker? (Y/N) 22

(ii) If Yes, how many cigarettes did you usually smoke a day? 23

(iii) At what age did you change to a pipe and / or cigars? years 25

12.4 (i) Do you smoke a pipe now?

Yes regularly	1	
No	2	27
Occasionally	3	

If NO or OCCASIONALLY go to question 12

(ii) If YES, how many ozs. a week do you smoke? ozs. 20

12.5 (i) Do you smoke a pipe now?

Yes regularly	1	
No	2	30
Occasionally	3	

(ii) If YES, how many cigars do you smoke a day?

Large	31
Small	32

If you smoke ANYTHING currently, go to question 13.

12.6 (i) Have you ever smoked for a more than 1 month ? (Y/N) [ ] 35

How much did you usually smoke

Cigarettes (per day)		[ ][ ] 36 38
Pipe (ozs) (per week)		[ ][ ] 40
Cigars (per day)	Large	[ ][ ] 42
	Small	

If NO, go to question 13.

(ii) At what age did you start smoking? [ ][ ] years 44

(iii) At what age did you finally stop smoking? [ ][ ] years 46

(iv) What was the maximum time between these two ages for which you gave up smoking? [ ][ ] years 48

13 EXERCISE

13.1 (i) Do you usually walk or cycle in the course of your journeys to or from work each day?

No	1
Walk	2
Cycle	3

[ ] 50

If YES, how many minutes do these journeys take? [ ][ ] mins 51

(ii) Apart from your journeys to or from work, do you usually walk or cycle on weekdays?

No	1
Walk	2
Cycle	3

[ ] 50

If YES, how many minutes do you walk/cycle each day? [ ][ ] mins 51

(iii) Would you say that in your occupation you are physically :

Very active	1
Fairly active	2
Average	3
Fairly inactive	4
Very inactive	5

[ ] 56

13.2 On average, a man of your age spends 4 hours on most weekends on some of the following activities: walking, gardening, household chores, DIY projects. Compared to such a man, how physically active do you consider yourself?

Very active	1
Fairly active	2
Average	3
Fairly inactive	4
Very inactive	5

[ ] 57

13.3 Apart from these activities, do you take active physical exercise, e.g. running, digging, swimming, tennis, golf, sailing, etc.

No	1	
Occassionally	2	☐ 58
Frequently	3	

If NO or Occasionally – stop here.

13.4 Please state type of activity.....

13.5 How many years have you been involved in this activity? ☐☐ years 59

13.6 How many times a month (on average) do you undertake these activities?

Winter	☐☐	61
Summer	☐☐	63

Administrator	☐	65
Coder	☐	66

Appendix 3C. Postal questionnaire in 1992

Selected questions on physical activity

18.0 *Physical activity*

18.1 Do you usually walk or cycle in the course of your journey to or from work each day?

No	☐ 1	
Walk	☐ 2	39
Cycle	☐ 3	
Not applicable	☐ 4	

If YES,

18.2 How many minutes do these journeys take in total each day? ☐ minutes 40-42

18.3 Apart from any journeys to or from work, do you usually walk or cycle on weekdays?

No	☐ 1	
Walk	☐ 2	43
Cycle	☐ 3	

If YES,

18.4 How many minutes do these journeys take in total each day? ☐ minutes 44-46

18.5 Would you say that in your occupation you are or were physically

Very active	☐ 1	
Fairly active	☐ 2	
Average	☐ 3	47
Fairly inactive	☐ 4	
Very inactive	☐ 5	

18.6 *On average a man of your age spends 4 hours on most weekends on some of the following activities:*
walking, gardening, household chores, DIY projects.

Compared to such a man, how physically active do you consider yourself?

Very active	☐ 1	
Fairly active	☐ 2	
Average	☐ 3	48
Fairly inactive	☐ 4	
Very inactive	☐ 5	

card 3

18.7 How many hours a week do you spend gardening

	In the spring/summer	In the autumn/ winter?	
Hours of light gardening work per week	☐	☐	49-52
Hours of moderate gardening work per week	☐	☐	53-56
Hours of heavy digging gardening work per week	☐	☐	57-60

18.8 Do you take active physical exercise such as running, swimming, golf, tennis, squash, jogging, bowls, cycling etc.?

No	☐ 1	
Occasionally (less than once a month)	☐ 2	61
Frequently (once a month or more)	☐ 3	

If you ticked **No** or **Occasionally** then please go to question 19.0

If you ticked **Frequently** (once a month or more),

18.9 Please state type of activities :

☐ *office use* ☐☐ 62-63

18.10 How many years have you been involved in this activities ? ☐ 64-65

18.11 How many **times** a month (on average) do you take part in this activities in

Winter	☐	66-67
Summer	☐	68-69

Appendix 3D. Postal questionnaire in 1996

Selected questions on physical activity

18.0 **Physical Activity**

18.1 Do you usually walk or cycle in the course of your journey to or from work each day ?

No	1
Walk	2
Cycle	3
Not applicable	4

If Yes,

18.2 How many minutes do these journeys take in total each day ? _____minutes

18.3 Apart from any journeys to or from work, do you usually walk or cycle on weekdays?

No	1
Walk	2
Cycle	3
Both	4

If Yes,

18.4 How many minutes do these journeys take in total each day ? _____minutes

18.5 Compared with a man who spends four hours on most weekends on activities such as: walking, gardening, household chores, DIY projects, how physically active would you consider yourself ?

Much more active	1
More active	2
Similar	3
Less active	4
Much less active	5

18.6 Do you take active physical exercise such as running, swimming, golf, tennis, squash, jogging, bowls, cycling etc.?

No	1
Occasionally (less than once a month)	2
Frequently (once a month or more)	3

If you ticked **frequently** please state type of activities :

office use

_____

How many years have you been involved in this activity ? _____

18.7 How many times a **month** (on average) do you take part in this activity?

In winter _____

In summer _____

Appendix 3E. Questionnaire in 1998-2000 at twenty-year follow-up

Selected questions on physical activity

Physical Activity

12.0 Do you make regular journeys every day or most days either walking or cycling ?

No	☐1
Walk	☐2
Cycle	☐3
Both	☐4

12.1 How long do you spend on all forms of walking in an average week ? ☐☐ hours

12.2 Which of the following best describes your usual walking pace

Slow	☐1
Steady average	☐2
Fairly brisk	☐3
Fast (at least 4 mph)	☐4

12.3 How long do you spend cycling in an average week ? ☐☐ hours

12.4 Compared with a man who spends four hours on most weekends on activities such as: walking, gardening, household chores, DIY projects, how physically active would you consider yourself?

Much more active	☐1
More active	☐2
Similar	☐3
Less active	☐4
Much less active	☐5

12.5 Do you take active physical exercise such as running, swimming, dancing, golf, tennis, squash, jogging, bowls, cycling, hiking, etc.?

No	☐1
Occasionally (less than once a month)	☐2
Frequently (once a month or more)	☐3

(a) If you ticked **frequently** please state type of activities : OFFICE USE

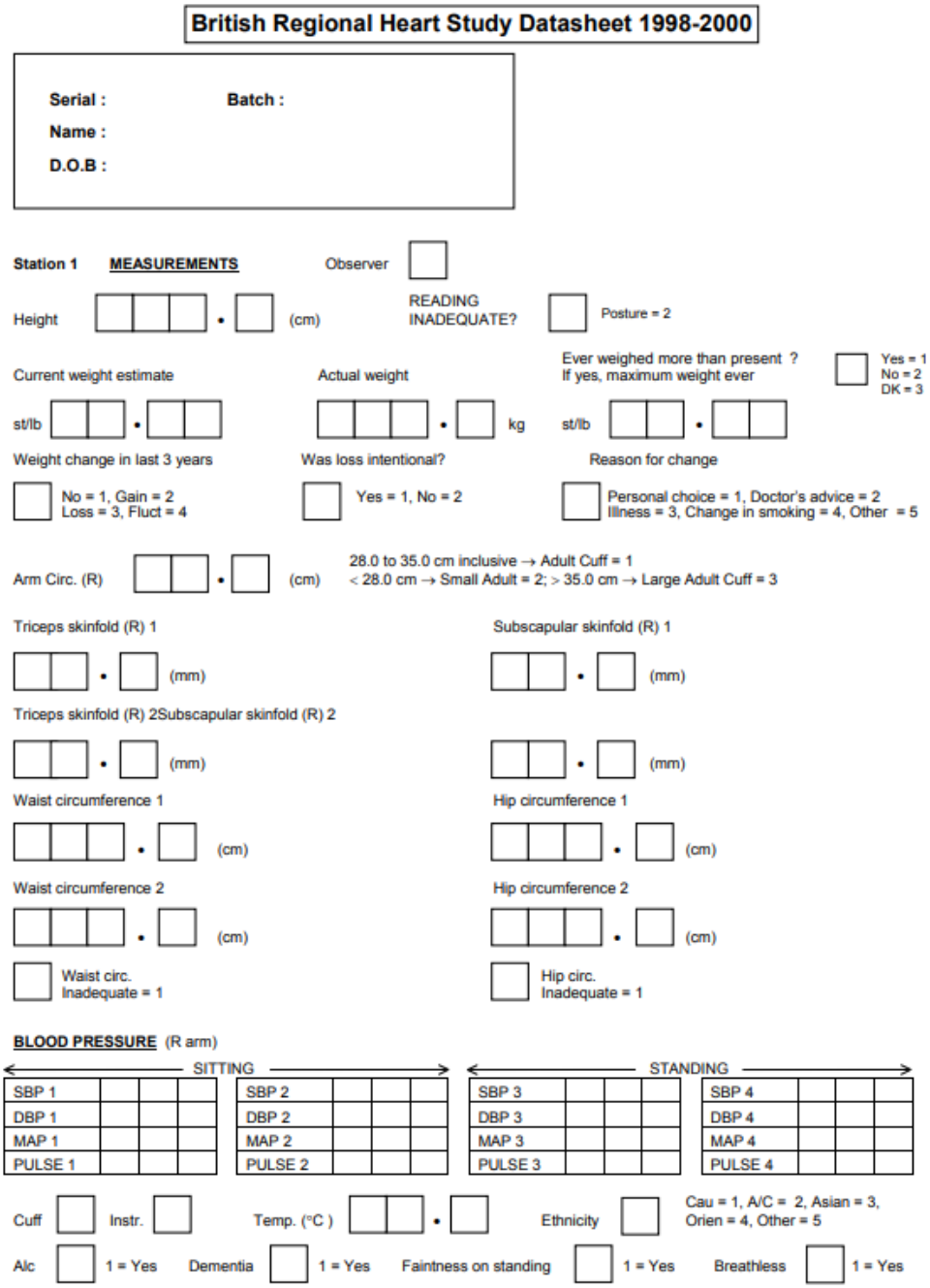
_____ ☐☐

(b) How many years have you been engaged in these sort of physical activities ? ☐☐

(c) How many times a **month** (on average) do you take part in these activities (give overall total)?

In winter ☐☐ In summer ☐☐

Appendix 3F. Data sheet from physical examination in 1998-2000 at twenty-year follow-up



British Regional Heart Study Datasheet 1998-2000

Serial : **Batch :**

Name :

D.O.B :

Station 1 **MEASUREMENTS** Observer

Height (cm) READING INADEQUATE? Posture = 2

Current weight estimate st/lb

Actual weight kg

Ever weighed more than present ? If yes, maximum weight ever st/lb Yes = 1 No = 2 DK = 3

Weight change in last 3 years No = 1, Gain = 2 Loss = 3, Fluct = 4

Was loss intentional? Yes = 1, No = 2

Reason for change Personal choice = 1, Doctor's advice = 2 Illness = 3, Change in smoking = 4, Other = 5

Arm Circ. (R) (cm) 28.0 to 35.0 cm inclusive → Adult Cuff = 1 < 28.0 cm → Small Adult = 2; > 35.0 cm → Large Adult Cuff = 3

Triceps skinfold (R) 1 (mm)

Subscapular skinfold (R) 1 (mm)

Triceps skinfold (R) 2Subscapular skinfold (R) 2 (mm)

(mm)

Waist circumference 1 (cm)

Hip circumference 1 (cm)

Waist circumference 2 (cm)

Hip circumference 2 (cm)

Waist circ. Inadequate = 1

Hip circ. Inadequate = 1

BLOOD PRESSURE (R arm)

SITTING								STANDING							
SBP 1				SBP 2				SBP 3				SBP 4			
DBP 1				DBP 2				DBP 3				DBP 4			
MAP 1				MAP 2				MAP 3				MAP 4			
PULSE 1				PULSE 2				PULSE 3				PULSE 4			

Cuff Instr. Temp. (°C) Ethnicity Cau = 1, A/C = 2, Asian = 3, Orien = 4, Other = 5

Alc 1 = Yes Dementia 1 = Yes Faintness on standing 1 = Yes Breathless 1 = Yes

SPIROMETRY Instr. ☐

No. Readings ☐☐ BTV % ☐☐.☐

FVC	☐.☐☐	Measured values only
FEV 0.5	☐.☐☐	
FEV 1	☐.☐☐	
PEF	☐☐☐	
FEF 25-75	☐.☐☐	
FEF 75-85	☐.☐☐	
FEF 25	☐.☐☐	
FEF 50	☐.☐☐	
FEF 75	☐.☐☐	

Readings inadequate? ☐ Inad=1

Spirometer Output

Station 2 Observer ☐

LEFT SIDE		RIGHT SIDE	
Ankle oedema ☐	Yes = 1, No = 2	Ankle oedema ☐	Yes = 1, No = 2
Leg ulcer ☐	Sole = 1, Ankle = 2, Shin = 3	Leg ulcer ☐	Sole = 1, Ankle = 2, Shin = 3
Pulses		Pulses	
Dorsalis Pedis ☐	Yes = 1, No = 2	Dorsalis Pedis ☐	Yes = 1, No = 2
Post Tibial ☐	Yes = 1, No = 2	Post Tibial ☐	Yes = 1, No = 2
Pacemaker ☐	Yes = 1, No = 2		

↓ Impedance ☐☐☐

ECG ☐ Yes = 1, No = 2

BLOOD SAMPLING

Success ☐ No = 0, Part = 1, All = 2 Failure ☐ Refusal = 1 No sample = 2 Time ☐☐ • ☐☐

↓

Tube missing (=1) ☐ ☐ ☐ ☐ ☐ ☐ ☐

AE FJ K LP QR T U

Station 3 **BLOOD ALIQUOTTING** Observer ☐

All tubes filled ? ☐ Yes =1, No = 2

Tube missing (=1)

☐☐☐☐☐ ☐☐☐☐☐ ☐

A B C D E F G H I J K

☐☐☐☐☐ ☐☐

L M N O P Q R

Appendix 4A. Participation within sport and exercise groupings at baseline

Sport group	Frequency
Bowling	
Bowls	85% (63)
Curling	4% (3)
Skittles	11% (8)
Dancing	
Ballroom	50% (21)
Unspecified	45% (19)
Sequence	5% (2)
Racquet sports	
Tennis	24% (75)
Badminton	35% (109)
Squash	32% (101)
Table tennis	9% (29)
Surface water sports	
Sailing/boating	79% (56)
Canoeing/Rowing	16% (11)
Other water sports	6% (4)
Cycling	
Leisure Cycling	10% (24)
Transport	89% (219)
Exercise bike	1% (3)
Aerobics/fitness training[a]	
Keep fit classes	23% (12)

Sport group	Frequency
Aerobics	64% (33)
Cardiovascular machines	14% (7)
Other (top 5 reported)	
Hunting/shooting	13% (15)
Officiating	12% (13)
Fishing	15% (17)
Hockey	9% (10)
Coaching	9% (10)

[a] Prevalence from 20-year follow up

Appendix 4B. Stability of physical activity variables categorised into 3 levels, n=3413

	Wave 1 to 2	Wave 1 to 3	Wave 1 to 4
	Kappa	Kappa	Kappa
Physically activity[a]	0.24	0.21	0.22
Sport participation[b]	0.33	0.31	0.31
Recreational activity[c]	0.19	0.14	0.13
Walking[d]	0.12	0.09	0.08

[a] Physical activity was categorised as low (inactive, occasional) medium (light, moderate) and high (moderately vigorous, vigorous)

[b] Sport participation was categorised as none, occasional (less than once a month) and frequently (once a month or more)

[c] Recreational activity was categorised as low (<4 hours at the weekend), medium (similar to 4 hours at the weekend) and high (>4 hours at the weekend)

[d] Walking was categorised as low (<20 minutes/day), medium (21-60 minutes/day) and high (>60 minutes/day)

Note. Kappa statistics are presented for participants with a valid physical activity score at all four time points (n=3413). Data on walking was missing for an additional 15 participants at 12 year follow up, 3 participants at 16-year follow up and 1 participant at 20-year follow up. Data on sport participation was missing for 33 participants at 12 year follow up, 68 participants at 16 year follow up and 34 participants at 20 year follow up.

Appendix 4C. Odds of being active at 20 year follow up according to baseline activity levels categorised into 3 levels.

		Model 1	Model 2	Model 3
	N	OR (95% CI)	OR (95% CI)	OR (95% CI)
Physical activity				
Low	1156	1.0	1.0	–
Medium	1321	**2.1 (1.8, 2.4)**	**2.0 (1.7, 2.4)**	
High	936	**5.3 (4.3, 6.5)**	**5.0 (4.0, 6.2)**	–
Sport				
None	1705	1.0	1.0	1.0
Occasional	392	**1.9 (1.5, 2.3)**	**1.8 (1.4, 2.3)**	**1.7 (1.3, 2.2)**
Frequent	1316	**3.3 (2.8, 3.9)**	**3.1 (2.6, 3.7)**	**3.0 (2.5, 3.5)**
Recreational activity				
Low	415	1.0	1.0	1.0
Medium	1086	**1.6 (1.3, 2.0)**	**1.5 (1.2, 1.9)**	**1.5 (1.1, 1.8)**
High	1912	**2.6 (2.1, 3.2)**	**2.5 (2.0, 3.1)**	**2.1 (1.7, 2.7)**
Walking				
Low	2495	1.0	1.0	1.0
Medium	802	**1.5 (1.2, 1.7)**	**1.5 (1.2, 1.7)**	**1.4 (1.2, 1.7)**
High	116	**2.0 (1.3, 3.2)**	**2.1 (1.3, 3.3)**	**2.1 (1.3, 3.4)**

[a] Physical activity at baseline was categorised as low (inactive, occasional) medium (light, moderate) and high (moderately vigorous, vigorous)

[b] Sport participation was categorised as none, occasional (less than once a month) and frequently (once a month or more)

[c] Recreational activity was categorised as low (<4 hours at the weekend), medium (similar to 4 hours at the weekend) and high (>4 hours at the weekend)

[d] Walking was categorised as low (<20 minutes/day), medium (21-60 minutes/day) and high (>60 minutes/day)

Model 1 adjusted for baseline age. Model 2, Model 1 + social class, BMI and smoking status at baseline. Model 3, Model 2 + all domains of activity respectively. Bold indicates statistical significance ($p<0.05$).

Appendix 5A. Model search process for physical activity trajectories (n=4952)

Number of groups	BIC	Log Bayes Factor (2*ΔBIC)	Estimated group %	Actual group %	Posterior probability
			66.6	67.2	0.95
2	-30739.6		33.4	32.8	0.92
			26.0	24.3	0.82
			49.4	51.4	0.83
3	-30442.9	593.4	24.6	24.3	0.90
			16.7	14.3	0.80
			50.1	53.5	0.84
			26.8	26.2	0.85
4	-30385.6	114.6	6.4	6.0	0.84
			5.9	6.3	0.73
			26.6	24.1	0.71
			37.5	39.8	0.72
			24.7	24.5	0.84
5	-30458.9	-146.6	5.4	5.3	0.84

BIC, Bayesian information criterion.

Models adjusted for employment status and number of CVD diagnoses as time-varying covariates, and occupational class, marital status, number of children, region, BMI, arthritis, bronchitis, blood pressure, breathlessness, chest pain, smoking status, alcohol consumption and breakfast consumption at baseline.

Appendix 5B. Determining the highest model function of the 3 physical activity trajectory groups (n=4952) [a,b]

	1st iteration		2nd iteration			
Group	**Highest function**	***p***	**Highest function**	***p***	**Final estimated group %**	**Final actual group %**
Group 1	Quadratic	<0.001	Quadratic	<0.001	26.3	24.6
Group 2	Quadratic	0.323	Linear	<0.001	49.2	51.1
Group 3	Quadratic	0.246	Linear	<0.001	24.5	24.3

[a]Starting with quadratic, the level of the polynomial function for each group was reduced at each iteration until each parameter estimate was statistically significant ($p<0.05$). [b]Models adjusted for employment status and number of CVD diagnoses as time-varying covariates, and occupational class, marital status, number of children, region, BMI, arthritis, bronchitis, blood pressure, breathlessness, chest pain, smoking status, alcohol consumption and breakfast consumption at baseline.

Appendix 5C. Trajectories of physical activity and the effects of time-varying predictors on trajectory shapes, by trajectory group (n=4962)[a]

	Parameter[b]	Estimate	SE	p value
Low, decreasing				
	Intercept	2.048	0.194	<0.001
	Linear	0.054	0.013	<0.001
	Quadratic	-0.004	0.001	<0.001
	Time-varying covariates			
	Not employed	-0.217	0.068	0.001
	N. of CVD diagnoses	-0.445	0.048	<0.001
	BMI	-0.037	0.007	<0.001
	Married	0.121	0.071	0.087
	Alcohol consumption†	0.042	0.023	0.07
	Quitting smoking	0.255	0.057	<0.000
Light Stable				
	Intercept	3.064	0.205	<0.001
	Time-varying covariates			
	Not employed	0.340	0.052	<0.001
	N. of CVD diagnoses	-0.139	0.045	0.002
	BMI	-0.057	0.007	<0.001
	Married	0.085	0.065	0.195
	Alcohol consumption†	0.091	0.021	<0.001
	Quitting smoking	0.392	0.055	<0.001

	Parameter[b]	Estimate	SE	p value
Moderate, increasing				
	Intercept	4.969	0.293	<0.001
	Linear	0.028	0.004	<0.001
	Time-varying covariates			
	Not employed	0.829	0.072	<0.001
	N. of CVD diagnoses	-0.106	0.066	0.109
	BMI	-0.077	0.010	<0.001
	Married	0.147	0.092	0.112
	Alcohol consumption†	0.099	0.033	0.003
	Quitting smoking	0.371	0.076	<0.001

[a]Estimates for time-varying covariates represent the shift in physical activity trajectory per unit change in exposure variable.

[b]Models adjusted for employment status and number of CVD diagnoses as time-varying covariates, and occupational class, marital status, number of children, region, BMI, arthritis, bronchitis, blood pressure, breathlessness, chest pain, smoking status, alcohol consumption and breakfast consumption at baseline

†Alcohol was entered as a 5-point categorical variable (none, occasional [<1 drink/week], light [1-15 drinks/week], moderate [16-42 drinks/week] or heavy [>42 drinks/week]).

Appendix 5D. Model search process for physical activity type trajectories

Number of groups	BIC	Log Bayes Factor (2*ΔBIC)	Estimated group %	Actual group %	Posterior probability
Sport/exercise (n=5116)					
			62.4	62.8	0.96
2	-15241.0		37.6	37.2	0.94
			36.0	41.2	0.83
			38.7	33.2	0.88
3	-15145.8	190.4	25.4	25.6	0.91
			36.9	42.3	0.84
			38.9	32.6	0.92
			12.4	12.7	0.73
4	-15214.0	-68.2	11.8	12.3	0.74
Recreational activity (n=5085)					
			50.0	49.3	0.88
2	-21538.8		50.0	50.7	0.87
			20.9	19.6	0.81
			63.2	61.9	0.90
3	-21446.8	184.0	16.0	18.6	0.78
			13.7	14.6	0.82
			38.5	30.5	0.94
			29.1	33.2	0.77
4	-21275.2	343.2	18.7	21.7	0.82
5	_[a]	_[a]	_[a]	_[a]	_[a]

Number of groups	BIC	Log Bayes Factor (2*ΔBIC)	Estimated group %	Actual group %	Posterior probability
Walking (n=5106)					
			66.6	67.2	0.95
2	-20386.3		33.4	32.8	0.92
			22.7	27.2	0.76
			59.4	59.1	0.84
3	-20347.1	78.4	17.9	13.7	0.76
			23.4	29.0	0.73
			60.9	59.1	0.91
			13.1	9.2	0.66
4	-20418.8	-143.4	2.6	2.6	0.77

BIC, Bayesian information criterion.

Models adjusted for employment status and number of CVD diagnoses as time-varying covariates, and occupational class, marital status, number of children, region, BMI, arthritis, bronchitis, blood pressure, breathlessness, chest pain, smoking status, alcohol consumption and breakfast consumption at baseline.

[a] Failed to converge

Appendix 5E. Determining the highest model function of the physical activity type trajectory groups [a,b]

	1st iteration		2nd iteration		3rd iteration		4th iteration		5th iteration			
Group	**Highest function**	***p***	**Highest function**	***p***	**Highest function**	***p***	**Highest function**	***p***	**Highest function**	***p***	**Final estimated group %**	**Final actual group %**
Sport/exercise (n=5116)												
Group 1	Quadratic	–[c]	Linear	<0.001							43.1	45.8
Group 2	Quadratic	–[c]	Linear	<0.001							33.9	30.4
Group 3	Quadratic	–[c]	Linear	<0.001							23.0	23.8
Recreational activity (n=5085)												
Group 1	Quadratic	<0.001									13.7	14.6
Group 2	Quadratic	<0.001									38.5	30.5
Group 3	Quadratic	<0.001									29.1	33.2
Group 4	Quadratic	<0.001									18.7	21.7
Walking (n=5106)												

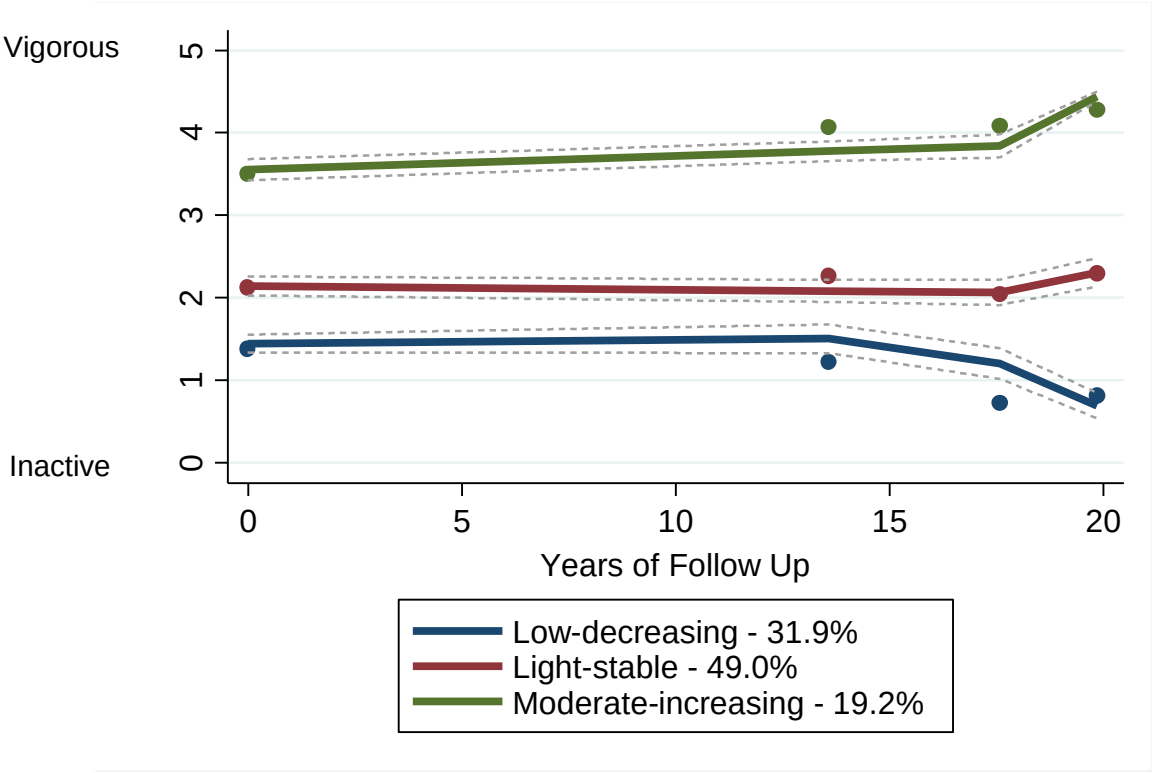
	1st iteration		2nd iteration		3rd iteration		4th iteration		5th iteration			
Group	**Highest function**	***p***	**Highest function**	***p***	**Highest function**	***p***	**Highest function**	***p***	**Highest function**	***p***	**Final estimated group %**	**Final actual group %**
Group 1	Quadratic	<0.001	Quadratic	<0.001	Quadratic	0.999	Linear	–[c]	Intercept	<0.001	28.1	27.2
Group 2	Quadratic	<0.05	Quadratic	0.193	Linear	<0.001	Linear	–[c]	Linear	<0.001	60.4	64.6
Group 3	Quadratic	0.813	Linear	<0.001	Linear	<0.001	Linear	–[c]	Linear	<0.001	11.5	8.3

[a]Starting with quadratic, the level of the polynomial function for each group was reduced at each iteration until each parameter estimate was statistically significant ($p<0.05$). [b]Models adjusted for employment status and number of CVD diagnoses as time-varying covariates, and occupational class, marital status, number of children, region, BMI, arthritis, bronchitis, blood pressure, breathlessness, chest pain, smoking status, alcohol consumption and breakfast consumption at baseline. [c]Models failed to converge.

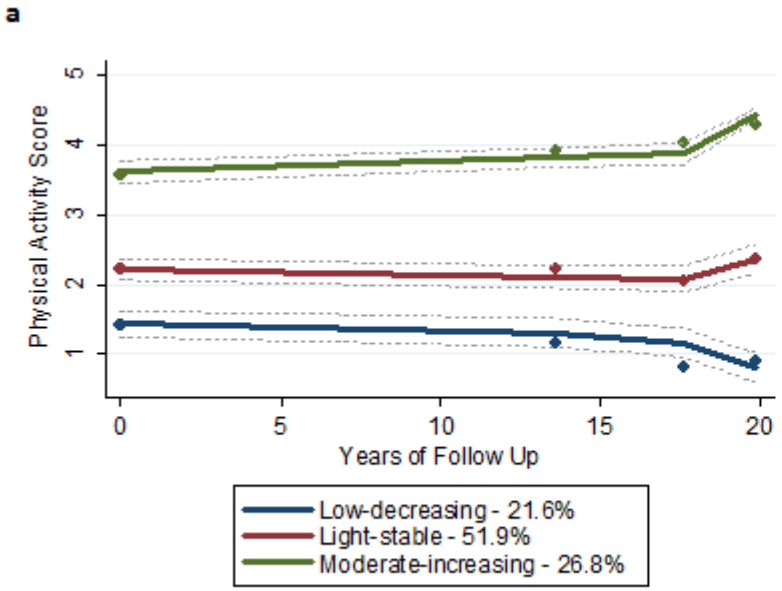
Appendix 5F. Cross tabulation showing concordance between overall and physical activity type trajectories, % (n) (n=4894)

	Total physical activity		
	Low, decreasing (n=1205)	Light stable (n=2493)	Moderate, increasing (n=1196)
Walking			
Consistently low (n=1315)	55 (660)	19 (476)	15 (179)
Low, increasing (n=3169)	44 (525)	71 (1757)	74 (887)
Moderate, increasing (n=410)	2 (20)	10 (260)	11 (130)
Sport/exercise			
Consistently none (n=2199)	88 (1060)	45 (1130)	1 (9)
Consistently occasional (n=1506)	12 (145)	46 (1133)	19 (228)
Consistently frequent (n=1189)	0 (0)	9 (230)	80 (959)
Recreational activity			
Moderate, decreasing (n=701)	44 (531)	6 (148)	2 (22)
Consistently moderate (n=1487)	31 (374)	33 (830)	24 (283)
High, decreasing (n=1626)	23 (280)	39 (965)	32 (381)
Consistently high (1080)	2 (20)	22 (550)	43 (510)

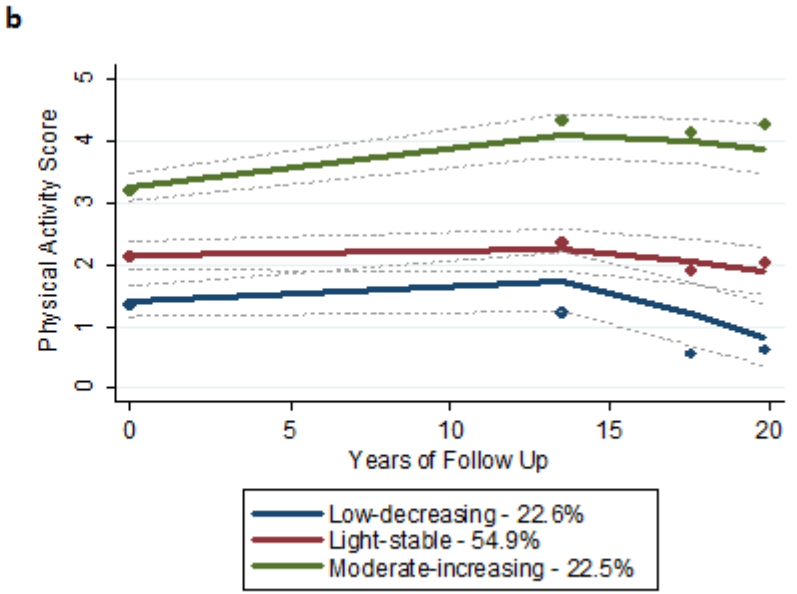
Appendix 5G. Physical activity trajectories and 95% CIs in men with at least one physical activity measure (n=7646)



Appendix 5H.a. Physical activity trajectories and 95% CIs in younger men (mean age at baseline, 45.1 ± 3.0)

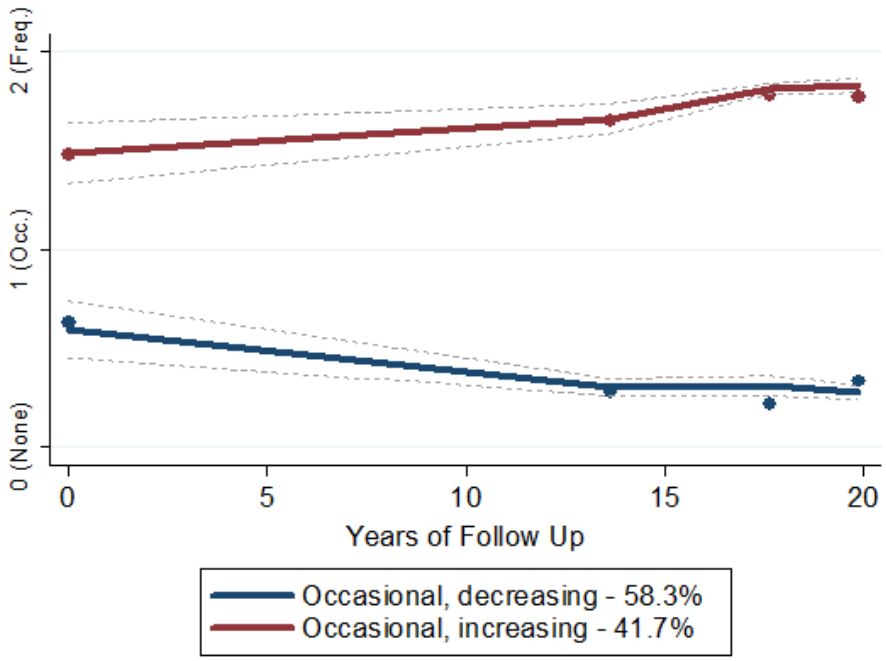


Appendix 5H.b. Physical activity trajectories and 95% CIs in older men (mean age at baseline, 54.8 ± 2.8)



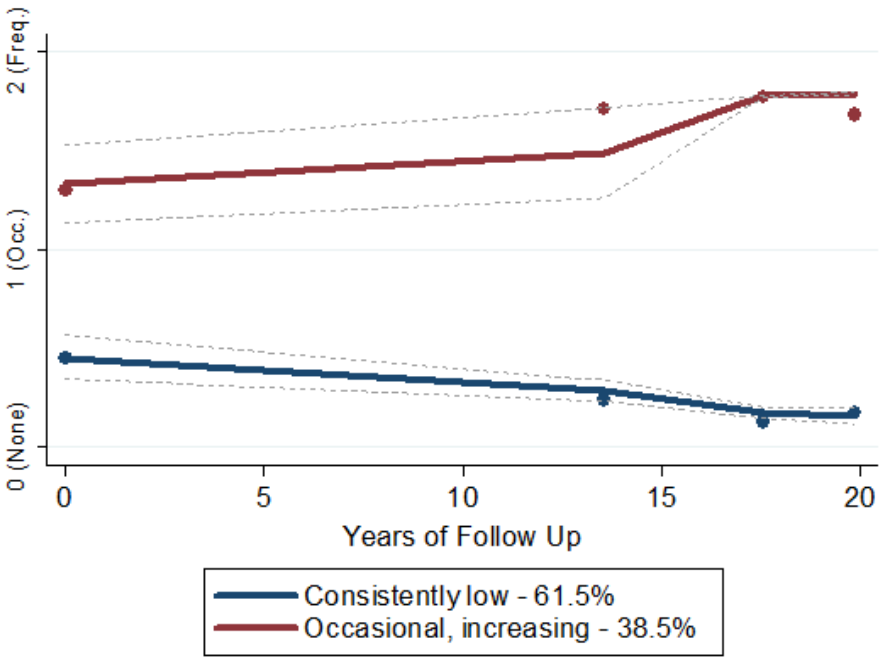
Appendix 5I.a. Sport/exercise trajectories and 95% CIs in younger men (mean age at baseline, 45.1 ± 3.0)

a



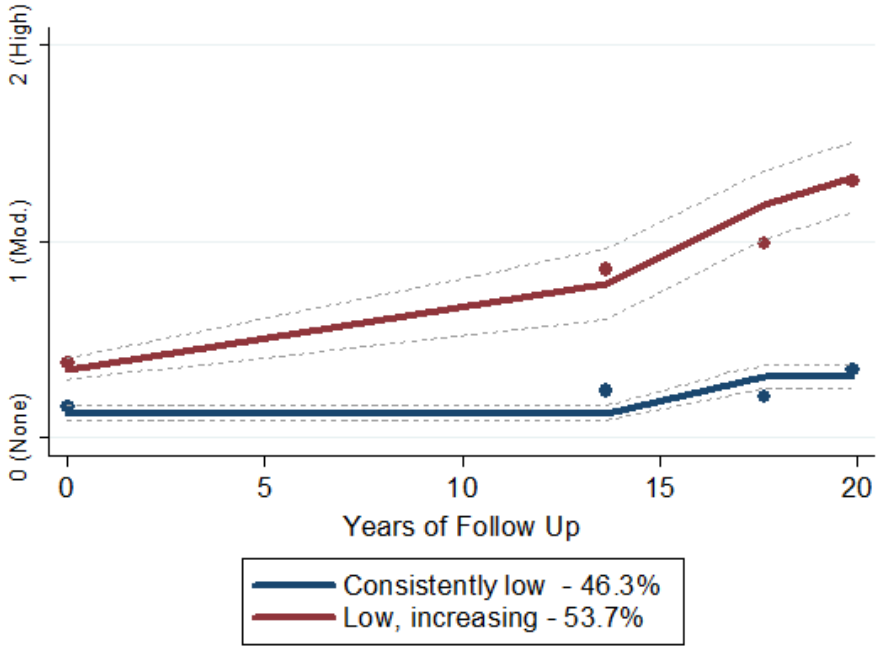
Appendix 5I.b. Sport/exercise trajectories and 95% CIs in older men (mean age at baseline, 54.8 ± 2.8)

b



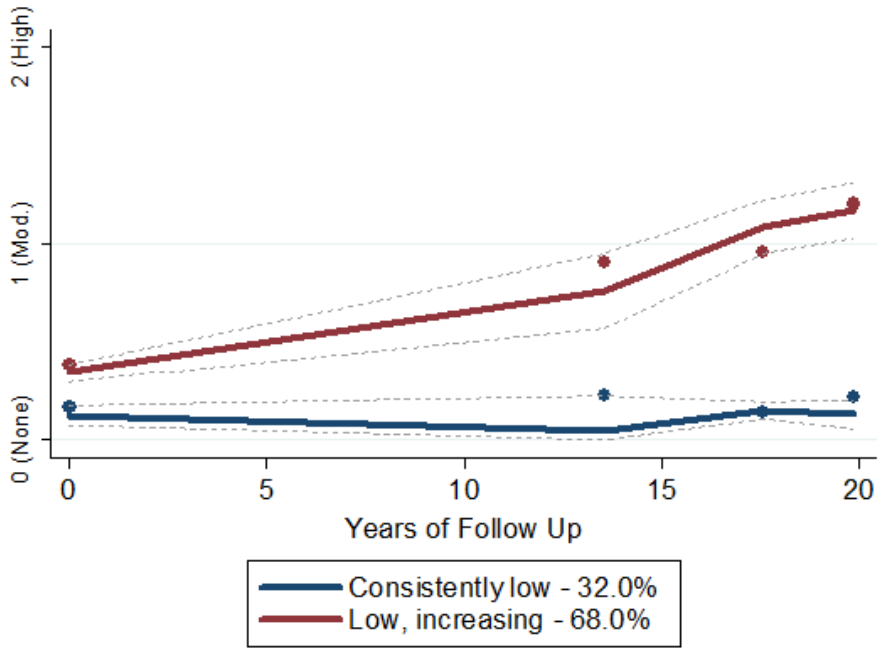
Appendix 5J.a. Walking trajectories and 95% CIs in younger men (mean age at baseline, 45.1 ± 3.0)

a



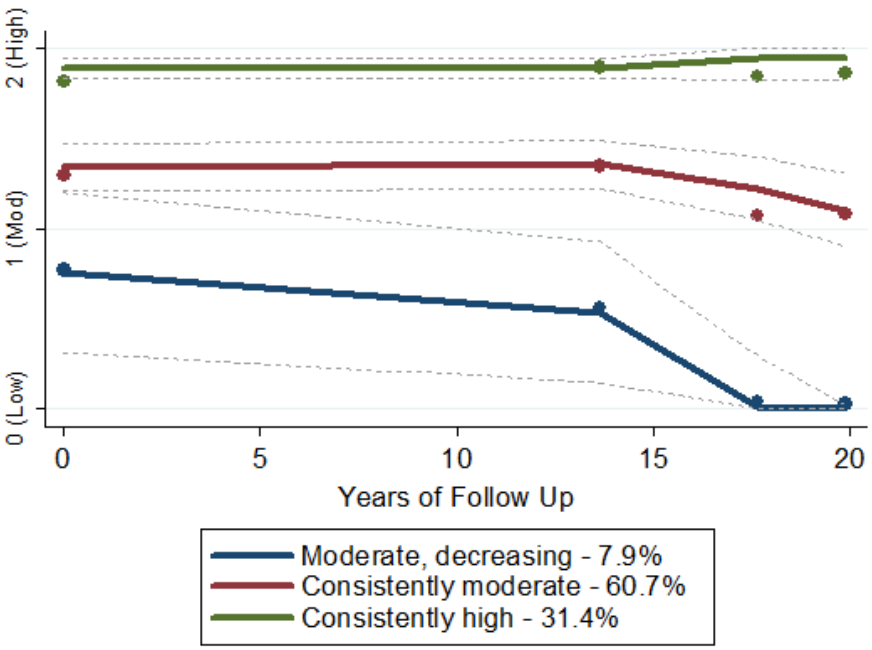
Appendix 5J.b. Walking trajectories and 95% CIs in older men (mean age at baseline, 54.8 ± 2.8)

b



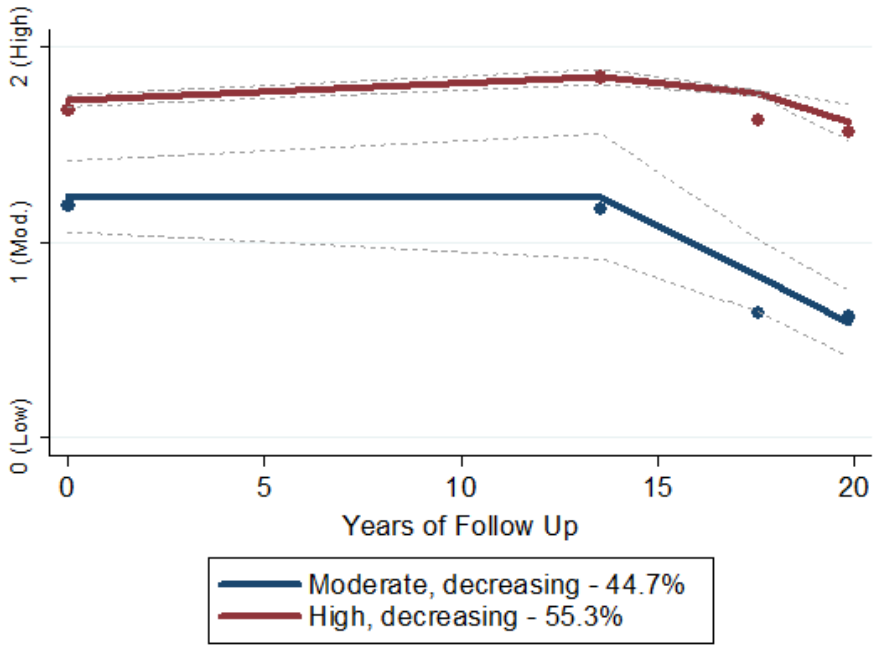
Appendix 5K.a. Recreational activity trajectories and 95% CIs in younger men (mean age at baseline, 45.1 ± 3.0)

a



Appendix 5K.b. Recreational activity trajectories and 95% CIs in older men (mean age at baseline, 54.8 ± 2.8)

b



Appendix 6A. Model Search Process for Physical Activity Trajectories in Participants with CVD biomarker data (n=3,331)

Number of groups	BIC	Log Bayes Factor (2*ΔBIC)	Estimated group %	Actual group %	Posterior probability
			64.5	65.0	0.95
2	-21645.4		35.5	35.0	0.93
			23.7	21.8	0.81
			49.5	51.5	0.83
3	-21483.3	324.2	26.8	26.7	0.91
			13.6	11.2	0.81
			50.0	53.0	0.85
			29.4	28.9	0.86
4	-21454.3	58.0	7.1	7.0	0.85
			3.3	3.5	0.78
			14.3	11.5	0.72
			46.9	49.9	0.82
			28.6	28.3	0.86
5	-21521.5	-134.4	7.0	6.8	0.85

BIC, Bayesian information criterion.

Models adjusted for employment status and number of cardiovascular disease diagnoses as time-varying covariates, and occupational class, marital status, number of children, region, body mass index , arthritis, bronchitis, blood pressure, breathlessness, chest pain, smoking status, alcohol consumption and breakfast consumption at baseline.

Appendix 6B. Determining the Highest Model Function of the 3 Physical Activity Trajectory Groups in Participants with CVD biomarker data (n=3,331) [ab]

	1st iteration		2nd iteration			
Group	**Highest function**	***P***	**Highest function**	***p***	**Final estimated group %**	**Final actual group %**
Group 1	Quadratic	<0.001	Quadratic	<0.001	23.3	21.3
Group 2	Quadratic	0.795	Linear	0.008	49.8	51.8
Group 3	Quadratic	0.233	Linear	<0.001	26.9	27.0

[a] Starting with quadratic, the level of the polynomial function for each group was reduced at each iteration until each parameter estimate was statistically significant ($p<0.05$). [b] Models adjusted for employment status and number of cardiovascular disease diagnoses as time-varying covariates, and occupational class, marital status, number of children, region, body mass index, arthritis, bronchitis, blood pressure, breathlessness, chest pain, smoking status, alcohol consumption and breakfast consumption at baseline.

Appendix 6C. P-values from likelihood ratio tests comparing model with current physical activity score only (at age 60-79 years) to a model additionally including the GBTM-derived trajectory group

	P value from likelihood ratio tests 20-year physical activity score only model with + GBTM trajectory group
Metabolic markers	
Triglycerides, mmol/L[a]	0.004
Glucose, mmol/L[a]	<0.001
Insulin, µ/mL[a]	<0.001
FEV1, L[ab]	0.007
Waist circumference (cm)[a]	<0.001
Inflammatory/hemostatic markers	
CRP (mg/l)[ac]	0.02
IL-6 (pg/ml)[ac]	0.09
Factor VIII, IU/dL[ad]	0.05
tPA, ng/mL[ad]	0.03
Cardiac markers	
Hs-TnT, pg/mL[ac]	0.007

All models adjusted for age, occupational class, region of residence, smoking status, alcohol consumption and lipid-lowering medication

[a] additionally adjusted for blood pressure-lowering medication

[b] FEV_1 was standardised for height by multiplying FEV_1 by the square of the mean population height (metres) divided by each participant's height.

[c] log transformed

[d] additionally adjusted for warfarin

Appendix 6D. Adjusted association[a] (B, 95% CI) between 20-Year physical activity trajectories and cardiovascular markers at 20-Year follow up from linear or logistic regression models[b], without adjustment for adiposity

	PHYSICAL ACTIVITY TRAJECTORY GROUPS				
Outcome measure	**Light Stable**		**Moderate, increasing**		
	B coefficient	95% CI	B coefficient	95% CI	p trend
Metabolic markers					
HDL, mmol/L [c]	0.00	-0.03, 0.03	**0.05**	**0.02, 0.09**	0.001
LDL, mmol/L [c]	**0.08**	**0.00, 0.17**	0.03	-0.07, 0.13	0.636
Total cholesterol, mmol/L [c]	0.03	-0.06, 0.12	-0.02	-0.13, 0.09	0.627
Triglycerides, mmol/L [c]	**-0.07**	**-0.11, -0.03**	**-0.12**	**-0.17, -0.08**	<0.001
Hypertension [d]	**0.71**	**0.59, 0.85**	**0.58**	**0.47, 0.72**	-
Glucose, mmol/L [c]	**-0.03**	**-0.05, -0.01**	**-0.04**	**-0.06, -0.02**	<0.001

	PHYSICAL ACTIVITY TRAJECTORY GROUPS				
Outcome measure	**Light Stable**		**Moderate, increasing**		
	B coefficient	95% CI	B coefficient	95% CI	p trend
Insulin, µ/mL [c]	**-0.17**	**-0.23, -0.12**	**-0.23**	**-0.29, -0.17**	<0.001
HbA1C, mmols/l [ce]	**-0.03**	**-0.04, -0.01**	**-0.03**	**-0.04, -0.01**	0.001
FEV_1, L [cf]	**15.33**	**10.08, 20.58**	**24.05**	**17.97, 30.13**	<0.001
Waist circumference (cm) [c]	**-3.25**	**-4.13, -2.36**	**-4.22**	**-5.24, -3.19**	<0.001
Inflammatory/hemostatic markers					
IL-6, pg/ml [ce]	**-0.15**	**-0.21, -0.10**	**-0.22**	**-0.28, -0.15**	<0.001
CRP, mg/L [ce]	**-0.28**	**-0.37, -0.18**	**-0.37**	**-0.48, -0.26**	<0.001

	PHYSICAL ACTIVITY TRAJECTORY GROUPS				
Outcome measure	**Light Stable**		**Moderate, increasing**		
	B coefficient	95% CI	B coefficient	95% CI	p trend
Factor VIII, IU/dL [cg]	**-5.84**	**-8.54, -3.15**	**-6.8**	**-9.92, -3.68**	<0.001
vWF, IU/dL [cg]	**-6.64**	**-10.54, -2.74**	**-7.61**	**-12.12, -3.10**	0.002
tPA, ng/mL [cg]	**-1.07**	**-1.45, -0.70**	**-1.55**	**-1.98, -1.12**	<0.001
d-dimer, ng/mL [ceg]	**-0.11**	**-0.17, -0.04**	**-0.12**	**-0.20, -0.04**	0.004
Cardiac markers					
Hs-TnT, pg/mL [ce]	**-0.09**	**-0.13, -0.05**	**-0.05**	**-0.10, -0.01**	0.05
NT-proBNP, pg/mL [ceh]	-0.06	-0.15, 0.04	-0.04	-0.15, 0.08	0.58

Abbreviations: CI, confidence interval; OR, odds ratio; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1C, haemoglobin A1c; FEV_1, forced expiratory volume in 1 second; IL-6, interleukin-6; CRP, c-reactive protein; vWF, von Willebrand factor; tPA, tissue plasminogen activator antigen; Hs-TnT, high-sensitivity cardiac troponin T; NT-proBNP, n-terminal pro-brain natriuretic peptide

[a]All models adjusted for age, occupational class, region of residence, smoking status, alcohol consumption and lipid-lowering medication

[b]Low, decreasing group served as the reference group

[c] additionally adjusted for blood pressure-lowering medication

[d] presented as an odds ratio and 95% confidence interval. Hypertension, high systolic (≥160 mmHg) or diastolic (≥100 mmHg) blood pressure or taking anti-hypertensive medication

[e] log transformed

[f] FEV_1 was standardised for height by multiplying FEV_1 by the square of the mean population height (metres) divided by each participant's height.

[g] additionally adjusted for warfarin

[h] Data were missing for an additional 194 men (n=3,137)

Bold indicates statistical significance ($p<0.05$).

Appendix 6E. Adjusted association[a] (B, 95% CI) between 20-year physical activity trajectories and cardiovascular markers at 20-year follow up from linear or logistic regression models[b] excluding men with CVD and diabetes at 20-year follow up (N=2,691)

	PHYSICAL ACTIVITY TRAJECTORY GROUPS				
Outcome measure	**Light stable**		**Moderate, increasing**		
	B coefficient	95% CI	B coefficient	95% CI	p trend
Metabolic markers					
HDL, mmol/L [c]	-0.03	-0.06, 0.01	0.01	-0.03, 0.05	0.443
LDL, mmol/L [c]	0.09	-0.01, 0.19	0.04	-0.07, 0.15	0.597
Total cholesterol, mmol/L [c]	0.07	-0.04, 0.18	0.03	-0.10, 0.15	0.835
Triglycerides, mmol/L [c]	0.00	-0.04, 0.05	-0.03	-0.08, 0.02	0.192
Hypertension [d]	**0.80**	**0.65, 0.99**	**0.72**	**0.57, 0.92**	-
Glucose, mmol/L [c]	0.00	-0.01, 0.01	0	-0.01, 0.01	0.694
Insulin, µ/mL [c]	-0.05	-0.10, 0.01	**-0.09**	**-0.15, -0.03**	0.002
HbA1C, mmols/l [ce]	-0.01	-0.02, 0.01	-0.01	-0.02, 0.01	0.27
FEV_1, L [cf]	**12.22**	**6.13, 18.30**	**21.06**	**14.11, 28.01**	<0.001

	PHYSICAL ACTIVITY TRAJECTORY GROUPS				
Outcome measure	**Light stable**		**Moderate, increasing**		
	B coefficient	95% CI	B coefficient	95% CI	p trend
Waist circumference (cm) [c]	**-3.01**	**-3.99, -2.02**	**-4.18**	**-5.31, -3.05**	<0.001
Inflammatory/hemostatic markers					
IL-6, pg/ml [ce]	**-0.14**	**-0.20, -0.08**	**-0.2**	**-0.27, -0.13**	<0.001
CRP, mg/L [ce]	**-0.19**	**-0.30, -0.09**	**-0.28**	**-0.40, -0.16**	<0.001
Factor VIII, IU/dL [cg]	-3.04	-6.10, 0.01	**-4.04**	**-7.53, -0.06**	0.03
vWF, IU/dL [cg]	**-4.62**	**-8.96, -0.28**	-4.88	-9.84, 0.08	0.078
tPA, ng/mL [cg]	**-0.63**	**-1.02, -0.24**	**-0.89**	**-1.34, -0.44**	<0.001
d-dimer, ng/mL [ceg]	**-0.1**	**-0.17, -0.02**	**-0.11**	**-0.20, -0.03**	0.017
Cardiac markers					
Hs-TnT, pg/mL [ce]	**-0.06**	**-0.11, -0.02**	-0.05	-0.10, 0.01	0.161
NT-proBNP, pg/mL [ceh]	-0.1	-0.16, 0.05	-0.08	-0.20, 0.05	0.235

Abbreviations: CI, confidence interval; OR, odds ratio; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1C, haemoglobin A1c; FEV_1, forced expiratory volume in 1 second; IL-6, interleukin-6; CRP, c-reactive protein; vWF, von Willebrand factor; tPA, tissue plasminogen activator antigen; Hs-TnT, high-sensitivity cardiac troponin T; NT-proBNP, n-terminal pro-brain natriuretic peptide

[a]All models adjusted for age, occupational class, region of residence, smoking status, alcohol consumption and waist circumference (where waist circumference was the outcome models adjusted for all other factors except waist circumference) and lipid-lowering medication

[b]Low, decreasing group served as the reference group

[c] additionally adjusted for blood pressure-lowering medication

[d] presented as an odds ratio and 95% confidence interval. Hypertension, high systolic (≥160 mmHg) or diastolic (≥100 mmHg) blood pressure or taking anti-hypertensive medication

[e] log transformed

[f] FEV_1 was standardised for height by multiplying FEV_1 by the square of the mean population height (metres) divided by each participant's height.

[g] additionally adjusted for warfarin

[h] data were missing for an additional 159 men (n=2,532)

Bold indicates statistical significance ($p<0.05$).

Appendix 7A. Model Search Process for Physical Activity Trajectories (n=3,231)

Number of groups	BIC	Log Bayes Factor (2*ΔBIC)	Estimated group %	Actual group %	Posterior probability
			64.3	64.8	0.95
2	-21050.2		35.7	35.2	0.93
			24.8	22.9	0.82
			49.1	50.9	0.84
3	-20880.7	339.0	26.1	26.2	0.90
			15.1	12.7	0.81
			49.1	52.2	0.84
			28.7	28.0	0.86
4	-20859.1	43.2	7.2	7.1	0.84
			4.0	4.5	0.77
			16.9	13.6	0.73
			44.1	47.3	0.80
			28.1	27.9	0.85
5	-20923.2	-134.4	6.9	6.8	0.85

BIC, Bayesian information criterion.

Models adjusted for employment status and number of cardiovascular disease diagnoses as time-varying covariates, and occupational class, marital status, number of children, region, body mass index , arthritis, bronchitis, blood pressure, breathlessness, chest pain, smoking status, alcohol consumption and breakfast consumption at baseline.

Appendix 7B. Determining the highest model function of the 3 physical activity trajectory groups (n=3,231)[ab]

	1st iteration		2nd iteration			
Group	**Highest function**	***p***	**Highest function**	***p***	**Final estimated group %**	**Final actual group %**
Group 1	Quadratic	<0.001	Quadratic	<0.001	24.5	22.7
Group 2	Quadratic	0.937	Linear	0.019	49.3	51.0
Group 3	Quadratic	0.173	Linear	<0.001	26.2	26.3

[a] Starting with quadratic, the level of the polynomial function for each group was reduced at each iteration until each parameter estimate was statistically significant ($p<0.05$). [b] Models adjusted for employment status and number of cardiovascular disease diagnoses as time-varying covariates, and occupational class, marital status, number of children, region, body mass index, arthritis, bronchitis, blood pressure, breathlessness, chest pain, smoking status, alcohol consumption and breakfast consumption at baseline.

Appendix 7C. P-values from likelihood ratio tests comparing a model with current physical activity score only (at age 60-79 years) to models additionally including the GBTM-derived trajectory group

	P value from likelihood ratio tests 20-year physical activity score only model with + GBTM trajectory group	
	Model 1	Model 2
Deaths (all cause)	0.11	0.39
Major CHD events (fatal + non-fatal)[a]	0.28	0.30
Major stroke events (fatal + non-fatal)[b]	0.96	0.86
CVD mortality[c]	0.03	0.10
All CVD events (fatal + non-fatal)[d]	0.37	0.46

[a] Fatal MI was defined as ICD-9 codes 410–414. Non-fatal MI was defined as heart attack or coronary thrombosis, in accordance with the World Health Organisation diagnostic criteria.

[b] Fatal stroke was defined as ICD-9 codes 430–438. Non-fatal stroke events included those that caused a neurological deficit for >24 hours.

[c] Fatal CVD was defined as ICD-9 codes 390–459.

[d] All CVD events included all fatal CVD (ICD-9 codes 390–459) and non-fatal MI and stroke as described above.

Model 1, adjusted for age, occupational class, marital status, alcohol consumption, smoking status, region, previous diagnosis of MI, stroke or diabetes. Model 2, Model 1 + LDL, HDL, systolic blood pressure, insulin, waist circumference and FEV_1, IL-6, vWF, Hs-TnT and NT-proBNP

Appendix 7D. Prospective association between GBTM-derived physical activity trajectory groups (from baseline [1978/80] to 20-year follow up [1998/2000]) and all-cause/cause-specific mortality and CVD events from 1998/2000 to 2016 in men without pre-existing CVD (n=2922)

Outcome	Trajectory group	N	N.o. of events	Person-years	Mortality/1000 person-years	Model 1	Model 2	Model 3	Model 4
						Hazard Ratio (95% CI)			
Deaths (all cause)	Low, decreasing	1126	686	13945.6	49.2	Referent	Referent	Referent	Referent
	Light stable	1191	575	16573.4	34.7	**0.82 (0.73, 0.91)**	**0.86 (0.77, 0.97)**	**0.88 (0.78, 0.99)**	0.90 (0.81, 1.01)
	Moderate, increasing	605	252	8784.7	28.7	**0.70 (0.60, 0.81)**	**0.76 (0.65, 0.88)**	**0.77 (0.67, 0.90)**	**0.81 (0.70, 0.95)**
	p trend					<0.001	<0.001	0.001	0.005
Major CHD events (fatal + non-fatal)	Low, decreasing	1126	144	13553.0	10.6	Referent	Referent	Referent	Referent
	Light stable	1191	92	16102.1	5.7	**0.67 (0.51, 0.88)**	**0.69 (0.53, 0.90)**	**0.70 (0.53, 0.91)**	**0.74 (0.56, 0.97)**
	Moderate, increasing	605	37	8563.6	4.3	**0.54 (0.37, 0.78)**	**0.58 (0.40, 0.84)**	**0.59 (0.40, 0.85)**	**0.66 (0.45, 0.96)**
	p trend					<0.001	0.001	0.001	0.011
Major stroke events (fatal + non-fatal)	Low, decreasing	1126	124	13379.6	9.3	Referent	Referent	Referent	Referent
	Light stable	1191	111	16039.6	6.9	0.81 (0.62, 1.05)	0.82 (0.63, 1.07)	0.83 (0.64, 1.09)	0.85 (0.65, 1.10)
	Moderate, increasing	605	58	8564.0	6.8	0.81 (0.58, 1.11)	0.82 (0.59, 1.14)	0.84 (0.61, 1.17)	0.87 (0.62, 1.20)

Outcome	Trajectory group	N	N.o. of events	Person-years	Mortality/1000 person-years	Model 1	Model 2	Model 3	Model 4
						Hazard Ratio (95% CI)			
	p trend					0.126	0.172	0.221	0.301
CVD mortality	Low, decreasing	1126	240	13945.6	17.2	Referent	Referent	Referent	Referent
	Light stable	1191	173	16573.4	10.4	**0.73 (0.60, 0.89)**	**0.75 (0.61, 0.91)**	**0.76 (0.62, 0.93)**	**0.80 (0.65, 0.98)**
	Moderate, increasing	605	73	8784.7	8.3	**0.60 (0.46, 0.79)**	**0.59 (0.47, 0.76)**	**0.66 (0.50, 0.79)**	**0.73 (0.56, 0.96)**
	p trend					<0.001	<0.001	0.001	0.010
All CVD events (fatal + non-fatal)	Low, decreasing	1126	347	13015.9	26.7	Referent	Referent	Referent	Referent
	Light stable	1191	283	15604.0	18.1	**0.78 (0.67, 0.92)**	**0.80 (0.68, 0.94)**	**0.81 (0.69, 0.95)**	**0.83 (0.71, 0.98)**
	Moderate, increasing	605	132	8347.1	15.8	**0.71 (0.58, 0.87)**	**0.74 (0.60, 0.91)**	**0.75 (0.61, 0.93)**	**0.80 (0.65, 0.99)**
	p trend					<0.001	0.001	0.003	0.016

Abbreviations: GBTM, group-based trajectory modelling; MI, myocardial infarction; CVD, stroke/MI

Model 1, adjusted for age, occupational class, marital status, alcohol consumption, smoking status, region, previous diagnosis of MI, stroke or diabetes. Model 2, Model 1 + LDL, HDL, systolic blood pressure, insulin, waist circumference and FEV_1. Model 3, Model 2 + IL-6 and vWF. Model 4, Model 3 + Hs-TnT and NT-proBNP. Bold indicates statistical significance ($p<0.05$).

Appendix 7E. Association between physical activity trajectories and subsequent risk of CVD events and all-cause and CVD mortality excluding the first two years of follow up

Outcome	Trajectory group	N	N.o. of events	Person-years	Rate per 1000 person-years	Model 1	Model 2	Model 3	Model 4
						Hazard Ratio (95% CI)			
Deaths (all cause)	Low, decreasing	689	450	8354.4	53.9	Referent	Referent	Referent	Referent
	Light stable	1597	817	22158.8	36.9	**0.73 (0.65, 0.82)**	**0.79 (0.70, 0.89)**	**0.81 (0.72, 0.92)**	**0.84 (0.74, 0.94)**
	Moderate, increasing	828	351	12012.0	29.2	**0.64 (0.55, 0.74)**	**0.71 (0.61, 0.82)**	**0.74 (0.63, 0.85)**	**0.76 (0.65, 0.88)**
	p trend					<0.001	<0.001	<0.001	<0.001
Major CHD events (fatal + non-fatal)[a]	Low, decreasing	686	130	8139.0	16.0	Referent	Referent	Referent	Referent
	Light stable	1580	213	21451.2	9.9	**0.69 (0.55, 0.86)**	**0.71 (0.56, 0.89)**	**0.73 (0.58, 0.92)**	**0.74 (0.59, 0.94)**
	Moderate, increasing	821	80	11640.7	6.9	**0.55 (0.41, 0.74)**	**0.59 (0.44, 0.80)**	**0.62 (0.63, 0.85)**	**0.62 (0.46, 0.83)**
	p trend					<0.001	<0.001	0.001	0.001
Major stroke events (fatal + non-fatal)[b]	Low, decreasing	678	64	8045.1	8.0	Referent	Referent	Referent	Referent

Outcome	Trajectory group	N	N.o. of events	Person-years	Rate per 1000 person-years	Model 1	Model 2	Model 3	Model 4
						Hazard Ratio (95% CI)			
	Light stable	1585	172	21239.7	8.1	1.07 (0.80, 1.44)	1.12 (0.83, 1.51)	1.16 (0.86, 1.57)	1.18 (0.88, 1.60)
	Moderate, increasing	825	80	11661.9	6.9	0.96 (0.68, 1.35)	1.02 (0.72, 1.44)	1.06 (0.75, 1.51)	1.08 (0.76, 1.53)
	p trend					0.763	0.993	0.813	0.747
CVD mortality[c]	Low, decreasing	689	179	8354.4	21.4	Referent	Referent	Referent	Referent
	Light stable	1597	272	22158.8	12.3	**0.63 (0.52, 0.76)**	**0.66 (0.54, 0.81)**	**0.68 (0.56, 0.83)**	**0.73 (0.60, 0.89)**
	Moderate, increasing	828	102	12012.0	8.5	**0.50 (0.39, 0.64)**	**0.55 (0.42, 0.71)**	**0.57 (0.44, 0.74)**	**0.60 (0.46, 0.78)**
	p trend					<0.001	<0.001	<0.001	<0.001
All CVD events (fatal + non-fatal)[d]	Low, decreasing	675	219	7844.0	27.9	Referent	Referent	Referent	Referent
	Light stable	1568	416	20600.8	20.2	**0.80 (0.67, 0.94)**	**0.82 (0.69, 0.98)**	0.85 (0.71, 1.01)	0.87 (0.73, 1.03)
	Moderate, increasing	818	175	11303.6	15.5	**0.68 (0.55, 0.84)**	**0.72 (0.58, 0.89)**	**0.75 (0.61, 0.93)**	**0.76 (0.61, 0.94)**
	p trend					<0.001	0.002	0.009	0.011

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CVD, stroke/MI; MI, myocardial infarction

[a] Fatal MI was defined as ICD-9 codes 410–414. Non-fatal MI was defined as heart attack or coronary thrombosis, in accordance with the World Health Organisation diagnostic criteria.

[b] Fatal stroke was defined as ICD-9 codes 430–438. Non-fatal stroke events included those that caused a neurological deficit for >24 hours.

[c] Fatal CVD was defined as ICD-9 codes 390–459.

[d] All CVD events included all fatal CVD (ICD-9 codes 390–459) and non-fatal MI and stroke as described above.

Model 1, adjusted for age, occupational class, marital status, alcohol consumption, smoking status, region, previous diagnosis of MI, stroke or diabetes. Model 2, Model 1 + LDL, HDL, systolic blood pressure, insulin, waist circumference and FEV_1. Model 3, Model 2 + IL-6 and vWF. Model 4, Model 3 + Hs-TnT and NT-proBNP. Boldface indicates statistical significance ($p<0.05$)

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