BODY COMPOSITION, DIETARY PATTERNS, CARDIOVASCULAR DISEASE AND MORTALITY IN OLDER AGE

THESIS presented for the degree of DOCTOR OF PHILOSOPHY

Field of study: Epidemiology

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DECLARATION OF AUTHORSHIP

I, Janice Atkins, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis. I have used data from the British Regional Heart Study, which is an on-going prospective cohort study on cardiovascular disease that began in 1978.

ABSTRACT

Obesity and poor quality diet are major interrelated risk factors for cardiovascular disease (CVD) and mortality, which are well established in middle-aged populations. However, there is controversy on the effects of obesity on CVD and mortality in the elderly. Since body composition changes with age (visceral fat increases and muscle mass decreases) it may be important to also account for muscle mass in the elderly. However, few studies have examined the combined effects of adiposity and sarcopenia (low muscle mass) on CVD risk and mortality in the elderly. There is also a paucity of data on the associations between dietary patterns and CVD risk and mortality in older age. This thesis uses the British Regional Heart Study, a population based prospective cohort of men, to investigate the impact of body composition (obesity and sarcopenia) and dietary patterns on the risk of cardiovascular endpoints and all-cause mortality in older age (60-79 years). The main findings are that sarcopenic men (defined using mid-arm muscle circumference) and obese men (defined using waist circumference) had a significantly increased risk of CVD mortality and all-cause mortality. Men with both sarcopenia and obesity showed the highest all-cause mortality risk, and also an increased CVD mortality risk although non-significant. Adherence to an *a priori* defined dietary pattern (the Elderly Dietary Index, a modified Mediterranean-style diet) was associated with a lower risk of CVD mortality and all-cause mortality. Adherence to a 'high fat/low fibre' diet, identified by principal component analysis, was associated with an increased risk of all-cause mortality but not CVD mortality. Adherence to a 'high sugar' diet was associated with an increased risk of coronary heart disease (CHD) events and CVD events. Body composition and dietary patterns are therefore important risk factors for CVD and all-cause mortality which persist in older age.

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FREQUENTLY USED ABBREVIATIONS

Data source

BRHS	British Regional Heart Study

Disease outcomes

CHD	Coronary heart disease
CVD	Cardiovascular disease
ICD-9	International Classification of diseases - ninth revision
MI	Myocardial infarction

Exposures

BIA	Bioelectrical impedance analysis
BMI	Body mass index
CRP	C-reactive protein
CT	Computerised tomography
DXA	Dual-energy X-ray absorptiometry
EDI	Elderly Dietary Index
FEV_1	Forced expiratory volume, in one second
FFM/FFMI	Fat-free mass/Fat-free mass index
FFQ	Food frequency questionnaire
FM/FMI	Fat mass/Fat mass index
HC	Hip circumference
HDI	Healthy Diet Indicator
HDL	High density lipoprotein cholesterol
HOMA-IR	Homeostasis model assessment insulin resistance
IL-6	Interleukin 6
LDL	Low density lipoprotein cholesterol
MAMC	Mid-arm muscle circumference
MDS	Mediterranean Diet Score
MetS	Metabolic syndrome
MRI	Magnetic resonance imaging

SBP	Systolic blood pressure
SMI	Skeletal muscle mass index
t-PA	Tissue plasminogen activator
vWF	von Willebrand factor
WHR	Waist-to-hip ratio
WC	Waist circumference

Statistical terms

CI	Confidence interval
HR	Hazard ratio
OR	Odds ratio
SD	Standard deviation

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CHAPTER 1 Introduction

1.1. Introduction and rationale for thesis

1.1.1. Cardiovascular disease in an ageing population

The population in the United Kingdom (UK) is ageing due to a steady increase in life expectancy over time. Since the 1930s, the number of people aged over 65 years in the UK has more than doubled[1] and by 2012, 23.0% of the population were aged over 60, a proportion which is predicted to increase to 29.6% by 2050[2]. The elderly are particularly at risk of non-communicable diseases and the key to healthy ageing is the prevention of diseases and disability[3]. Death rates from cardiovascular disease (CVD) have been falling in the UK since the early 1970s but CVD remains the main cause of mortality, accounting for nearly a third of all deaths in both men and women, and is a major contributor to morbidity and disability[4]. CVD is largely preventable, and much focus of prevention efforts has turned to promoting healthy lifestyle behaviours[5;6]. Diet and adiposity are recognised by the World Health Organization (WHO) as two major interrelated and modifiable determinants of CVD[7] and much emphasis of recent CVD prevention efforts have therefore been on promoting healthy eating and the prevention of obesity[5;6;8].

Whilst the major aetiological factors for CVD and mortality are well established (as summarised in Chapter 2, section 2.3.1), however, most research on its causes and prevention has focused on exposures in middle-aged populations (adults <60 years). The determinants of CVD and the scope for CVD prevention in later life (aged 60 years and above) remain uncertain. The effects of two major modifiable risk factors for CVD (obesity and diet) in middle age are known, but whether their effects persist in older adults is unclear. This is important as the risks of CVD are particularly high in older people so even small reductions in risk later in life can have considerable scope for health benefits[4;9].

1.1.2. **Body composition and CVD**

Overweight and obesity, abnormal or excessive fat accumulation, are major risk factors for cardiovascular morbidity and mortality in adult populations and the prevalence in middle-aged and older adults is continuing to rise over time[10;11]. Obesity prevalence, also increases with age; 85% of men and 75% of women aged 65-74 years are overweight or obese[12], making it an important public health problem in an ageing population. However, the impact of being overweight and of obesity in the elderly on CVD and mortality remain controversial. There is considerable debate in the literature regarding the ideal body composition in the elderly, with many studies showing that being overweight or obese, as defined by body mass index (BMI), does not appear to be harmful and may even be associated with lower, rather than higher, mortality[13;14]. Important changes in body composition occur with age including a relative increase in fat tissue and a gradual decline in muscle mass[3]. Since BMI combines both fat mass and muscle mass, which have opposing effects on the risk of morbidity and mortality, the validity of the use of BMI in the elderly may be limited[15;16]. It may therefore be important to consider alternative measures of adiposity, and also muscle mass, when assessing CVD risk in the elderly. Sarcopenia has been defined as the age-associated loss of skeletal muscle mass and has been associated with metabolic impairment, CVD risk factors, physical disability and mortality[17]. Paradoxically, sarcopenia is often associated with obesity[18-21]. Recently, the concept of sarcopenic obesity has emerged which refers to sarcopenia coupled with high levels of adipose tissue[18;22]. Thus sarcopenia with obesity may synergistically increase their effect on metabolic disorders, CVD and mortality. However, it is unclear what the determinants of the combination of high adiposity and low muscle mass are in the elderly, and also what are the associated risks of cardiovascular morbidity and mortality.

1.1.3. **Diet and CVD**

Similarly, the importance of diet in the prevention of chronic disease morbidity and mortality has been well established in middle-aged populations, and may be particularly important in the elderly, who are at high risk of CVD and other chronic diseases, but there is a paucity of data on optimal dietary patterns in the elderly. Studies investigating diet and

CVD and mortality have previously focused on individual foods or nutrients[23], with particularly strong evidence that the intake of salt[24] and saturated fats[25] are positively associated with CVD risk and that the intake of fruits and vegetables are inversely associated with CVD risk[26;27]. However, recently attention has turned to investigating overall dietary patterns and health outcomes[28]. Dietary patterns can be assessed using both *a priori* methods (hypothesis oriented or theoretically defined approaches which are *a priori* in nature, since they use available scientific evidence to generate predefined dietary scores or indexes based on dietary recommendations or guidelines) and *a posteriori* method (data-driven or exploratory approaches which are *a posteriori* in nature, since dietary patterns are derived from the available data, based on statistical methods such as principal component analysis or cluster analysis)[29;30]. To date, dietary patterns and the risk of CVD and mortality have largely been studied in middle-aged populations, many of which have focused on the 'Mediterranean diet'[31;32]. However, only a limited number of studies have investigated the effect of diet on cardiovascular risk factors in older populations[33]. Fewer still have identified usual patterns of diet protective against CVD and mortality, which can be translated to the average older UK population.

This thesis will focus on addressing several important questions on the role of body composition (adiposity and in particular low muscle mass) and dietary patterns on CVD and mortality in older age (over 60 years). These questions have important public health implications for recommendations on the ideal body composition and dietary patterns of older adults and thus for the prevention of CVD and mortality.

1.2. Thesis objectives

The overall aim of this thesis is therefore to investigate the impact of measures of body composition (adiposity and muscle mass) and dietary patterns on the risk of cardiovascular endpoints (coronary heart disease [CHD] events; CVD events; CVD mortality) and all-cause mortality in older men. The specific objectives of the thesis are to:

1. Examine the associations between various body composition measures (adiposity and in particular low muscle mass) and cardiovascular risk factors in older age (60-79 years).
2. Examine the associations between adiposity, muscle mass and the risk of CVD and mortality in older age.
3. Examine the associations between *a priori* dietary patterns (using predefined diet scores) and cardiovascular risk factors (including the influence of social circumstances) and the risk of CVD and mortality in older age.
4. Examine the associations between *a posteriori* dietary patterns (derived from principal component analysis) and cardiovascular risk factors, and the risk of CVD and mortality in older age.

1.3. Overview of methodology

This epidemiological research is a statistical analysis of data collected for the British Regional Heart Study (BRHS), an established prospective cohort study of cardiovascular disease. The BRHS comprises 7735 middle-aged British men drawn from one general practice in each of 24 towns representing all major British geographic regions[34]. The men were initially recruited between 1978 and 1980, aged 40-59 years. Since recruitment, participants have been followed up for over 30 years, by postal questionnaire and through the National Health Service Central Register and reports from general practitioners for cardiovascular mortality and morbidity. After 20 years of follow-up, between 1998-2000, study participants were re-examined, including a physical examination, blood measurements and the completion of questionnaires[35]. Study participants have continued to be followed up from that point to the present day. A more detailed description of the BRHS can be found in Chapter 3.

The BRHS is a suitable cohort for studying the objectives of this thesis as it provides detailed assessment of a range of body composition measures (including adiposity and muscle mass), dietary data from a food frequency questionnaire and comprehensive information on cardiovascular risk factors of the study participants at the 20 year re-

examination. The BRHS is also a population-based study comprising a socioeconomically and geographically representative sample of British men. The BRHS also provides regular and objective measurements on CHD events, CVD events and mortality, with very high rates of follow-up. This will enable the investigation of measures of body composition and dietary patterns in relation to CVD and mortality in older men. However, the study sample is made up predominantly of white Europeans men and does not include women or ethnic minority groups.

This thesis has used data specifically from the 20 year BRHS re-examination of 4252 men, aged 60-79 years, with follow-up data on cardiovascular outcomes and mortality until 2010. The four main outcomes assessed in this thesis were CHD events (defined as non-fatal MI or fatal CHD, excluding angina); CVD events (defined as non-fatal MI, non-fatal stroke or fatal CVD); CVD mortality and all-cause mortality. All statistical analyses have been carried out using Stata versions 12-13 (Stata Corp., College Station, Texas).

1.4. Structure of the thesis

The structure of the thesis is as follows: Chapter 1 provides an introduction to the relationship between body composition, dietary patterns and risk of CVD and mortality and outlines the importance of understanding these relationships in older age, and presents objectives, methodology overview, structure of the thesis and thesis publications. Chapter 2 presents the epidemiological and aetiological background to CVD and includes literature reviews of the associations between body composition and dietary patterns with CVD and mortality in older age. Chapter 3 describes the British Regional Heart Study design and methodology, the data used to address the thesis objectives and methods used to analyse data. Chapter 4 is the first of five results chapters and examines the associations between various measures of adiposity and muscle mass and cardiovascular risk factors in older age, using cross-sectional data from the 20 year re-examination. Chapter 5 examines the associations between adiposity, muscle mass and risk of CVD and mortality in older age, using baseline body composition measurements from the 20 year re-examination (1998-

2000) and follow-up data on CVD and mortality until 2010. Chapter 6 describes the diet of the BRHS cohort and examines the associations between *a priori* diet quality scores, cardiovascular risk factors and the risk of CVD and mortality, use baseline dietary data from the FFQ completed at the 20 year re-examination (1998-2000) and follow-up data on CVD and mortality until 2010. Chapter 7 further develops the findings from Chapter 6 by examining the influence of social circumstances on *a priori* diet quality scores in older age. Chapter 8 examines the associations between *a posteriori* dietary patterns, cardiovascular risk factors and the risk of CVD and mortality using baseline dietary data from the FFQ completed at the 20 year re-examination (1998-2000) and follow-up data on CVD and mortality until 2010. Each results chapter consists of a brief introduction specific to analyses of that chapter, methods (including subjects and methods of data collection and statistical analysis), results of analyses presented as tables and graphs, and a discussion including a summary of the main findings, comparison with previous literature and strengths and limitations. Chapter 9 is the concluding chapter, which brings together the key findings of all results chapters, together with implications for public health and future epidemiological research.

1.5. Thesis publications

Four first-author papers[36-39] based on the material in this thesis have been published in peer-reviewed journals to date, together with a review article[40] and a book chapter[41]. These publications are listed below. For completeness, a 'letter to the editor' written about one of these papers[42] and our response to this[43] are also included. A list of oral and poster presentations giving at conferences based on the material in this thesis can also be found in Appendix I and Appendix II respectively.

1. **Atkins JL**, Whincup PH, Morris RW, Wannamethee SG. Low muscle mass in older men: the role of lifestyle, diet and cardiovascular risk factors. J Nutr Health Aging 2014; 18(1):26-33.

2. **Atkins JL**, Whincup PH, Morris RW, Lennon LT, Papacosta O, Wannamethee SG. Sarcopenic obesity and risk of cardiovascular disease and mortality: a population-based cohort study of older men. J Am Geriatr Soc. 2014; 62(2):253-260.
    - ***Letter to the editor:*** Safer U, Tasci I, Safer VB. Comment on "Sarcopenic obesity and risk of cardiovascular disease and mortality: a population-based cohort study of older men". J Am Geriatr Soc 2014; 62(6): 1208.
    - ***Response to a letter to the editor:*** **Atkins JL**, Whincup PH, Morris RW, Wannamethee SG. Response to Safer et al. J Am Geriatr Soc 2014;62(6):1208-9.

3. **Atkins JL**, Whincup PH, Morris RW, Lennon LT, Papacosta O, Wannamethee SG. High Diet Quality Is Associated with a Lower Risk of Cardiovascular Disease and All-Cause Mortality in Older Men. J Nutr 2014;144(5):673-80.

4. **Atkins JL**, Ramsay SE, Whincup PH, et al. Diet quality in older age: the influence of childhood and adult socio-economic circumstances. Br J Nutr 2015: 113 (9): 1441–52.

5. **Atkins JL**, Wannamethee SG. The Effect of Sarcopenic Obesity on Cardiovascular Disease and All-Cause Mortality in Older People. Rev Clin Gerontol. 2015; 25 (2) 86-97.

6. **Atkins JL**, Wannamethee SG. Chapter 13. Diet quality and cardiovascular disease prevention. In Bendich A, Deckelbaum RJ (Eds), Preventive Nutrition: The Comprehensive Guide for Health Professionals. 5th Edition. Humana Press: 2015.

CHAPTER 2 Literature review

2.1. Introduction

This chapter presents the epidemiological and aetiological background to cardiovascular disease (CVD), and reviews existing studies of the associations between body composition and dietary patterns with CVD and mortality in older age. Section 2.2 describes the epidemiology and pathophysiology of CVD and the importance of CVD in older age. Section 2.3 details the literature on the aetiology of CVD, including established and emerging risk factors. Section 2.4 explores body composition as a major risk factor for CVD, including approaches to measuring body composition and a review of the evidence for an association between body composition and risk of CVD and mortality in older age. Section 2.5 explores dietary patterns as a major risk factor for CVD, including methods of assessing dietary intake and a review of the evidence for an association between dietary patterns and risk of CVD and mortality in older age. Finally, section 2.6 summarises the issues arising from the literature review and restates the purpose of the thesis.

2.2. Overview of cardiovascular disease

2.2.1. Epidemiology and pathophysiology of CVD

The epidemiological transition has meant that over time the main cause of death worldwide has shifted from communicable to non-communicable diseases (NCDs). Of the 57 million deaths which occurred globally in 2008, 63% of these were due to NCDs[44] and of these, CVD is the largest single cause of death[6;45]. Death rates from CVD have been falling in the UK since the early 1970s but CVD remains the main cause of mortality, accounting for nearly 180,000 deaths in 2010; nearly a third of all deaths in both men and women[4]. Nearly half (45%) of all CVD deaths in the UK are from coronary heart disease (CHD) and over a quarter (28%) are from stroke[4]. CHD is the single most common cause of death in the UK. The incidence of CHD is higher in men than in women and in 2010 just below one in five male deaths and one in eight female deaths were due to CHD[4]. CVD is a major contributor to morbidity and disability, with an estimated cost to the UK economy of £29.1 billion in 2004, due to

health care costs (60%), productivity losses due to mortality and morbidity (23%) and informal care-related costs (17%)[46].

The main forms of CVD in the UK are CHD (coronary [ischaemic] heart disease) and cerebrovascular disease (particularly stroke). Atherosclerosis is the common underlying disease process responsible for almost all CHD (coronary atherosclerosis) and a substantial proportion of stroke (carotid atherosclerosis) and develops over many years. Atherosclerosis is a complex pathological process characterised by chronic inflammation in the artery walls, where fatty materials and cholesterol are deposited (forming atherosclerotic plaques), narrowing the arterial lumen, obstructing blood flow and making the arteries less pliable[4;6;47]. These plaques can eventually rupture, triggering the formation of a thrombus which, if large enough, may occlude a coronary blood vessel or a cerebral blood vessel[6].

The clinical manifestations of CHD include angina pectoris, acute myocardial infarction (MI) and sudden ischaemic death[47-49]. Angina pectoris is characterised by chest pain due to ischaemia of the myocardium and can be stable or unstable. Stable angina is likely to cause regular and predictable symptoms. Unstable angina can cause prolonged chest pain even at rest or low levels of activity or can be previously diagnosed angina that has become more frequent, longer in duration, or lower in threshold to activity[50]. Acute MI (a 'heart attack') can be fatal or non-fatal and is caused by necrosis of myocardial tissue due to blockage of a coronary artery. Symptoms include chest pain, which can often radiate to the jaw, neck, arms and back, shortness of breath, dizziness, nausea and an overwhelming sense of anxiety. MI can also be silent; asymptomatic and only diagnosed retrospectively through electrocardiograms[51]. The World Health Organization criteria for myocardial infarction are any two of these three conditions: prolonged chest pain, positive electrocardiogram findings and raised cardiac enzyme levels[52;53].

The clinical manifestations of cerebrovascular disease include transient ischaemic attacks (TIAs) and strokes[47;48]. A TIA is caused by a temporary disruption in cerebral blood flow, with symptoms (including facial weakness, arm weakness and speech problems) disappearing within 24 hours. Stroke however, is more severe with

permanent symptoms. The current universal definition of stroke, as defined by the Stroke Council of the American Heart Association and the American Stroke Association, is: "Central nervous system infarction is brain, spinal cord, or retinal cell death attributable to ischemia, based on pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution and/or clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting ≥ 24 hours or until death, and other etiologies excluded"[54].

2.2.2. **The importance of CVD in older age**

The population in the UK is ageing due to a steady increase in life expectancy over time. Since the 1930s, the number of people aged over 65 years in the UK has more than doubled[1] and by 2012, 23.0% of the population were aged over 60, a proportion which is predicted to increase to 29.6% by 2050[2]. Older adults are at an increased risk of developing non-communicable diseases and the majority of the burden from CVD in the UK population occurs at older ages, with 74% of all deaths from diseases of the circulatory system, 68% of all deaths from CHD and 83% of all deaths from stroke occurring in people older than 75 years[4]. The risk of CVD increases dramatically with age in both men and women[9]. Comparing CHD incidence between younger and older age groups in England shows that between 30-54 years and 75-84 years, rates increases more than 10-fold in men and more than 30-fold in women[55]. The prevalence of CVD also increases greatly with age with a much steeper increase in men than in women, ranging from 3.3% of men and 4.8% of women aged 16-24 to 53.8% and 31.1% respectively aged 85 and over[56]. The population burden of CVD morbidity and disability in older people is also further increased by the increasing survival rates following myocardial infarction[57].

The burden of CVD in older adults is therefore an important public health problem and the UK in particular has significantly greater rates of age-standardised years of lives lost from cardiovascular and circulatory disorders than many other comparable high income countries[58]. Even small relative risk reductions in CVD in older adults could considerably reduce absolute mortality and cardiovascular morbidity and disability

risks. Therefore, it is particularly important to identify and reduce exposure to risk factors for CVD incidence in older ages[59].

2.3. Aetiology of CVD

2.3.1. Established risk factors for CVD

CVD is largely preventable, and well-established major risk factors are raised blood pressure (hypertension), high low density lipoprotein cholesterol and cigarette smoking, followed by harmful use of alcohol, physical inactivity, raised blood sugar levels, overweight/obesity and poor diet quality[5;6]. These risk factors cause damage to coronary and cerebral blood vessels due to atherosclerosis. The World Health Organization (WHO) attributes 61% of cardiovascular deaths to the following eight major risk factors - alcohol use, tobacco use, high blood pressure, high body mass index, high cholesterol, high blood glucose, low fruit and vegetable intake, and physical inactivity[7].

Blood pressure: It is estimated that 45% of cardiovascular deaths worldwide can be attributed to raised blood pressure[7]. There is a strong positive association between systolic blood pressure (SBP) and diastolic blood pressure (DBP) and risk of cardiovascular mortality, seen above the usual SBP of 115 mmHg and DBP of 75 mmHg[60]. The association between blood pressure and stroke mortality is stronger than for CHD mortality; at ages 40-69 years, each 20 mmHg increase in SBP (or approximately 10 mmHg increase in DBP) is associated with more than a two-fold increase in stroke mortality and a two-fold increase in CHD mortality. The increased risk of cardiovascular mortality associated with hypertension also persists, but is attenuated, in older age[60].

Cholesterol: Globally, 16% of cardiovascular deaths can be attributed to raised cholesterol[7]. The Prospective Studies Collaboration showed that on average, 1 mmol/L lower total cholesterol was associated with about a half the risk of CHD mortality in early middle-age (40-49 years) and about a sixth of the risk in old age (70-89 years)[61]. This study also showed a positive association between total cholesterol and stroke mortality in early middle age (40–59 years), but total cholesterol was negatively related

to stroke mortality in older age (70-89 years). The low density lipoprotein (LDL) and high density lipoprotein (HDL) components of total cholesterol have opposing effects on CHD mortality - the Prospective Studies Collaboration showed that on average 1 mmol/L lower non-HDL cholesterol and 0·33 mmol/L higher HDL cholesterol, were each associated with about a third lower CHD mortality risk[61]. However, stroke was not significantly associated with non-HDL or HDL cholesterol in this study[61].

Dietary fat intake is a major determinant of blood cholesterol levels. A high intake of dietary cholesterol increases blood cholesterol and this is mainly determined by the intake of saturated fatty acids, where as polyunsaturated fatty acids lower blood cholesterol levels[62;63].

Cigarette smoking: is estimated to cause almost 10% of cardiovascular disease worldwide[7] and there is evidence that smoking increases risk of mortality 2 to 3 fold[64]. There is a significant body of evidence from prospective studies on the beneficial effects of smoking cessation on CHD mortality and stroke mortality, with a 50-year follow-up in the British Doctors Study showing that the age of quitting has a major impact on life expectancy, with those who quit between 35 and 44 years of age having the same survival rates as those who had never smoked[64]. Cigarette smoking also persists as a strong independent risk factor for cardiovascular events and mortality at older ages[64-66].

Alcohol: There is also evidence that alcohol consumption is associated with CVD risk. Many studies have shown a U-shaped or J-shaped relationship between alcohol consumption and risk of CVD, with an increased risk in those who abstain from alcohol and those who drink excessively compared to light or moderate drinkers[67;68]. A meta-analysis of prospective cohort studies showed that the lowest risk of CHD mortality occurred with 1-2 drinks a day, but for stroke mortality the lowest risk was for ≤ 1 drink per day[68].

Physical inactivity: is well established as a risk factor for CVD, with insufficient activity described as less than 5 sessions of 30 minutes of moderate activity per week, or less than 3 sessions of 20 minutes of vigorous activity per week[6]. Individuals who are insufficiently physically active have a 20% to 30% increase in all-cause mortality risk compared to those who engage in at least 30 minutes of moderate intensity physical activity most days of the week[6]. A recent meta-analysis also showed that individuals performing a moderate level of leisure time physical activity had a 12% lower risk of CHD mortality and those performing a high level of activity had a 27% lower risk[69]. Similarly, a meta-analysis reported that moderate physical activity was associated with an 11% lower risk of stoke outcomes and high physical activity was associated with a 19% lower risk[70]. Studies have also shown that the association between higher physical activity and lower CVD risk persists in older age[71;72].

Blood glucose: High blood glucose (hyperglyceamia) increases the risk of cardiovascular mortality, with global estimates that 21% of CHD mortality and 13% of stroke mortality are attributable to raised blood glucose, including people with and without established diabetes[7;73]. Diabetes specifically, is defined as a fasting plasma glucose level of $\geq$ 7.0 mmol/l, and type 1 and type 2 diabetes mellitus are associated with a significantly elevated risk of CVD. The Emerging Risk Factors Collaboration carried out a meta-analysis which estimated the hazard ratio (HR) for all vascular deaths, comparing diabetes versus no diabetes, as 2.32 (95% CI: 2.11-2.56)[74].

Overweight/Obesity: Another important modifiable risk factor for CVD is high adiposity, with overweight and obesity showing consistent strong associations with CVD risk in middle-aged populations[75-79]. Some studies suggest that measures of central adiposity (waist circumference and waist-to-hip ratio) are stronger predictors of cardiovascular risk than BMI (a measure of whole-body adiposity)[75;79]. Despite the well-established associations between obesity and increased cardiovascular risk in middle age, the effect of obesity on CVD and mortality in older adults is controversial. This evidence for associations between obesity and CVD and mortality in middle-aged and older adult populations will be explored in detail in section 2.4.

Poor diet quality: is another important behavioural risk factor that is well-established in the aetiology of CVD. Various individual aspects of diet have been associated with an increased risk of CVD, including high saturated fat intake[25], high salt intake[24] and low fruit and vegetable consumption[26;27] and this risk can be reduced by the replacement of saturated fats with unsaturated fats, limiting salt intake and increasing fruit and vegetable consumption. Recently there has been a shift in focus to overall dietary patterns, with the adherence to a Mediterranean-style diet in particular showing significant reductions in CVD risk in a recent meta-analysis[31]. However, despite the well-established associations between diet and increased cardiovascular risk in middle age, there is a paucity of data on the effects of diet (specifically dietary patterns) on CVD in older adults[33]. This evidence for associations between diet/dietary patterns and CVD and mortality in middle-aged and older adult populations will be explored in detail in section 2.5.

2.3.2. **Emerging risk factors for CVD**

In addition to the established risk factors for CVD described in section 2.3.1, a range of emerging risk factors have developed as being implicated in the aetiology of CVD, including markers of inflammation, and endothelial and haemostatic dysfunction since they are associated with arterial plaque formation, plaque rupture and thrombosis[80;81]. Prospective studies and meta-analyses have shown that markers of inflammation, particularly acute phase proteins (e.g. C-reactive protein [CRP][82]) and circulating proinflammatory cytokines (e.g. interleukin 6 [IL-6][83]) are related to CVD risk. Similarly, haemostatic markers (e.g. fibrinogen[84], von Willebrand factor [vWF][84;85], and tissue plasminogen activator [t-PA][86]) and markers of endothelial dysfunction (D-dimer)[84] are associated with an increased CVD risk in adult populations. Emerging risk factors may be particularly important in older age as many inflammatory and haemostatic markers have shown very high circulating concentrations in older age groups, with effects on CVD which persist in this age group[87;88]. Additionally, some of these emerging risk markers are strongly related to other established cardiovascular risk factors such as smoking, alcohol intake, physical inactivity, obesity and blood lipids[71;89-92].

2.3.3. **Conceptual framework for the influence of risk factors on CVD**

The eight major modifiable risk factors for CVD (hypertension, high LDL cholesterol, cigarette smoking, heavy alcohol intake, physical inactivity, raised blood sugar levels, overweight/obesity and poor diet quality[5;6]) mentioned above in section 2.3.1 and the emerging risk factors for CVD mentioned in section 2.3.2 can be conceptualised within a causal framework. Cigarette smoking, heavy alcohol intake, physical inactivity and poor diet quality, can be thought of as behavioural or lifestyle risk factors for CVD, with cigarette smoking being the strongest[7]. These factors may at least in part impact on other risk factors that act directly (e.g. blood lipids, blood pressure), as well as having direct effects. Physiological risk factors for CVD include overweight/obesity, high blood pressure, high LDL and raised blood sugar levels which are known to be causally linked to CVD[7;10]. These causal risk factors can operate via a 'critical period' model as early as in utero, with fetal undernutrition being associated with an increased risk of CHD, or an 'accumulation of risk' model throughout the life course[93;94].

Emerging risk factors, including inflammatory markers and haemostatic factors, are a reflection of the physiological status of an individual and can be strong predictors of cardiovascular events[80;81]. However, whether such factors may be acting as causal risk factors for CVD or just risk markers of underlying causal factors has been questioned[86;95;96]. Chronic inflammation has been implicated in the pathogenesis of atherosclerosis[97] but causality has not been established for many of the inflammatory markers implicated. For example, CRP is a strong powerful risk marker for CVD but Mendelian randomisation studies have not established CRP as a causal agent for CVD[98]. However, CRP is a downstream marker for interleukin-6 (IL-6) activity, a major proinflammatory cytokine which has been causally related to CVD[83;99;100]. Similarly, prospective studies and meta-analyses have shown haemostatic markers such as von Willebrand factor ([vWF] a marker of endothelial dysfunction) and fibrin d-dimer (a marker of coagulation and fibrinolysis) are associated with increased risk of CHD[86;101] but causality has not been established for these markers. Nevertheless, although markers such as CRP, vWF and d-dimer may only be risk markers for CVD risk, they are of interest as they may be indicators of the inflammatory and haemostatic pathways.

The effects of two particular interrelated risk factors (body composition and dietary patterns) on CVD and mortality will now be addressed in detail in sections 2.4 and 2.5 respectively.

2.4. Body composition, CVD risk and all-cause mortality

This section will address the effects of two components of body composition (body fatness/adiposity and lean mass/muscle mass) on CVD and mortality, and body fatness/adiposity will be addressed first.

2.4.1. Assessing and defining adiposity and obesity

Overweight and obesity are defined by WHO as "abnormal or excessive fat accumulation that may impair health"[10]. There are many available methods of body composition assessment used in clinical practice and for epidemiological research to measure whole-body or regional adiposity[102;103]. In epidemiological studies, the most commonly used methods to estimate body composition include combinations of weight and height, skinfold thickness measurements and body circumferences[104]. The most commonly used measure of obesity is body mass index (BMI), defined as weight (kg) divided by height squared (m^2), giving the units kg/m^2. Underweight is defined as a BMI of less than 18.5 kg/m^2, a normal healthy weight is defined as a BMI of 18.5-24.9 kg/m^2, and overweight and obesity are defined as BMI cut points of greater than or equal to 25 kg/m^2 and 30 kg/m^2 respectively[105;106]. BMI is a measure of whole-body adiposity, and it was originally known as the Quetelet index since the formula was first proposed by Adolphe Quetelet, a Belgian mathematician, in 1832[107;108]. The term BMI was first referred to by Ancel Keys in 1972 in a paper which found that BMI was the best proxy for body fat percentage among ratios of weight and height[109]. However, there are serious doubts on the validity of BMI to represent adiposity accurately, since it does not distinguish between fat mass and lean mass[15;110].

Skinfold anthropometry is also frequently used in body composition assessment, in which measurement of subcutaneous fat using skinfold calipers allows adiposity to be estimated. Typically, triceps and subscapular skinfold thickness have been used as

relative measures of extremity and truncal obesity respectively[104]. This method has the advantages of being quick, and requiring noncomplex portable equipment, but it is dependent on the training and skill of the observers so is therefore most suited to research settings[111].

In recent years there has been more of a focus on the distribution of body fat, with measures of central or visceral adiposity being commonly used to define obesity, due to the suggestion that these measures are more closely related to CVD. Waist circumference (WC) and waist-to-hip ratio (WHR) are two such measures, which can be assessed relatively easily with measuring tape and hence are suitable methods for use in epidemiological studies. WHO define central obesity using sex-specific cut-points for WC (>102 cm for men and >88cm for women) and WHR (≥ 0.90 cm for men and ≥ 0.85 cm for women)[105 112].

Bioelectrical impedance analysis (BIA) is a noninvasive technique which consists of passing a low amplitude electrical current through the body and measuring the resistance, based on the principle that lean body mass, which consists largely of ions in water solution, conducts electricity far better than fat tissue does[104;113-115]. The measure of resistance is then used to estimate lean body mass and (indirectly) fat mass. This technique has the advantages of being relatively quick and easy to use, with inexpensive, portable equipment but this technique is dependent on the validity of the equations used to calculate fat-free mass from the bioelectrical impedance measures[114].

Newer body imaging techniques based on electrical resistance and impedance have also become available including magnetic resonance imaging (MRI), computerised tomography (CT) and dual energy x-ray absorptiometry (DXA). DXA is a technique used increasingly to measure fat and fat-free mass. DXA scanners generate X-rays at two different energies, making use of the differential attenuation of the energies to calculate the bone mineral content and soft tissue composition of the scanned region[116]. DXA has a very low dose of radiation, and hence is a safe but expensive method, which is used more often in clinical rather than in research settings.

2.4.2. **Epidemiology of obesity**

Obesity is an important public health problem and it is well recognised as a major risk factor for CVD morbidity and mortality in adult populations[75-79], as introduced in section 2.3.1, and the evidence for this will be further explored in section 2.4.3. The prevalence of obesity continues to increase globally, and this is the case in both middle-aged and older adult populations. Since 1980, the prevalence of obesity has more than doubled worldwide[10;11]. The prevalence of obesity is also increasing with age; in an ageing population this is particularly important in terms of an increased risk of CVD morbidity and mortality and hence an added burden on healthcare resources[117;118]. Overweight and obesity are extremely prevalent in older British adults[4;12]. In 2010, it was estimated that 35% of men and 32% of women aged 16 to 24 were overweight or obese which rose to 81% of men and 74% of women aged 65 to 74[4]. An increasing trend was also seen in the prevalence of central obesity with age, and this was especially the case in men. An estimated 13% of men and 18% of women aged 16 to 24 had central obesity which compared to 49% of men and 64% of women aged 65 to 74[4].

2.4.3. **Obesity, CVD risk and all-cause mortality in middle-aged populations**

Obesity is well recognised as a major risk factor for CVD morbidity and mortality in adult populations, with many studies showing J or U-shaped associations between BMI-defined obesity and the aforementioned outcomes[75-79;119-121]. Collaborative analyses of 57 prospective cohorts, of men and women aged 35 to 89 year olds, showed a U-shaped association between BMI and mortality, with the lowest risk in those with normal BMI (22.5-25 kg/m^2)[76]. Above this range, a strong positive association was seen for CVD mortality with a 40% increase in risk for each 5 kg/m^2 increase in BMI. Measures of central obesity have also shown associations with CVD in middle age populations, with evidence that they may be stronger predictors of risk than BMI. A meta-analysis of nine British cohorts in middle aged populations showed that measures of visceral adiposity (WC and WHR) were significantly and positively associated with total and CVD mortality, but BMI was not associated with CVD risk[79]. Stronger evidence has been provided by a similar but larger meta-analysis which was carried out in 58 prospective cohort studies, across 17 countries[78]. A slightly greater magnitude of effect was

observed for the association between measures of central adiposity, compared to total adiposity, with CVD risk; hazard ratios for CVD risk were 1.27 for waist circumference, 1.25 for waist-to-hip ratio and 1.23 for BMI, for a 1 standard deviation increase in each measure[78]. Also, the INTERHEART study found that abdominal obesity was a much more significant risk factor for MI than BMI, and estimated that 63% of MIs in Western Europe are due to abdominal obesity (a high waist-to-hip ratio)[75].

2.4.4. **Body composition, CVD risk and all-cause mortality in older age**

Although strong evidence has shown that obesity and overweight are important determinants of the risk of CVD and mortality in middle age, their role in later life is controversial[13;122]. In particular, the relationship between BMI and mortality is less clearly defined in older age, with many studies showing that being overweight, as defined by BMI, does not appear to be harmful and may even be associated with lower, rather than higher, mortality[13;14;123]. A systematic review and meta-analysis of 26 studies of healthy men and women, aged 65 years or older, found that BMI in the overweight range was not associated with a significantly increased mortality risk, and BMI in the moderately obese range was only associated with a modest 10% increase in mortality risk[14]. Similarly, a more recent large meta-analysis of 32 studies, which included almost 200,000 individuals aged 65 or older, showed a U-shaped relationship between BMI and all-cause mortality[124]. Overweight was not associated with an increased mortality risk, with the lowest risk seen in those with a BMI between 24.0 and 30.9 kg/m^2, and risk only began to increase when BMI exceeded 33 kg/m^2 [124].

In recently years it has been suggested that measures of adiposity such as WC and WHR, which better reflect central adiposity, may be more useful at assessing obesity risk than BMI as they are better at predicting CVD and mortality in older subjects [13;79;122;125-127]. A recent meta-analysis of 29 elderly cohorts, which included over 58,000 men and women aged 65 to 74 years, showed positive associations between WC and all-cause and cardiovascular mortality risks, which was consistent across BMI categories[127]. Similarly, a recent systematic literature review identified 16 studies which

assessed the impact of obesity on mortality in the elderly, and concluded that WC is as effective, if not more, than BMI as a risk factor for mortality in older adults[128].

Allison et al hypothesised that the frequently observed U-shaped relationships between BMI and mortality are due to the opposing effects of fat mass and fat-free mass (both of which influence BMI) on mortality[15]. Using data from the National Health and Nutrition Examination Surveys (NHANES I and NHANES II), Allison et al showed that there is a positive association between fat mass and mortality but an inverse association between fat-free mass and mortality (see Figure 2.1). Ageing is associated with important changes to body composition; typically visceral fat increases and there is a substantial decreases in fat-free mass (FFM) and muscle mass, meaning that overall body weight and BMI may remain relatively unchanged[3;13;18;22]. Since BMI depends not only on adiposity but also on muscle mass, which has opposing effects on mortality, the validity of the use of BMI in measuring the impact of obesity in the elderly may therefore be limited[15;16]. The aforementioned studies[14;124] which have used BMI to assess obesity in the elderly can therefore be criticised on this basis. Therefore to fully understand the effects of body composition in the elderly, it may be important to take both fat mass and lean mass, assessed independently, into account.

2.4.5. **Epidemiology of sarcopenia**

Sarcopenia describes the age-associated loss of skeletal muscle mass and muscle function[129], and is often associated with visceral obesity[18-21]. Sarcopenia has a multifactorial aetiology, which is not fully understood. However, several underlying mechanisms of this age-related muscle loss have been recognised including neuronal and hormonal changes, poor nutrition (especially low protein intake), physical inactivity and inflammation[18;130-133]. Given the body composition changes which occur with increasing age, sarcopenia often coexists with an increase in fat mass. Recently, a new concept of obesity has emerged, 'sarcopenic obesity' which refers to the simultaneous existence of sarcopenia and high levels of adipose tissue in individuals[18;22]. Visceral fat is a major risk factor in the development of both metabolic disorders (hypertension, dyslipidemia and insulin resistance) and CVD. Sarcopenia has also been shown to be

associated with CVD risk factors and risk of adverse health outcomes including physical disability and mortality[19;134-138]. Visceral fat and muscle mass are known to be related in a pathogenic sense and share common inflammatory pathways[18]. Therefore it is hypothesised that sarcopenia and obesity may act synergistically, so that sarcopenic obesity may have a greater effect on metabolic disorders, CVD and mortality than either obesity or sarcopenia alone[18-22]. The interaction between sarcopenia and obesity, with rising prevalence in an ageing population, is becoming an important public health issue in the older adults[18]. Sarcopenia is therefore a separate component of body composition requiring investigation in relation to CVD and mortality.

2.4.6. **Assessment and definitions of sarcopenia and sarcopenic obesity**

Sarcopenia is the term used to refer to the age-associated loss of skeletal muscle mass and function. The name was first coined by Rosenberg in 1989 (with Greek origins of 'sarx' for flesh and 'penia' for loss) who suggested that no decline with age is more dramatic or potentially more functionally significant than the decline in lean body mass[139;140]. Sarcopenia is associated with increased risks of functional impairment and physical disability[131;141;142] which account for substantial healthcare costs; in the USA in 2000 the estimated costs attributable to sarcopenia were $18.5 billion, based on the increased risk of physical disability in older adults[143]. Sarcopenia is common in the elderly with prevalence estimated to be between 5% and 13% among 60 to 70 year olds, rising to 11% to 50% for those aged over 80 years[144]. This large amount of variability in prevalence estimates is likely to be related to the wide range of measurement methods and cut-off points which are used to define sarcopenia[144]. It is widely accepted that four body composition phenotypes exist in older age (normal, sarcopenic, obese and sarcopenic obese). However, despite this, to date there is no universally accepted operational definition or classification for either sarcopenia or sarcopenic obesity[17;138]. No International Classification of Disease (ICD) codes exist for sarcopenia and there are no standard treatment guidelines[145].

Many different definitions of sarcopenia have been used in previous literature[17;19] based on differing measurement methods to assess total or skeletal muscle mass, including

body imaging techniques (MRI, CT and DXA), BIA and anthropometric measures[18]. MRI and CT are regarded as the two gold standards methods for muscle mass assessment[146]. However, due to the associated high costs, limited access to equipment in some settings and concerns about radiation exposure, the use of whole-body imaging methods is usually limited to clinical practice[17]. Anthropometric measures used to assess muscle mass also include measures based on body circumferences, and these are quick and simple measures often used in epidemiological research, but do not take muscle fat infiltration into account. Mid-upper arm circumference (MUAC) can be measured in combination with triceps skinfold thickness, to estimate mid-arm muscle circumference (MAMC), which correlates strongly with more accurate dual-energy X-ray absorptiometry measures of lean mass[147;148]. Calf circumference is another anthropometric measure also positively correlated with muscle mass[149].

Baumgartner et al first defined sarcopenia as appendicular skeletal muscle mass (ASM), assessed by DXA adjusted for height, two standard deviations below the sex-specific reference for a young healthy person[131]. Another commonly used sarcopenia definition was developed by Janssen et al, using BIA to determine skeletal muscle mass[141;150]. In 2009, The European Working Group on Sarcopenia in Older People (EWGSOP) proposed a clinical definition of sarcopenia for case finding in older individuals. The EWGSOP proposed definition includes the presence of both low muscle mass and low muscle function (either low strength and/or low physical performance)[17]. The EWGSOP suggested algorithm for sarcopenia suggests using handgrip strength to measure muscle strength, and gait speed to measure physical performance[17]. A systematic review of studies which used the EWGSOP definition to define sarcopenia in adults age 50 years or over, found substantial prevalence estimates in most geriatric settings, but there was wide variation in prevalence estimates; 1 to 29% in community-dwelling populations, 14 to 33% in long-term care populations and 10% in an acute hospital-care population[151]. A similar definition was proposed by the International Working Group on Sarcopenia (IWGS) in 2011, who suggested that diagnosis is based on a low whole-body or appendicular fat-free mass in combination with poor physical functioning[134].

The term 'sarcopenic obesity' was first coined by Baumgartner et al[22] and is it defined by a combination of sarcopenia and obesity. However, like sarcopenia, there is no universally accepted definition of sarcopenic obesity, so a wide variety of measures of obesity (described in section 2.4.1) and muscle mass or function measures (described here in section 2.4.6) have previously been used[21]. However, the lack of agreement on a definition for the diagnosis of sarcopenic obesity presents major drawbacks both clinically and for research[152]. Also, although sarcopenia is defined as the age-associated loss of muscle over time, most sarcopenia definitions are based on assessment at a single time point only.

2.4.7. **Sarcopenia, sarcopenic obesity and cardiovascular risk factors in older age**

Numerous population studies have shown that sarcopenia is cross-sectionally associated with established and emerging cardiovascular risk factors[137], including insulin resistance[153], dyslipidemia[154], hypertension[155], arterial stiffness[156] and inflammatory markers[157-159]. In addition, many studies have examined the associations between sarcopenic obesity and established cardiovascular risk factors, although not all have shown that the sarcopenic obese group have the most adverse metabolic and cardiovascular risk profile[154;155;160-173]. Table 2.1 summarises relevant studies that investigate the associations of sarcopenic obesity and cardiovascular risk factors in older people.

Several cross-sectional studies carried out in Korean older adults found that sarcopenic obese individuals had the worse cardiovascular risk profile; sarcopenic obesity (based on skeletal muscle mass assessed by DXA and obesity assessed by CT, DXA, BMI or WC) was associated with lower cardiorespiratory fitness, a higher risk of hypertension, dyslipidemia and insulin resistance, higher fasting glucose levels, and up to an 8-fold increase in metabolic syndrome (MetS) risk compared to non-sarcopenic, non-obese[154;155;160-167]. Comparably, sarcopenic obese Taiwanese older adults (defined by BIA and BMI) also had the highest risk of MetS. Compared to the non-sarcopenic, non-obese group, the sarcopenic obese group had a 12-fold increase in risk and the sarcopenic group had only a 2-fold increase in risk[168]. In a large cross-sectional analysis

of over 14,000 adults from NHANES III, the sarcopenic obese group (defined by BIA and BMI) showed the highest risk of dysglycemia and insulin resistance[169].

However, not all studies show that sarcopenic obese individuals have the worst cardiovascular risk profiles; some cross-sectional studies have suggested that obese older adults may have higher levels of cardiovascular risk factors than sarcopenic obese individuals. Older adults from the New Mexico Aging Process Study, aged 60 years or over, found that the prevalence of MetS and hypertension was highest in the non-sarcopenic obese group, followed by the sarcopenic obese group (assessed using DXA measurements)[170]. Studies in postmenopausal women have also shown that sarcopenic obese individuals did not show an unfavourable metabolic profile compared to non-sarcopenic obese individuals[171] and that glucose level, lipid profile and blood pressure were not significantly different between sarcopenic obese and non-sarcopenic, non-obese individuals[172].

Despite inflammation being strongly associated with both sarcopenia and obesity[89;157], conflicting results have been found regarding the relationship between inflammatory and haemostatic markers and sarcopenic obesity. Cross-sectional analysis of older adults from the "Invecchiare in Chianti" (InCHIANTI) study, aged 65 years and older, showed that sarcopenic obesity (based on grip strength and WC measurements) was associated with higher levels of inflammatory markers including CRP and IL-6[173]. Comparably, sarcopenic obese adult Korean women had the highest CRP levels[167]. However, analysis of baseline data from the Trial of Angiotensin Converting Enzyme Inhibition and Novel Cardiovascular Risk Factors study found there were no significant interactions between sarcopenia and obesity with CRP, IL-6 or plasminogen activator inhibitor[174] and another study found that CRP levels were not significantly different between sarcopenic obese and non-sarcopenic, non-obese postmenopausal women[172].

In summary, many studies suggest that sarcopenia is associated with established and emerging cardiovascular risk factors. However, whether sarcopenic obese individuals have the worst cardiovascular risk profile seems unclear.

2.4.8. **Sarcopenia, sarcopenic obesity and CVD risk in older age**

Section 2.4.7 reviewed the evidence of associations between sarcopenia and sarcopenic obesity with cardiovascular risk factors. However, despite the growth of literature in this field over the last decade, to date very few studies have examined the prospective associations between sarcopenia, and sarcopenic obesity with CVD in older people[137;152]. Table 2.2 summarises relevant studies that investigate the associations of sarcopenic obesity with CVD risk and mortality in older people.

Cross-sectional analysis of baseline data from the New Mexico Aging Process Study compared CVD prevalence in older adults, aged 60 years and over, between sarcopenic obesity groups (defined by ASM and percent body fat from DXA)[170]. The prevalence of CVD in sarcopenic individuals was the highest (18.3%), compared to that of non-sarcopenic, non-obese individuals (13.7%) and sarcopenic obese (11.5%). However, the difference in prevalence across these groups was not significant. A cross-sectional study of 1578 male and female participants, aged 65 years or older, from KNHANES found that in crude analysis although the sarcopenic obesity group (based on ASM from DXA and BMI $\geq$ 25) showed a slightly higher prevalence of CVD (12.3%) compared to non-sarcopenic obese (10.0%), this difference was non-significant[175]. However, in adjusted analysis sarcopenia was associated with CVD independent of other well known risk factors, renal function and medication (OR: 1.77, 95% CI: 1.08-2.90). Another larger cross-sectional study using KNHANES data, analysed the association between sarcopenia (defined using ASM) and the prevalence of CVDs in over 7,000 men and women aged 50 or over[176]. The prevalence of CVD was positively associated with sarcopenia in men after adjusting for cardiovascular risk factors (Class I sarcopenic, OR: 1.82, 95% CI: 1.24-2.67; Class II sarcopenic, OR: 2.35, 95% CI: 1.26-4.40). However, no significant association was found in women. Within all of these cross-sectional studies, the assessment of body composition and cardiovascular risk factors was at the same time point so reverse causality is possible.

To my knowledge, only one prospective study has examined the association between sarcopenic obesity groups and CVD risk. Stephen et al analysed data from the Cardiovascular Health Study, a moderately large prospective study of 3366 community-

dwelling older men and women (aged 65 years or above) over eight years of follow-up[177]. They found that compared to the normal body composition group, the risk of CVD events was not significantly elevated in the sarcopenic or sarcopenic obese groups, when defined using WC and BIA-measured muscle mass. When sarcopenia and obesity was determined by WC and grip strength, CVD risk was not significantly increased in the sarcopenic group but was increased by 23% in the sarcopenic obese group, with borderline significance (HR: 1.23, 95% CI: 0.99-1.54; adjusted for age, sex, ethnicity, income, smoking, alcohol and cognitive function). These results imply that muscle strength could be particularly important when assessing the association between sarcopenic obesity and CVD risk.

Overall, it seems that findings from these cross-sectional studies and the one available prospective study do not provide sufficient evidence to reach a conclusion regarding the association between either sarcopenia or sarcopenic obesity with CVD risk.

2.4.9. **Sarcopenia, sarcopenic obesity and all-cause mortality in older age**

In contrast to the limited evidence on sarcopenia and CVD risk, several prospective studies have examined the association between sarcopenia and the risk of all-cause mortality, and have provided consistent evidence that low muscle mass (defined using various measurement methods) is associated with an increased risk of mortality in older adults. Simple anthropometric assessments of muscle mass, such as body circumference measurements, have been shown to be associated with mortality risk. Data from the Longitudinal Aging Study Amsterdam, a population-based cohort of 1,667 older adults, aged 65 and above, found that MUAC is more strongly associated with mortality than calf circumference, over 15 years of follow-up; the hazard ratio for mortality per 1 standard deviation lower MUAC was 1.79 (95% CI: 1.48-2.16)[178]. Similarly, a small prospective study of 357 Italian community dwelling older adults, aged over 80 years, from The Aging and Longevity Study in the Sirente Geographic Area (ilSIRENTE Study), had MAMC measured at baseline and were followed up for 4 years[179]. Participants in the highest tertile of MAMC had a lower risk of mortality compared to those in the lowest tertile (adjusted HR: 0.45, 95% CI: 0.23-0.87). Another study in 1396 older Australians, aged 70 years and older, with low corrected arm muscle area (CAMA), derived from a standard formula which takes MUAC and triceps skinfold

thickness into account, had almost twice the risk of mortality at 8-year follow-up (HR: 1.94, 95% CI1.25-3.00)[180].

Similarly, estimates of skeletal muscle mass derived from BIA measures have also been inversely associated with mortality. In Korean men and women, aged 65 and over, in the highest quartile of lean mass and lean mass index (kg/m^2) mortality risk was reduced by 84% (95% CI: 45-96%) and 69% (95% CI: 12-89%) respectively[181] compared with the lowest quartile. Comparable associations have also been found with low muscle mass, measured by DXA. In a prospective cohort of Chilean community dwelling adults, it was found that appendicular FFM (from DXA) was a strong predictor of mortality[182]. In 477 adults aged 65 years and over from the Longitudinal Aging Study Amsterdam, lower appendicular skeletal muscle mass and lower leg fat mass were also strongly associated with an increased mortality risk[183]. However, these associations were not significant in women[183].

Strong associations have also been found between sarcopenia (defined using the EWGSOP definition which combines measures of muscle mass and muscle function) and all-cause mortality. Older participants aged 80 years and over, from the ilSIRENTE Study, with the EWGSOP-defined sarcopenia, had 2.32 times the mortality risk than that of non-sarcopenic participants (95% CI: 1.01-5.43), over 7 years of follow-up[184]. A similar magnitude of association was observed in an elderly Mexican population, aged over 70 years, that also used the EWGSOP definition of sarcopenia[185]; the risk of mortality was 2.39 times higher in sarcopenic compared to non-sarcopenic older adults (95% CI: 1.05-5.43) over 3 years of follow-up.

Some studies have suggested that decline in muscle strength is a stronger independent predictor of mortality than muscle mass[186;187]. A cohort of community-dwelling older Korean men with sarcopenia, defined using the EWGSOP definition, were at 4 times greater risk of mortality than men without sarcopenia. However, when individual components of the sarcopenia definition were examined, the associations with muscle function (leg muscle strength, and short physical performance battery test score) were

stronger than for muscle mass (assessed by ASM/height^2, from DXA)[188]. This possibility is also supported by data from the Health, Aging and Body Composition (Health ABC) study, which showed that knee extension strength and grip strength were strongly inversely associated with mortality, but that muscle size, determined by CT area or DXA regional lean mass was not strongly related to mortality[189]. This strong association seen between muscle strength and mortality was independent of muscle mass[189].

However, only a few prospective studies have specifically examined the association between sarcopenic obesity and the all-cause mortality risk in healthy individuals[190-194]. Table 2.2 summarises relevant studies that investigate the associations of sarcopenic obesity with mortality and CVD in older people. A small prospective study in a population with a specific prevalent disease, 250 patients with gastrointestinal or respiratory cancers, found that sarcopenic obese patients had a significantly higher risk of mortality compared to those with obesity alone[190]. An increased all-cause mortality risk in sarcopenic obese participants has also been found in a large community-based study; a previous report from the BRHS examined anthropometric indexes of body composition in relation to mortality over six years of follow-up, including more than 4,000 older men, aged 60 to 79 years. The results showed that muscle mass (indicated by MAMC) was significantly and inversely associated with mortality, and men with a high WC (>102cm) and in the lowest quartile of MAMC had a 55% increased risk of all-cause mortality compared to those with normal WC and MAMC[191].

Mortality risk was assessed in relation to sarcopenia and sarcopenic obesity in NHANES III, with over 4,000 participants, aged 60 years or above, followed prospectively for 14 years[192]. Sarcopenic and sarcopenic obese women (based on skeletal muscle mass and body fat measurement, from BIA) had a 35% and 29% significantly increased risk of mortality respectively compared to women without sarcopenia or obesity, after adjustment for age, gender, ethnicity and cardiovascular risk factors[192]. However, the risk of death with sarcopenia and sarcopenic obesity was not significant in men in this cohort. The InCHIANTI study classified 934 male and female

participants aged 65 years and above into one of six sarcopenic obesity groups, based on the presence of absence of sarcopenia (defined using calf skeletal muscle) and whether participants were obese, overweight or normal (according to BMI)[193]. This study followed participants for six years prospectively and found no significant difference in mortality risk across the six sarcopenic obesity groups.

One prospective study[194], with over 30 years of follow-up, has also used a measure of muscle strength instead of muscle mass to define sarcopenic obesity in relation to mortality risk. In over 6,000 adult men aged 45 to 68 years, there was a significant increase in risk of mortality in both men with sarcopenia and in men with sarcopenic obesity[194]. Among men who were of normal BMI (20-24.99 kg/m^2), those in the lowest grip strength tertile had a 25% increased risk of mortality compared to normal weight men in the highest grip strength tertile[194]. Among men who were overweight (BMI $\geq$ 25 kg/m^2) those in the lowest grip strength tertile had a 39% increased risk of mortality compared to normal weight men in the highest grip strength tertile.

In summary, the association between obesity and sarcopenia, measured either by muscle mass or muscle function or a combination of the two, and an increased risk of all-cause mortality seems to be fairly well documented in the literature. However, in contrast, there is a paucity of prospective studies which have examined the association between sarcopenic obesity and all-cause mortality risk. The available evidence on whether the presence of sarcopenic obesity increases the risk of all-cause mortality in older adults is inconclusive.

2.5. Dietary patterns, CVD risk and all-cause mortality

2.5.1. **Methods of dietary assessment**

2.5.1.2 Measuring dietary intake

Diet is a complex exposure and measuring intake accurately and precisely is very difficult. Several self-reported measurement methods have been used to assess dietary intake in epidemiological studies, but there are associated issues of measurement error

including problems surrounding recall bias, social desirability in reporting, and under or over reporting of total energy intake[104;195;196]. One of the most commonly used methods for assessing dietary intake is the food frequency questionnaire (FFQ)[197]. The FFQ approach requires participants to report their usual frequency of consumption of a number of food or drink items from a list for a specified time period. Information on portion size may also be collected. Relative or absolute nutrient intakes can be estimated from FFQs using an associated database of all food and drink items included in the questionnaire[198]. Many validated FFQs have been used previously with adaptations for different populations and purposes, but the completeness of the food/drink list is crucial in the food frequency method. Advantages of the FFQ method include the fact that data on usual individual dietary intake is collected, information on total diet is obtained, they are low cost to administer and they do not influence eating behaviour[199]. However, disadvantages include the fact that FFQs are cognitively difficult for participants to complete, dietary intake is not quantifiably precise and misreporting of intake is common[199].

Food records or diaries are an alternative dietary assessment method, in which participants record everything they ate or drank over a specified period of time, and this method can be supplemented by weighing. Theoretically, diet intake is recorded at the time of eating and details can be recorded by writing them down, using dictaphones, computer recording, photographs, and self-recording scales[199;200]. 24-hour dietary recall is another frequently used method, in which a participant recalls everything they ate or drank over the past 24 hours. The recall is typically conducted by interview either face-to-face or via telephone, and may be paper based or computer assisted. These two methods share the advantage of being able to quantify dietary intake, but both have the disadvantages of a high investigator cost, intake is often underreported and many days are needed to capture an individual's usual intake[199]. Food records specifically are not prone to recall bias but this method may affect eating behaviour, where as 24-hour dietary recall does not affect eating behaviour[199].

Another more recent method of dietary assessment, which overcomes some of the problems surrounding self-reported dietary data collection, is the use of biomarkers. Nutritional biomarkers are objectively measured indicators of dietary exposure, which have also been used to calibrate the measurement error in self-reported dietary data[201]. However, since nutritional biomarkers are expensive to collect, store and analyse, and due to the limited number of valid biomarkers, they are used less frequently in population based studies.

In summary, a range of measurement methods can be used to assess dietary intake. For the purposes of this thesis, dietary intake has been measured using data already collected for the BRHS from a FFQ which was self-completed by participants at the twenty year re-examination (see section 3.3.2 for details).

2.5.1.2 Examining dietary patterns

Historically, studies investigating the associations between diet and risk of morbidity or mortality have focused on single foods items and specific dietary nutrients, which have been shown to be important in the risk of CVD[23;202;203]. However, this approach has several limitations; it does not take into account the fact that foods are eaten in combination, and that interactions and synergies between nutrients are likely to exist. Moreover, the effects of single nutrients may be too small to detect and single nutrient analysis may be confounded by the effects of overall dietary patterns[28;29;195]. In recent years the focus of nutritional epidemiology has shifted towards examining overall dietary patterns in relation to health outcomes[28;29]. This reflects the complex and multidimensional nature of diets consumed in the population, to examine the combined effects of the consumption of various foods/nutrients and to reflect 'real world' dietary preferences. Two main approaches have been developed to assess diet quality: (1) Hypothesis oriented or theoretically defined approaches which are *a priori* in nature, since they use available scientific evidence to generate predefined dietary scores or indexes based on dietary recommendations or guidelines; and (2) Data-driven or exploratory approaches which are *a posteriori* in nature, since dietary patterns are

derived from the available data based on factor analysis, such as principal component analysis, or cluster analysis[29;30].

2.5.1.3 Defining a priori dietary patterns

A variety of diverse *a priori* defined dietary scores and indexes have been developed to assess overall diet quality, based on adherence to healthy diet patterns, such as the Mediterranean diet, adherence to national or international nutrient or food related dietary guidelines or dietary variety-based scores[23;195;204-206]. Specific scores will be described in detail in section 2.5.3, when the evidence for association between such scores and risk of CVD and mortality in the elderly will be reviewed.

A priori methods such as diet quality scores or indexes do have some limitations. They may be culturally or regionally specific so may not be universally applicable[30]. Scores may also be dependent on the selected underlying dietary guidelines, which are related to morbidity and mortality risk generally but not specifically to the risk of a specific disease. Adding together equally weighed dietary components implies that each component is equally important to CVD risk, which may not be the case. Also, scores which dichotomise components do not take into account the full range of consumed foods, so using scoring ranges may be preferable to simple cut-offs[204].

2.5.1.4 Defining a posteriori dietary patterns

Many studies have used data-driven or exploratory approaches to assess overall diet quality and the two predominant approaches are factor analysis, such as principal component analysis, and cluster analysis[23;195;207]. Factor analysis or principal component analysis is a data-reduction technique which identifies foods that are frequently consumed together and aggregates food items or groups on the basis of the degree of correlation with one another[29;30]. Cluster analysis derives dietary patterns based on differences in dietary intakes between individuals who are separated into mutually exclusive groups[28;30]. In factor analysis, individuals are scored based on their degree of adherence to each derived dietary pattern, where as in cluster analysis individuals are assigned to one cluster only. Typical dietary patterns derived by such methods tend to

identify healthy or prudent and unhealthy or Western style patterns[207], and these types of dietary patterns have also been found in older European populations[208].

Using data-driven approaches to generate dietary patterns has the advantage of not making any prior assumptions but uses the existing data to characterise total diet, meaning that results can be meaningful, interpretable and can show some reproducibility across populations[30]. However, *a posteriori* methods of deriving dietary patterns, including factor analysis and cluster analysis, do have some considerations. Data is limited on the reproducibility and validity of these methods and subjectivity may be introduced when grouping dietary variables, making analytic choices about statistical methods and in selecting final dietary patterns to use[28;30;207]. Cluster analysis has low statistical power, compared to principal component analysis, and is also highly influence by extreme values[195;207]. It has also been suggested that principal component analysis may generate more meaningful and interpretable dietary patterns than cluster analysis[195;207].

In recent years, a new statistical method of identifying dietary patterns has been introduced. Reduced rank regression determines linear functions of predictors (such as food groups) by maximizing the explained variation in a set of intermediate response variables (such as disease-related nutrients or biomarkers). Reduced rank regression combines characteristics of both hypothesis driven approaches, since it used prior information for defining response variables, and exploratory approaches, as it uses dietary data from the study[29;209].

In summary, there are a range of approaches which have been used previously to define dietary patterns, each with their advantages and disadvantages. For the purposes of this thesis, both *a priori* (a range of diet scores) and *a posteriori* methods (principal component analysis) will be used to identify dietary patterns in the BRHS cohort (see section 3.3.2 for details) and their associations with CVD and mortality in older adults will be assessed.

2.5.2. **The importance of diet in relation to CVD risk and all-cause mortality**

Several aspects of the diet and nutrition are well recognised as a major risk factor for CVD morbidity and mortality in middle-aged populations, as introduced in section 2.3.1[6;8;23;202;210]. Since obesity results when there is an imbalance between energy intake and energy expenditure, dietary intake has a major impact on the prevalence of obesity in a population[6] and preventive nutrition has become a major focus of efforts to prevent CVD[210]. Various individual aspects of diet have been associated with an increased risk of CVD, including high saturated fat intake[25], high salt intake[24] and low fruit and vegetable consumption[26;27]. The Seven Countries Study was the first major study to investigate the role of diet in CVD in the early 1960s and showed a strong positive association between dietary saturated fat intake and CHD incidence, with a suggestion that increased blood cholesterol may act as a key intermediary between the two[211;212]. More recently, a meta-analysis of intervention studies has confirmed the beneficial effects of replacing saturated fat acids (SFA) with polyunsaturated fatty acids (PUFA) on CHD risk, with an overall pooled risk reduction of 19%[25]. Also a slightly later Cochrane review, also based on analysis of randomised controlled trials suggested that reducing saturated fat by reducing and/or modifying dietary fat reduces the risk of cardiovascular events by 14%[213].

There is also strong evidence from randomised controlled trials (RCTs) of a positive association between salt intake and risk of CVD and mortality. A meta-analysis, including six trials of both normotensive and hypertensive participants, of interventions for reduced dietary salt showed a 23% reduction in the risk of CVD events[24]. A low intake of fruit and vegetables has also long been implicated in the risk of CVD and mortality[214], with a modelling study estimating that achieving the dietary recommendation in the UK would prevent 33,000 deaths a year, mostly due to meeting the 5-a-day fruit and vegetable recommendation[215]. A recent meta-analysis of prospective studies found a 4% significant reduction in CVD mortality risk for each additional serving of fruit and vegetables per day[216]. The evidence of an association between a higher fruit and vegetable intake and a lower risk of CVD is based substantially on observational studies, but RCTs of a Mediterranean style dietary

pattern, which have included an important fruit and vegetable component, have also supported a potential link[26;217] (see Section 2.5.3.1).

In addition, many other aspects of diet have shown evidence of an association with CVD risk. An inverse association between fish consumption and CHD mortality has been reported[218]. Also, there is evidence for a positive association between red and processed meat intake and the risk of CVD and all-cause mortality[219;220], which ties in to the association with saturated fat[25].

Diet quality is particularly important in the elderly, since this age group are particularly vulnerable to malnutrition due to decreased food affordability and availability, lack of interest or awareness affecting intake, malabsorption or increased nutrient requirements, and unique considerations regarding socioeconomic circumstances and caregiving[221;222]. When these issues are coupled with the increased prevalence of CVD in the elderly, the impact of diet in the elderly becomes very important. However to date, dietary patterns and the risk of CVD and mortality have largely been studied in middle-aged populations, many of which have focused on the Mediterranean diet[31;32], which may have limited relevance in the UK[223]. However, evidence on the influence of dietary patterns on CVD risk and mortality in older subjects remains limited, especially within the UK[33]. Existing literature on the associations of dietary patterns (defined *a priori* and *a posteriori*) and risk of CVD and mortality in older adults will be reviewed in section 2.5.3 and section 2.5.4 respectively.

2.5.3. *A priori* dietary patterns, CVD risk and all-cause mortality in older age

2.5.3.1 Mediterranean Diet Score

A 'Mediterranean diet' reflects the dietary patterns characteristic of several olive growing countries in the Mediterranean Basin in the early 1960s including Greece, southern Italy and Spain[224]. It was first defined by Ancel Keys in the Seven Countries Study who observed lower incidence of CVD in some Mediterranean countries and hypothesised this was due to the dietary habits of these populations[225]. The traditional Mediterranean diet is characterised by an abundant consumption of olive oil as the main

source of dietary lipids, a high consumption of fruit, vegetables, legumes, cereals and nuts, a moderate to low consumption of fish, dairy and wine (consumed with meals), and a low consumption of meat and meat products[224] (Figure 2.2). The Mediterranean Diet Score (MDS) is the most commonly researched predefined dietary pattern and is based on adherence to a combination of food items characteristic of a Mediterranean-style diet. The MDS was first developed by Trichopoulou et al. in 1995[226] and was later revised to include fish intake[227]. The MDS ranges from 0 (minimal adherence) to 9 (maximal adherence). Persons whose consumption of beneficial components (vegetables; legumes; fruits and nuts; cereals; fish; monounsaturated/saturated lipids ratio) is below the sex-specific median are assigned a value 0 or otherwise a value of 1. Persons whose consumption of detrimental components (meat and dairy) is below the sex-specific median are assigned a value of 1 or otherwise a value of 0. For ethanol, men consuming between 10 and 50g and women consuming between 5 and 25g per day score 1.

Since the original MDS was developed, several modified versions have been used[228], but regardless of the slight variations in scores, the association with CVD has shown consistent beneficial results across studies. Numerous prospective cohort studies, based in European and North American adult populations, have shown consistent protective effects of adherence to a Mediterranean diet on the risk of CVD. A systematic review and meta-analysis carried out by Sofi et al. in 2010, which pooled data from 18 cohorts (including more than 2 million subjects and 50,000 deaths or incident cases) showed that a two point increase in MDS was associated with a 10% reduction in CVD incidence and mortality [pooled relative risk (RR): 0.90, 95% confidence interval (CI): 0.87-0.93][31]. This was followed up by Martinez-Gonzalez et al. in 2014, which included seven more recent prospective studies, including separate estimates for both men and women, and showed highly consistent results. A two point increase in MDS was associated with a 13% relative reduction in the incidence of CVD events (pooled RR: 0.87, 95% CI: 0.85-0.90)[217].

The strongest evidence of a causal association between adherence to a Mediterranean diet and the prevention of CVD comes from two RCTs. The Lyon Diet Heart Study, a randomised secondary prevention trial in over 600 French survivors of a first myocardial infarction (MI), compared an intervention of a Mediterranean diet to a control group receiving standard dietary advice[229]. Interim analysis after 27 months showed a 76% reduction in major coronary events in the Mediterranean diet group[229] and this protective effect was maintained for up to 4 years after the first MI[230]. In a large multicenter randomised primary prevention trial in Spain (PREDIMED), over 7,000 individuals at high cardiovascular risk were allocated to one of three diets: a Mediterranean diet supplemented with mixed nuts, a Mediterranean diet supplemented with extra-virgin olive oil and a control group receiving advice to reduce dietary fat[231]. The risk of major cardiovascular events, the primary end point, was reduced by 30% in the Mediterranean diet and olive oil group and by 28% in the Mediterranean diet and nuts group at 4.8 years of follow-up, at which point the trial was stopped on the basis of these results[231]. The risk of stroke, a secondary end point, was also reduced by 33% in the Mediterranean diet and olive oil group and by 46% in the Mediterranean diet and nuts group[231]. A recent review of the evidence of an association between adherence to a Mediterranean diet and the risk of CVD used meta-analysis to combine the results from these two aforementioned trials[229;231], showing a pooled CVD risk reduction of 38% after intervention with a Mediterranean diet (RR: 0.62, 95% CI 0.40-0.85)[217].

There is also evidence that the beneficial effects of a Mediterranean-style diet in reducing the risk of CVD persists in older adult populations. A recent review in elderly cohorts (ages 65 years or older) identified 20 studies assessing the relationship between the Mediterranean diet and cardiovascular disease, found that such a diet had benefits on risk factors for CVD (including lipoprotein levels, endothelium vasodilation, insulin resistance, the prevalence of the metabolic syndrome and antioxidant capacity), the incidence of MI and cardiovascular mortality[32]. However, while Mediterranean dietary patterns are associated with reduced CVD and mortality in many elderly European and US cohorts[32], there are a paucity of studies within an older UK population, where the prevalence of adherence to Mediterranean style dietary patterns has been shown to be low[223]. One study identified in people, aged 65 years and older, from the British Diet

and Nutrition Survey found that the MDS was associated with mortality (highest vs. lowest quartile; HR: 0.78, 95% CI: 0.62-0.98)[232].

The MDS has also been adapted for use in the elderly, with the Elderly Dietary Index (EDI) being developed as a slightly modified version, developed specifically to address adherence to nutritional recommendations for older people[233]. The EDI uses a 4-point scoring system for each food component and takes into consideration the U-shaped relation between certain food items and the risk of health outcomes, compared to the MDS which uses a dichotomous scoring system, based on a cut-off of the median intake of foods. It is therefore possible that the MDS may be too crude to apply to an older UK population in whom adherence to Mediterranean-style dietary components is low and the EDI may therefore be more suited[223]. The EDI has been shown to be associated with CVD risk factors in the older Mediterranean population in which it was developed. However, the EDI has not been applied to older populations in other countries, such as those in the UK.

2.5.3.2 Healthy Diet Indicator

The Healthy Diet Indicator (HDI) is another *a priori*–defined dietary score which was developed by Huijbregts et al. and is based on adherence to World Health Organization dietary guidelines for the intake of nutrients and food components[8;234]. The HDI consists of nine components (SFA; PUFA; protein; total carbohydrates; monosaccharides and disaccharides; dietary fibre; fruit and vegetables; pulses, nuts and seeds; cholesterol), each scoring one if the dietary guideline is met and zero otherwise, resulting in a total score range from 0 to 9. Further details of the components of the HDI and its scoring can be found in Table 2.3. The HDI has been found to be inversely associated with both all-cause and cardiovascular mortality risk in older European men from the Seven Countries Study, aged 50 to 70 years from Finland, Italy and the Netherlands, over 20 years of follow-up[234]. Men in the group with the highest HDI score, compared to the group with the lowest score, had a 13% lower risk of all-cause mortality and an 18% lower risk in CVD mortality, after adjustment for age, smoking and alcohol consumption. An inverse association between the HDI and mortality risk has also been seen in data from Healthy Ageing: a Longitudinal study in Europe (HALE)[235]. Participants, aged 70 to 90 years, with an HDI score above the median had a reduced

mortality risk compared to those below the median, after adjustments for age, gender, behavioural risk factors and chronic disease at baseline (HR: 0.89, 95% CI: 0.81-0.98).

A meta-analysis of 11 prospective cohorts of the Consortium on Health and Ageing: Network of cohorts in Europe and the United States (CHANCES) has also confirmed the inverse association seen between the HDI score and all-cause mortality risk. Pooled data from almost 400,000 participants, aged 60 years and over, found that for every 10-point increase in HDI score (based on a modified score ranging from 0 [least healthy diet] to 70 [healthiest diet]) there was a 10% reduced risk of all-cause mortality (HR: 0.90, 95% CI: 0.87-0.93)[236].

In contrast, two studies not included in this meta-analysis did not show significant associations between the HDI and risk of CVD and all-cause mortality. In a British population specifically, 972 participants from the British Diet and Nutrition Survey aged 65 years and older, no significant association was seen between the healthy diet score (a modified version of the HDI for a British population) and all-cause mortality during 14 years of follow-up[232]. Findings from an elderly cohort of 924 Swedish men, with a mean age of 71 years, also showed no association between HDI and all-cause mortality or CVD mortality over 10 years of follow-up[237]. However, these two aforementioned studies were relatively small in size so may not have had the power to exclude the effect size observed in the meta-analysis above.

2.5.3.3 Healthy Eating Index

The Healthy Eating Index (HEI) was originally proposed by the United States Department of Agriculture to measure adherence to Dietary Guidelines for Americans and the Food Guide Pyramid[238]. The HEI is a 10-component system made up of five food groups (grains, fruit, vegetable, milk and meat), four nutrients [total fat, SFA, cholesterol and sodium] and a measure of diet variety, with a total possible 100-point score. McCullough et al. developed a modified version of this score, the Alternative Healthy Eating Index (AHEI). The AHEI was designed to assess intake of food groups

and macronutrient sources associated with reduced chronic disease risk, and compared to the HEI it distinguishes quality within food groups and acknowledges the health benefits of unsaturated oils[239]. The AHEI consists of 9 components with a possible score from 2.5 to 87.5. This differs from the Mediterranean Diet Score, which uses dichotomous scoring components. Further details of the components of the AHEI and its scoring can be found in Table 2.4.

A study in two large American cohorts prospectively compared the AHEI and the HEI, and found that the AHEI was better at predicting CVD risk than the original HEI; 38, 615 men from the Health Professionals' Follow-up Study (aged 40 to 70 years) and 67,271 women from the Nurses' Health Study (aged 30 to 55 years), with AHEI scores in the top compared to the bottom quintile had a 39% and a 28% reduction in CVD risk respectively[240]. Similarly, in the Whitehall II cohort study of British adults aged 39 to 63 years, participants in the top compared to the bottom tertile of AHEI score showed a 24% lower all-cause mortality risk and a 42% lower CVD mortality risk after controlling for potential confounders[241]. The NIH-AARP Diet and Health Study has also found associations between the HEI and the AHEI and outcomes in older people aged 51 to 70 years; participants in the highest quintiles of scores were associated with a 15 to 28% lower risk of all-cause and CVD mortality, with slightly stronger associations for the AHEI[242].

2.5.3.4 Dietary Approaches to Stop Hypertension diet score

The Dietary Approaches to Stop Hypertension (DASH) diet is well established in the prevention and control of hypertension[243]. This dietary pattern is rich in fruits, vegetables, and low-fat dairy products, includes whole grains, legumes, fish, poultry and nuts, and is limited in sugar-sweetened foods, red meat and added fats. RCTS in adult populations have shown the DASH dietary pattern to lower both systolic blood pressure (SBP) and diastolic blood pressure (DBP), by 5.5 and 3.0 mmHg respectively[243]. As well as decreasing SBP and DBP, RCTs have also shown that DASH improved other CVD risk factors. A meta-analysis of RCTs found that an intervention

with the DASH diet resulted in significant reductions in total cholesterol (-0·20 mmol/l, 95 % CI: -0·31, -0·10) and LDL (-0·10 mmol/l, 95 % CI -0·20, -0·01; P= 0·03)[244].

In addition to examining cardiovascular risk factors, many studies have also assessed the associations between adherence to the DASH dietary pattern and the incidence of CVD. A recent systematic review identified six such prospective cohort studies in middle-aged populations and pooled analysis showed that a DASH-style diet was significantly associated with a lower risk of CVD, coronary heart disease (CHD), stroke and heart failure by 20%, 21%, 19% and 29% respectively[245].

Similar results have been shown in a limited number of older populations. The NIH-AARP Diet and Health Study has found associations between DASH diet patterns and risk of CVD and all-cause mortality in 492,823 older people aged 51 to 70 years; men in the highest quintile of scores had a 17% lower risk of all-cause mortality and a 14% lower risk of CVD mortality, with slightly larger risk reductions of 22% for both all-cause and CVD mortality in women[242]. However, a prospective study in Chinese older adults aged 65 years and over found no significant association between DASH dietary score and risk of stroke over 6 years of follow-up[246].

2.5.3.5 Other a priori defined dietary patterns

In addition to some of the most commonly used scores and indexes mentioned above, there are other less widely used dietary scores which have been developed, and in some cases tailored for specific populations or countries or designed to evaluate prevention efforts for specific diseases[205]. The Diet Quality Index (DQI) is an eight component score based on food group and nutrient-based recommendations from the American Food and Nutrition Board[247]. DQI components consist of intake of the following: total fat; SFAs; cholesterol; fruit and vegetables; breads, cereal and legumes; protein; sodium; calcium. Prospective analyses, based on the American Cancer Society Cancer Prevention Study II Nutrition Cohort, a cohort of 115,833 US adults aged 50 to 79 years, showed that the a higher DQI, which was indicative of a poorer quality diet, was

positively associated with all-cause and CVD mortality rates in both women and men[248]. However, in fully adjusted models, only CVD mortality was significantly associated with the DQI and only in women (medium/low-quality diet vs. highest-quality diet; RR: 1.86, 95% CI: 1.19-2.89)[248].

Kant et al developed the Recommended Food Score (RFS) based on reported consumption of foods recommended by current dietary guidelines, including certain fruits, vegetables, cereal products, fish and low-fat dairy products[249]. Adherence to the RFS has shown a significant inverse association with both CVD mortality and all-cause mortality; a prospective study in 42,254 women, mean age 61 years, found a 31% reduced risk of all-cause mortality and a 33% reduced risk of CHD mortality in women of the highest compared to the lowest RFS quartile[249]. Similar results were found in a male Swedish cohort, aged 45 to 79 years; there was a 19% reduced risk of all-cause mortality and a 29% reduced risk of CVD mortality in men of a high RFS compared to a low RFS[249;250]. In an older British population specifically, participants aged 65 years and older from the British Diet and Nutrition Survey, a high RFS score was significantly associated with a reduced risk of all-cause mortality after adjustment for behavioural risk factors (highest vs. lowest quartile; HR: 0.67, 95% CI: 0.52-0.86)[232].

It has also been suggested that recall of usual dietary behaviours may be less prone to recall errors than specific types or amounts of food consumed[251]. An alternative approach to assessing healthy dietary patterns is the dietary behaviour score (DBS)[251]. The DBS is based on the usual consumption related to recommended dietary behaviour, including consumption of fruit, vegetables, whole grains, low-fat dairy and low-fat meats. In the American Association of Retired Persons Diet and Health Study, participants aged 50 to 71 years in the highest quintile of DBS, compared to the lowest had ~23–30% lower risk of CHD mortality[251].

In summary, adherence to healthy dietary patterns, identified by diet scores and indexes, has tended to show an inverse association with CVD and mortality risk in adult populations, but the consistency and magnitude of protective effects has varied across

studies. Consistent evidence from prospective studies has provided evidence for an inverse association between adherence to a Mediterranean diet and reduced CVD risk in the elderly, but the relevance of a Mediterranean diet to an older UK population is questionable and needs further exploration. There are a limited number of studies in elderly populations on other dietary patterns in relation to CVD and mortality risk, and specifically a paucity of studies on diet quality in older British populations.

2.5.4. *A posteriori* dietary patterns, CVD risk and all-cause mortality in older age

Dietary patterns can also be assessed using data-driven or exploratory approaches and the two predominant approaches are factor analysis, such as principal component analysis, and cluster analysis[23;195;207], as was described above in Section 2.5.1.4.

2.5.4.1 Factor analysis, CVD risk and all-cause mortality in older age

In the Nurses' Health Study, of 69,017 women aged 38 to 63 years, factor analysis identified two major dietary patterns – prudent (characterised by higher intakes of fruits, vegetables, legumes, fish, poultry, and whole grains) and Western (characterised by higher intakes of red and processed meats, sweets and desserts, French fries, and refined grains)[252]. The prudent diet score was associated with a reduced risk of CHD (quintile 5 vs. quintile 1 RR: 0.76, 95% CI: 0.60-0.98) and the Western diet was associated with an increased risk of CHD (quintile 5 vs. quintile 1 RR: 1.46, 95% CI: 1.07-1.99). Similarly, the Dutch European Investigation into Cancer and Nutrition (EPIC) study used principal component analysis to identify a prudent pattern (high intakes of fish, high-fibre products, raw vegetables and wine) and a Western pattern (high consumption of French fries, fast food, low-fibre products, other alcoholic drinks and soft drinks with sugar) and found that the prudent pattern was associated with a reduced risk of CHD (HR for extreme quartiles: 0.87, 95% CI: 0.75-1.00) and stroke (HR: 0.68, 95% CI: 0.53-0.88), but found no association with the Western dietary pattern[253].

Observational analysis within the PREDIMED RCT identified two major baseline dietary patterns using factor analysis based on 34 predefined food groups - a Western dietary pattern (rich in red and processed meats, alcohol, refined grains and whole dairy products) and a Mediterranean-type dietary pattern (MDP)[254]. Higher adherence to the

MDP was associated with a lower CVD risk (adjusted HR for fourth vs. first quartile: 0.52, 95% CI: 0.36- 0.74) but the Western pattern was not significantly associated with CVD risk.

Similar results have been shown in older populations, although the number of studies in this age group is limited. In the Dutch EPIC cohort, of women aged 60 to 69 years, principal component analysis identified three interpretable dietary patterns: 'Mediterranean-like', 'traditional Dutch dinner' and 'healthy traditional Dutch'. Only the healthy traditional Dutch dietary pattern was associated with all-cause mortality, with a 30% lower risk in those in the highest compared to the lowest tertile[255]. The EPIC-Elderly study also examined survival in relation to dietary patterns, derived by principal component analysis, in over 74,000 participants aged 60 years and older across ten European countries[256]. A 'plant-based' dietary pattern was identified, which showed an inverse association with all-cause mortality, with a one standard deviation increment corresponding to a 14% reduction in risk. However, in country-specific analysis, the association was absent in the UK. In another older British population, participants ages 65 years and above from the National Diet and Nutrition Survey identified four interpretable diet patterns using principal component analysis: 'Mediterranean–style', 'health aware', 'traditional' and 'sweet and fat'. Only the Mediterranean–style dietary pattern was associated with a reduced risk of all-cause mortality, with an 18% reduction in risk in those in the highest compared to the lowest tertile[257].

2.5.4.2 Cluster analysis, CVD risk and all-cause mortality in older age

In the Whitehall II study, a British prospective cohort of 7731 men and women with a mean age of 50 years, cluster analysis identified four dietary patterns at baseline: unhealthy (white bread, processed meat, fries, and full-cream milk), sweet (white bread, biscuits, cakes, processed meat, and high-fat dairy products), Mediterranean-like (fruit, vegetables, rice, pasta, and wine), and healthy (fruit, vegetables, whole-meal bread, low-fat dairy and little alcohol)[258]. Compared with the unhealthy cluster, the healthy cluster was associated with a reduced risk of CHD mortality (HR: 0.71, 95% CI: 0.51-0.98)

after adjustment for confounders. However the other dietary patterns were not associated with CHD risk and no dietary patterns were associated with all-cause mortality. Cluster analysis was also used in the EPIC-NL study, which identified a prudent dietary pattern and a Western pattern, similar to the patterns identified in this cohort using principal component analysis mentioned above. Individuals in the prudent cluster showed a reduced risk of CHD (HR: 0.91, 95% CI: 0.82-1.00) and stroke (HR: 0.79, 95% CI: 0.67-0.94) compared to those in the Western cluster[253].

In an older population specifically, cluster analysis of data from the Cardiovascular Health Study, including 4610 participants aged 65 and over, found that the 'healthy' diet cluster was inversely associated with mortality, the 'unhealthy' cluster was positively associated with mortality and the 'low 4' cluster (distinguished by higher alcohol consumption) was inversely associated with risk of cardiovascular events[259]. Similarly, in the Health ABC study, a prospective cohort of 3,075 participants, aged 70 to 79, six clusters of dietary patterns were identified[260]. The 'high-fat dairy products' and the 'sweet and desserts' clusters had a 1.4-fold increased mortality risk compared to the 'healthy foods' cluster, after adjusting for confounders. Another prospective study in community-dwelling older adults in Pennsylvania, mean age of 76 years, identified three dietary patterns via cluster analysis: 'sweets and dairy', health-conscious' and 'Western'[261]. However, there were no significant associations between any dietary patterns and CVD or mortality.

In summary, the use of factor analysis or cluster analysis typically identifies two major types of dietary patterns – prudent (healthy) and Western (unhealthy). There have been more studies assessing the association between *a posteriori* dietary patterns and all-cause mortality risk, compared to CVD risk. Healthy/prudent dietary patterns have tended to show inverse associations with CVD and mortality risk, where as unhealthy/Western have either shown positive associations or no significant association at all. In the elderly specifically, there are a limited number of studies that have used *a posteriori* methods to define dietary patterns in relation to CVD, particularly, and mortality risk, and specifically a paucity of studies in older British populations.

2.6. Summary of literature review findings

CVD is the biggest cause of death and disability worldwide. The importance of CVD was highlighted in section 2.2, and this is especially the case in the elderly who are at increased risks of CVD and the existence of an ageing population further increase the burden from CVD. Section 2.3 outlines both well-established major risk factors and other emerging risk factors for CVD. Obesity, and hence diet, are two crucial risk factors to consider in the aetiology of CVD. Obesity is a major public health problem as prevalence continues to increase over time, and prevalence also increases with age. Therefore obesity and diet may be particularly important risk factors for CVD in the elderly (as described in section 2.4). However, there are some gaps in the current literature regarding their effects in the elderly.

The impact of being overweight and of obesity in the elderly on CVD and mortality are controversial, with many studies showing that being overweight or obese, as defined by BMI, does not appear to be harmful and may even be associated with lower, rather than higher, mortality (as reviewed in section 2.4.4). Since body composition changes with age, visceral fat increases and muscle mass decreases, and the two have opposing effects on mortality risk, it may also be important to measure muscle mass in relation to CVD and mortality risk in the elderly. Sarcopenia has been defined as the age-associated loss of skeletal muscle mass and has been associated with metabolic impairment, CVD risk factors, physical disability and mortality and is also often associated with obesity. Recently, a new concept of sarcopenic obesity has emerged in older adults, which refers to the sarcopenia coupled with high levels of adipose tissue. Thus sarcopenia with obesity may synergistically increase their effect on metabolic disorders, CVD and mortality, but the literature in this area is inconclusive. As reviewed in section 2.4.7, there is evidence which suggests that sarcopenia is associated with established and emerging cardiovascular risk factors in older age. However, whether sarcopenic individuals who are also obese have the most adverse cardiovascular risk profile is unclear. The literature review on the associations between sarcopenia and sarcopenic obesity with the risk of CVD (section 2.4.8) and mortality (section 2.4.9) revealed that there is a paucity of prospective studies in the elderly. The effects of

sarcopenia and sarcopenic obesity on CVD and mortality in older age therefore remain unclear.

Dietary intake is an important established risk factor for CVD and mortality, and has a significant impact on the prevalence of obesity in the population. In recent years the focus of dietary research has shifted from single nutrients and food items to overall diet quality, assessed by hypothesis driven, *a priori*, approaches which generate diet scores and indexes, or data-driven, *a posteriori*, approaches such as factor analysis and cluster analysis (as outlined in section 2.5.1). Epidemiological evidence has shown that adherence to healthy dietary patterns, identified from either *a priori* or *a posteriori* methods, has tended to show an inverse association with risk of CVD and mortality, but the magnitude of protective effects has varied across studies. Consistent evidence from prospective studies has provided evidence for an inverse association between adherence to a Mediterranean diet and reduced CVD risk in the elderly, but whether a Mediterranean diet is applicable to an older UK population is questionable. There are a limited number of studies in elderly populations on other *a priori* defined dietary patterns in relation to CVD and mortality risk, and specifically a paucity of studies on diet quality in older British populations (as reviewed in section 2.5.3). Defining dietary patterns *a posteriori*, either by using factor analysis or cluster analysis, has typically identified two major types of dietary patterns – healthy/prudent and unhealthy/Western. Healthy/prudent dietary patterns have tended to show inverse associations with CVD and mortality risk, where as unhealthy/Western have either shown positive associations or no significant association at all. In the elderly specifically, there are a limited number of studies that have used *a posteriori* methods to define dietary patterns in relation to CVD, particularly, and mortality risk, and specifically a paucity of studies in older British populations (as reviewed in section 2.5.4). It is therefore unclear what the optimal dietary patterns are for prevention of CVD and mortality in the elderly, especially in British populations.

To date studies have not fully addressed the effect of sarcopenic obesity on the risk of CVD and mortality in older adults, or the role of dietary patterns in predicting CVD or

mortality risk in older UK population. This thesis will address current gaps in the literature on the importance of body composition and dietary patterns in the aetiology of CVD and mortality in older adults. Specifically, the review raises several questions which this thesis will address, including: 1) How are sarcopenia, and the combination of sarcopenia and obesity, associated with cardiovascular risk factors in older age? 2) Do sarcopenia, and combined measures of sarcopenia and obesity, increase the risks of CVD and mortality in older age? 3) To what extent are *a priori* diet quality scores associated with cardiovascular risk factors and the risk of CVD and mortality in older age? and 4) To what extent are *a posteriori* dietary patterns associated with cardiovascular risk factors, and the risk of CVD and mortality in older age?

Table 2.1 Summary of studies investigating the association between sarcopenic obesity and cardiovascular risk factors in older people

Author, year	Study	Study design	Population	Sarcopenic obesity measurement	Outcomes	Main findings
Baumgartner, 2004[170]	New Mexico Aging Process Study	Cross-sectional analysis at baseline of a prospective cohort (8y follow-up)	*n* = 451 Men and women Aged ≥ 60y	DXA (ASM; % body fat)	Instrumental activities of daily living disability	Baseline prevalence of MetS and hypertension was highest in non-sarcopenic obese, followed by SO group.
Cesari, 2005[174]	Trial of Angiotensin Converting Enzyme Inhibition and Novel Cardiovascular Risk Factors study	Cross-sectional	*n* = 286 Participants with a high cardiovascular risk. Men and women. Aged > 55y	DXA (appendicular lean mass; % FM)	CRP; IL-6; PAI-1	No significant interactions were found between sarcopenia and obesity with CRP, IL-6 or PAI-1.
Schrager, 2007[173]	InCHIANTI Study	Cross-sectional	*n* = 871 Men and women Aged ≥ 65y	Grip strength; WC; BMI ≥ 30 kg/m^2	Inflammatory markers	SO associated with elevated levels of inflammatory markers including CRP and IL-6.
Kim, 2009[160]	Korean Sarcopenic Obesity Study	Cross-sectional	*n* = 526 Men and women Aged ≥ 20y	DXA (ASM; SMI; % body fat)	MetS	Women with SO (identified using SMI) has a 3-fold increased risk of MetS and non-sarcopenic obese had a 2-fold increased risk of MetS compared with normal subjects. Similar associations found in men although not significant.
Messier 2009[171]		Cross-sectional	*n* = 136 Healthy overweight or obese postmenopausal women. Aged 46-70y	DXA (ASM); CT	BP; HDL; LDL; TC; TG; insulin level; glucose level	Sarcopenic overweight/obese women did not show an unfavourable metabolic profile compared to non-sarcopenic overweight/obese women.

Table 2.1 *Continued*. Summary of studies investigating the association between sarcopenic obesity and cardiovascular risk factors in older people

Author, year	Study	Study design	Population	Sarcopenic obesity measurement	Outcomes	Main findings
Srikanthan, 2010[169]	NHANES III	Cross-sectional	*n* = 14528 Men and women Aged > 20y	BIA (SMI); BMI ≥ 30 kg/m^2	HOMA-IR; glycosylated hemoglobin level.	SO group had the highest risk of insulin resistance and dysglycemia.
Lim, 2010[161]	Korean Longitudinal Study on Health and Aging	Cross-sectional	*n* = 565 Men and women Aged ≥ 65y	DXA (ASM); CT (VFA)	MetS	SO group at highest risk of insulin resistance and MetS, with an 8-fold increase in risk of MetS compared to non-sarcopenic, non-obese.
Chung, 2012[162]	KNHANES	Cross-sectional	*n* = 2943 Men and women Aged ≥ 60y	DXA (ASM); BMI ≥ 25 kg/m^2	BP; glucose tolerance indices; lipid profiles; inflammatory markers	SO group was associated with a higher risk of insulin resistance, MetS and CV risk factors than any other group.
Hwang, 2012[163]	KNHANES	Cross-sectional	*n* = 2221 Men and women Aged ≥ 60y	DXA (ASM); WC (≥ 90cm for men; ≥ 85cm for women)	Insulin level; lipid levels; glucose levels	SO was associated with higher fasting glucose level and triglyceride level in women, and higher serum insulin level in men and women.

Table 2.1 *Continued*. Summary of studies investigating the association between sarcopenic obesity and cardiovascular risk factors in older people

Author, year	Study	Study design	Population	Sarcopenic obesity measurement	Outcomes	Main findings
Kim, 2013[167]	Korean Sarcopenic Obesity Study	Cross-sectional	*n* = 493 Men and women Aged ≥ 20y	DXA (ASM); CT (VFA)	CRP; HOMA-IR	In women, the SO group had higher levels of insulin resistance and CRP compared to the non-SO group. In men, the SO group had higher levels of insulin resistance compared to the non-SO group.
Lu, 2013[168]		Cross-sectional	*n* = 600 Community dwelling Taiwanese adults Men and women Aged 63.6y (SD=10.1)	BIA (skeletal muscle mass); BMI ≥ 25 kg/m^2	MetS	SO group at highest risk of MetS, with a 12-fold increase in risk compared to non-sarcopenic, non-obese.
Park, 2013[164]	KNHANES	Cross-sectional	*n* = 6832 Men and women Aged ≥ 19y	DXA (ASM); WC (≥ 90cm for men; ≥ 85cm for women)	BP	The odds of hypertension were higher in the SO group compared to the obese, sarcopenic and normal body composition groups.
Baek, 2014[154]	KNHANES	Cross-sectional	*n* = 3483 Men and women Aged ≥ 65y	DXA (ASM); BMI ≥ 25 kg/m^2	Lipid levels	SO was associated with an increased risk of dyslipidemia compared with sarcopenia or obesity alone.
Han, 2014[155]	KNHANES	Cross-sectional	*n* = 4846 Men and women Aged ≥ 60y	DXA (ASM); BMI ≥ 25 kg/m^2	BP	The odds of hypertension were highest in the sarcopenic obese group compared to all other groups.

Table 2.1 *Continued*. Summary of studies investigating the association between sarcopenic obesity and cardiovascular risk factors in older people

Author, year	Study	Study design	Population	Sarcopenic obesity measurement	Outcomes	Main findings
Kim, 2014[166]		Cross-sectional	*n* = 298 Korean patients visiting hospital for a regular checkup Men and women Aged 20-70y	DXA (SMI); CT (VFA)	Cardiorespiratory fitness	SO strongly associated with cardiorespiratory fitness. Lowest cardiorespiratory fitness seen in SO group.
Park, 2014[165]	KNHANES	Cross-sectional	*n* = 6832 Men and women Aged ≥ 19y	DXA (ASM); WC (≥ 90cm for men; 80cm for women)	MetS	SO was associated with an increased risk of MetS in women compared to non-sarcopenic obese.
Dos Santos, 2014[172]		Cross-sectional	*n* = 149 Postmenopausal Brazilian women Aged 67.2y (SD=6.1)	DXA (appendicular FFM; FM)	BP; glucose level; TC; HDL; LDL; TG; CRP	No significant difference in BP, glucose level, TC, HDL, LDL, T and CRP between SO and non-SO groups.

ASM, appendicular skeletal muscle mass; BIA, bioelectrical impedance analysis; BMI, body mass index; BP, blood pressure; CRP, C-reactive protein; CT, computerised tomography; DXA, dual energy x-ray absorptiometry; FM, fat mass; FFM, fat-free mass; HDL, high density lipoprotein; HOMA-IR, homeostatic model assessment insulin resistance; IL-6, interleukin 6; KNHANES, Korea National Health and Nutrition Examination Survey; LDL, low density lipoprotein; MetS, metabolic syndrome; NHANES, National Health and Nutrition Examination Survey PAI-1, plasminogen activator inhibitor; SMI, skeletal muscle mass index; SO, sarcopenic obesity; TC, total cholesterol; TG, triglyceride; VFA, visceral fat area; WC, waist circumference.

Adapted from Atkins et al, 2015[40].

Table 2.2 Summary of studies investigating the association between sarcopenic obesity and cardiovascular disease and mortality in older people

Author, year	Study	Study design	Population	Sarcopenic obesity measurement	Outcomes	Main findings
Rantanen, 2000[194]		Prospective cohort (30y follow-up)	*n* = 6040 Healthy adults from Hawaii Men Aged 45-68y	Grip strength; BMI	Mortality	Overweight men (BMI ≥ 25 kg/m^2) in the lowest grip strength tertile had 1.39 times the risk of mortality compared to normal weight men in the highest tertile.
Wannamethee, 2007[191]	British Regional Heart Study	Prospective cohort (6y follow-up)	*n* = 4107 Men Aged 60-79y	MAMC; BIA (FM; FFM); WC; WHR	Mortality	A composite measure of WC and MAMC most effectively predicted mortality. SO, based on high WC (>102cm) and low MAMC (lowest quartile), showed a 55% increase in mortality risk compared to non-sarcopenic, non-obese.
Prado, 2008[190]		Prospective cohort (follow-up unknown)	*n* = 250 Obese Canadian patients with respiratory or gastrointestinal cancers. Men and women Aged 35-88y	CT (muscle cross-sectional area); BMI ≥ 30 kg/m^2	Mortality	Patients with SO had a higher rate of mortality compared to those with obesity alone.
Cesari, 2009[193]	InCHIANTI Study	Prospective cohort (6y follow-up)	*n* = 934 Men and women Aged ≥ 65y	CT (calf skeletal muscle; calf FM); BMI	Mortality	No significant difference reported in mortality risk across six SO groups.

Table 2.2 *Continued*. Summary of studies investigating the association between sarcopenic obesity and cardiovascular disease and mortality in older people

Author, year	Study	Study design	Population	Sarcopenic obesity measurement	Outcomes	Main findings
Stephen, 2009[177]	Cardiovascular Health Study	Prospective cohort (8y follow-up)	*n* = 3366 Men and women Aged ≥ 65y	BIA (skeletal muscle mass); grip strength; WC	CVD; CHD; stroke	SO, based on muscle strength but not muscle mass, was modestly associated with a 23% increased risk of CVD.
Batsis, 2014[192]	NHANES III	Prospective cohort (14y follow-up)	*n* = 4652 Men and women Aged ≥ 60y	BIA (Skeletal muscle mass; % body fat)	Mortality	Women with SO had a higher mortality risk than those without sarcopenia or obesity. For men, the risk of mortality associated with SO was not significant.
Baumgartner, 2004[170]	New Mexico Aging Process Study	Cross-sectional analysis at baseline of a prospective cohort (8y follow-up)	*n* = 451 Men and women Aged ≥ 60y	DXA (ASM; % body fat)	Instrumental activities of daily living disability	At baseline, subjects with SO did not show a higher prevalence of CVD.
Chin, 2013[175]	KNHANES	Cross-sectional	*n* = 1578 Men and women Aged ≥ 65y	DXA (ASM); BMI ≥ 25 kg/m^2	CVD	SO group showed higher prevalence of CVD (12.3%) compared to non-sarcopenic obese (10.0%), but difference was non-significant.

ASM, appendicular skeletal muscle mass; BIA, bioelectrical impedance analysis; BMI, body mass index; CHD, coronary heart disease; CT, computerised tomography; CVD, cardiovascular disease; DXA, dual energy x-ray absorptiometry; FM, fat mass; FFM, fat-free mass; KNHANES, Korea National Health and Nutrition Examination Survey; MAMC, mid-arm muscle circumference; NHANES, National Health and Nutrition Examination Survey; SO, sarcopenic obesity; WC, waist circumference; WHR, waist-to-hip ratio.

Adapted from Atkins et al, 2015[40] .

Table 2.3 Healthy Diet Indicator components and scoring criteria

Component	Score = 0	Score = 1
Saturated fatty acids (% energy)	>10	0-10
Polyunsaturated fatty acids (% energy)	<3 and >7	3-7
Protein (% energy)	<10 and >15	10-15
Total carbohydrates (% energy)	<50 and >70	50-70
Monosaccharides and disaccharides (% energy)	>10	0-10
Dietary fibre (g/day)	<27 and >40	27-40
Cholesterol (mg/d)	>300	0-300
Fruits and vegetables (g/day)	<400	>400
Pulses, nuts, seeds (g/day)	<30	>30
Total score	0	9

Healthy Diet Indictor components and scoring as used by Huijbregts et al[234].

Table 2.4 Alternative Healthy Eating Index components and scoring criteria

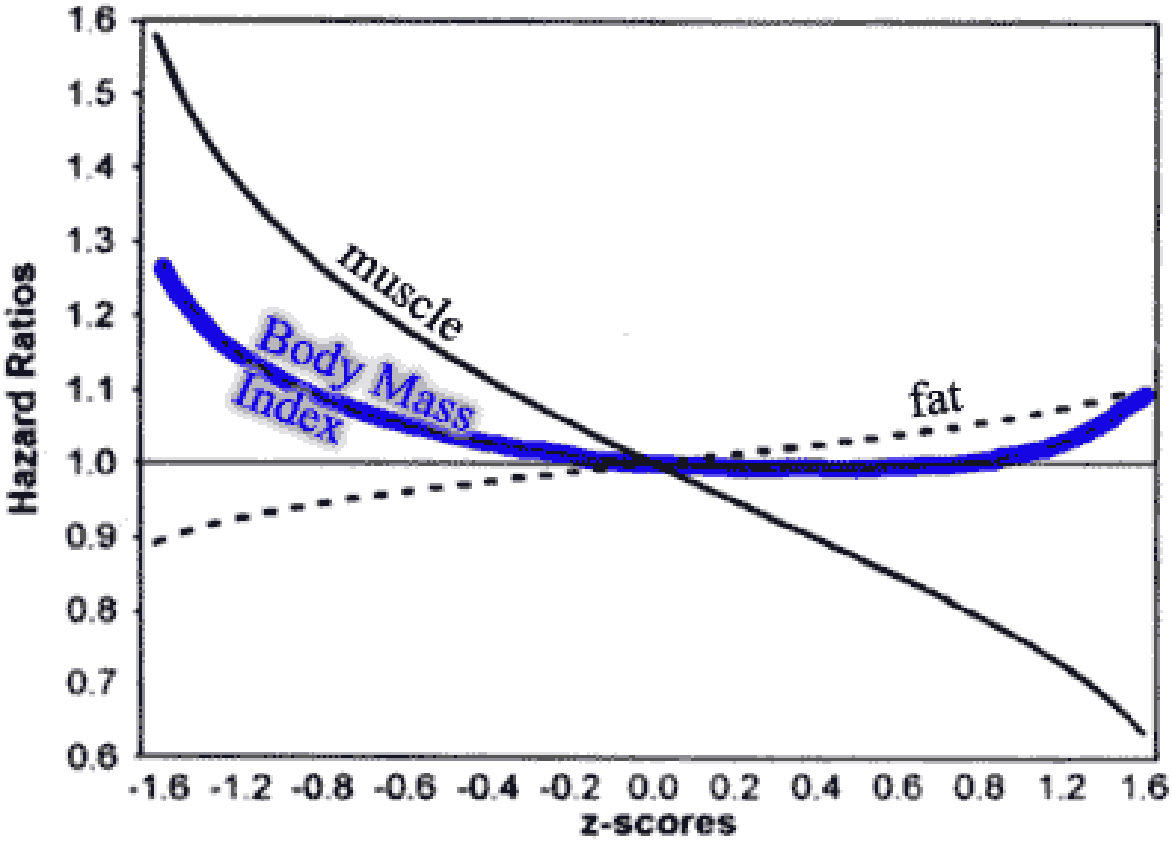
Component	**Score = 0***	**Score = 10***
Vegetables (servings/day)	0	5
Fruit (servings/day)	0	4
Nuts and soya protein (servings/day)	0	1
Ratio of white to red meat	0	4
Cereal fibre (g/d)	0	15
Trans fat (% of energy)	≥ 4	≤ 0.5
Ratio of PUFA to SFA	≤ 0.1	≥ 1
Duration of multivitamin use†	< 5 years	≥ 5 years
Alcohol (servings/day)	Men: 0 or > 3.5 Women: 0 or > 2.5	Men: 1.5-2.5 Women: 0.5-1.5
Total score	2.5	87.5

Alternative Healthy Eating Index components and scoring as used by McCullough et al[239].

*Minimum score is 0. Maximum score is 10. Intermediate intakes are scored proportionately between 0 and 10.

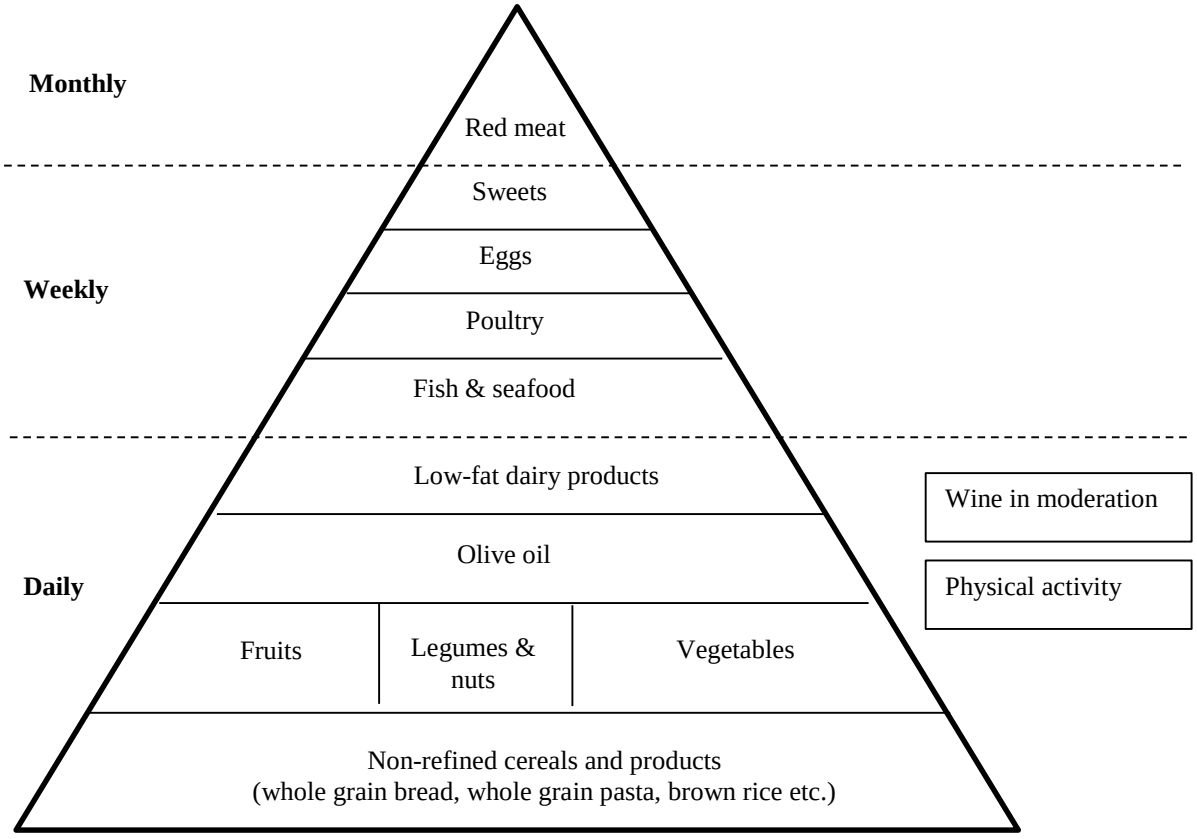
†For multivitamins, the minimum score is 2.5 and the maximum score is 7.5.

Figure 2.1 Hazard ratios for the associations between measures of body composition and all-cause mortality



Source: Adapted from Allison et al[15]. Data from NHANES I and NHANES II. Subscapular and triceps skinfolds thickness were used as fat mass indicators. Upper arm circumference was used as a fat-free mass indicator.

Figure 2.2 Mediterranean diet pyramid



Source: Adapted from the Supreme Scientific Health Council, Ministry of Health and Welfare Greece[262].

CHAPTER 3 Methodology

3.1. Introduction

This thesis consists of epidemiological analysis of data from the British Regional Heart Study (BRHS), an established prospective cohort study of cardiovascular disease. The BRHS was initiated in 1978-80 in men aged 40-59 years drawn from one general practice in each of 24 towns across Britain[34]. Since recruitment, this cohort has been followed up for morbidity through general practice records, and for mortality through the National Health Service Central Register. A physical examination involved a range of physiological measurements, including body composition, and the collection of a blood sample was carried out at the start of the study and at follow-up 20 years later[35]. Participants have also completed questionnaires at regular intervals during the follow-up, which have provided self-reported information on health and disease, lifestyle, dietary intake, and personal and socioeconomic circumstances.

This chapter consists of an overview of the BRHS, including the study design and methodology (section 3.2), a description of the data used in this thesis, including measures of body composition, diet, other relevant cardiovascular risk factors and outcomes (section 3.3), strengths of the data source for the intended analysis (section 3.4) and a brief overview of statistical methods (section 3.5). Specific details of statistical analyses for each of the results chapters are described in more detail in each of the relevant chapters (Chapters 4 to 8).

3.2. The British Regional Heart Study

3.2.1. Description of data source

The British Regional Heart Study (BRHS) is a large, prospective, population-based cohort study of cardiovascular disease (CVD), in a socioeconomically and geographically representative sample of British men, drawn from a general practice in 24 towns in Great Britain[34]. This cohort of 7735 participants was examined at baseline in 1978-80, aged 40-59 years. The cohort has been continuously followed up for mortality and morbidity from baseline until the present. The main aim of the BRHS was to explain the substantial regional variations in mortality from cardiovascular disease in Great Britain, by assessing the role of environmental, socioeconomic, and personal risk

factors[34;263]. Over time, as the cohort has aged, there has been an increasing focus on the aetiology and prevention of cardiovascular disease in older ages.

3.2.2. **Selection procedures**

Towns represented all major geographic regions in Great Britain (England, Scotland and Wales) and seven criteria were established for selecting towns[34;263]:

1. All standard regions should be represented.
2. Towns should be discrete entities with populations of 50,000-100,000 at the 1971 Census. In England one larger town was included (Ipswich). In Scotland, some towns below 50,000 were considered to obtain a reasonable number of suitable towns.
3. The choice of towns within regions should reflect the variations in mortality from CVD and water hardness.
4. Towns were to be representative of the region in socioeconomic terms.
5. Towns with noticeable population movement or with unusual population structure were avoided.
6. The study included some towns that were apparent "outliers" when CVD mortality and water hardness were plotted against each other, for example Hartlepool, Exeter, and Harrogate.
7. When similar towns met the above criteria, random selection was made between the towns.

Figure 3.1 shows 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 selected from one general practice in each town to achieve a good initial response and subsequent feedback[34]. Practice selection was selected based on its size (practice population >7,500), its representativeness of socioeconomic composition and characteristics of the town population and the willingness of the Practice to participate. From the age and sex register of each general practice about 400 men aged 40-59 years were selected randomly, stratified into equal five-year age groups (40-44,

45-49, 50-54 and 55-59 years). Men with severe mental or physical disability were excluded (6-10% per practice) and the remaining participants were invited to take part. Invitations were sent to almost 10,000 men, signed by their GPs, encouraging them to attend the cardiovascular health check at a local venue, usually the Practice premises. The response rate for those men invited was 78%, with 18 of the 24 towns having a response rate of 75% or more (Table 3.1). This resulted in a total of 7735 men being recruited into the study, which equates to approximately 300 men from each town[34;264].

3.2.3. **Baseline examination**

At the start of the study in 1978-80, 7735 men aged 40-59 years attended a physical examination carried out in each of the towns. A series of measurements were made by three trained nurses, including anthropometric and physiological measurements, including height, weight, blood pressure, electrocardiogram, and lung function. In addition, a blood sample was collected and the men completed a nurse-administered questionnaire on health and lifestyle factors. All baseline examinations were completed by 1980. All participants provided written informed consent, obtained in accordance with the Declaration of Helsinki. Ethical approval was obtained from all relevant local research ethics committees.

3.2.4. **Follow-up of participants from baseline**

Since the baseline examination in 1978-80, the cohort has been followed up for morbidity outcomes, mortality and by regular postal questionnaires until the present[35;264], as shown in Figure 3.2. A re-examination was also carried out after 20 years of follow-up (1998-2000), and after 32 years of follow-up (2010-2012).

3.2.4.1 Mortality

Information on death was collected through the established "tagging" procedures provided by the National Health Service Central Register in Southport for England and Wales, and in Edinburgh for Scotland[264]. The Central Register sent death certificates containing identification details, date and place of death and cause of death coded using the International Classification of Diseases ninth revision (ICD-9) and subsequently the tenth edition (ICD-10). Events were also verified by general practices that provided information on deaths as part of a periodic review (see section 3.2.4.2 below).

3.2.4.2 Morbidity

Evidence regarding non-fatal events was obtained by on-going reports from general practitioners and by regular reviews of the patients' medical records[264]. At 2-yearly intervals a standard medical record review form was sent to the general practice (see Appendix III for details) requesting confirmation of each man's continuing registration, current address, and any new cardiovascular events (including myocardial infarction, angina, stroke, transient ischaemic attack and heart failure), new diagnoses of cancer or diabetes or cardiovascular treatments (coronary artery bypass graft, coronary angioplasty) which have occurred within the last two years. All new non-fatal myocardial infarction and stroke events reported by the practices are followed up with an enquiry form to the general practitioner or hospital consultant to obtain confirmatory evidence that case criteria have been met[264;265]. Criteria for diagnosis of non-fatal myocardial infarction are based on World Health Organization criteria for myocardial infarction, including the presence of any two of three of the following: prolonged chest pain, positive electrocardiogram findings and raised cardiac enzyme levels[52;53]. The criteria for stroke are based on an acute disturbance of cerebral function of vascular origin, producing a neurological deficit lasting for more than 24 hours[54;264].

Men who have re-registered with another general practice are traced to the new Practice. In addition to the original 24 practices, the study now includes over 850 general practices nationwide; follow-up of participants has been maintained for 98% of surviving men throughout.

3.2.4.3 Follow-up questionnaires

Follow-up questionnaire have been sent to participants at regular intervals since the initial physical examination and questionnaire, which was completed at baseline in 1978-80 (see Figure 3.2). The first postal questionnaire after baseline was sent out in 1983-85, followed by postal questionnaires in 1992 and 1996. At the twenty year re-examination, in 1998-2000, participants also completed a questionnaire and were sent a separate postal food frequency questionnaire (see section 3.3.2). Following this, postal questionnaires were also sent out in 2003, 2005 and 2007. In 2010-12, a questionnaire was also completed at the 32 year re-examination.

3.2.4.4 Twenty year re-examination

After twenty years of follow-up from baseline, participants (then aged 60-79 years) were invited for a re-examination which took place between 1998 and 2000[264;266]. Of the 5565 surviving men, 4252 men (77% of survivors) attended the re-examination at a local health centre. Men underwent a physical examination (see Appendix IV for further details of the information collected) and completed a general questionnaire, including information on lifestyle and medical history (Appendix V)[264;266]. All men were asked to provide a fasting blood sample, which was collected by using the Sarstedt Monovette system (Sarstedt, Numbrecht, Germany)[267]. Participants without diabetes were requested to fast for a minimum of 6 hours prior to their appointment time and to drink only water. Men attended measurement session at a specified time between 08:00 and 18:00 hours. Within 6 hours of the blood sample collection time, plasma and serum samples were centrifuged, separated and frozen at –20 degrees Celsius and transferred to central laboratories for analysis. Between 1998 and 2000, participants also completed a separate postal food frequency questionnaire (Appendix VI). Further details of the data collected at the re-examination are described in Section 3.3.

3.3. Data used in this thesis

Data from the BRHS has been used to assess the relationships between measures of body composition (adiposity and muscle mass) and dietary patterns with the risk of cardiovascular outcome sand mortality. This thesis has primarily used available data from the 20 year re-examination, including measurements made at the physical examination and data collected via the two questionnaires, and follow-up data on mortality and morbidity until June 2010. In addition, some socioeconomic variables have been used from earlier questionnaires at 1978-80 (baseline), 1992 and 1996. This section will present how data on the major exposure variables (body composition and diet), additional risk factors and outcomes variables used in this thesis were collected and defined.

3.3.1. **Body composition measures**

Anthropometric body composition measurements at re-examination in 1998-2000 included height, weight, waist circumference, hip circumference, subscapular skinfold thickness, triceps skinfold thickness and mid-upper arm circumference. Bioelectrical impedance analysis (BIA) was also carried out to measure fat mass and fat-free mass. Subjects were measured in light clothing without shoes. The number of participants with available data for each of the measures of body composition, together with the mean measurements in this cohort will be presented in Chapter 4 (Table 4.1).

3.3.1.1 Anthropometric measurements

Height and Weight: Height and weight were both measured while the participants were standing. Height was measured with a Harpenden stadiometer to the last complete 0.1 cm. Weight was measured with a Soehnle digital electronic scale to the last complete 0.1 kg. Body mass index (BMI) was calculated for each man in kg/m^2.

Waist/Hip circumference: Waist and hip circumferences were measured in duplicate with an insertion tape (CMS Ltd, London, United Kingdom) to the last complete 0.1 cm and the mean of the two readings was taken. The measurement of waist circumference was taken at the midpoint between the iliac crest and the lower ribs measured at the sides. Hip circumference was measured at the point of maximum circumference over the buttocks. Waist-to-hip ratio was calculated as waist divided by hip circumference (cm). Waist circumference and hip circumference were adjusted for observer variation.

A small repeatability study was carried out to examine within-subject variation for BMI, waist circumference and waist-to-hip ratio in 110 participants measured by the same team of observers on both occasions. The correlations between measurements taken 1 week apart were 0.99 for BMI, 0.99 for waist circumference and 0.93 for waist-to-hip ratio[267]. The within-subject correlations for waist circumference were similar in non-obese (BMI <30 kg/m, r = 0.99) and obese men (BMI $\geq$ 30 kg/m, r = 0.97)[267].

Subscapular/Triceps skinfold thickness: Subscapular and triceps skinfold thicknesses were measured in duplicate with a Holtain skinfold caliper to the last complete 0.1 mm,

on the right side only. Triceps skinfold thickness was measured at the mid-upper arm, with the arm pendant. The mean of the two readings was taken. Subscapular skinfold and triceps skinfold measurements were adjusted for observer variation.

Mid-upper arm circumference: The mid-upper arm was defined, and the mid-upper arm circumference was measured once in the right arm pendant with an insertion tape (CMS Ltd, London, United Kingdom) to the last complete 0.1 cm. Mid-arm muscle circumference (MAMC) was calculated as: mid-upper arm circumference (cm) - 0.3142 x triceps skinfold thickness (mm)[148].

Weight loss: At re-examination, participants were also asked to report whether their weight had changed in the previous three years: no; weight gain; weight loss; fluctuation. A dichotomous weight loss variable was created (Yes: weight loss; No: no change, gain or fluctuation).

3.3.1.2 Bioelectrical impedance analysis

Fat mass (FM) and fat-free mass (FFM) were determined by bioelectrical impedance analysis (BIA) using a Bodystat 500 arm-leg body composition analyser (Bodystat Ltd, Douglas, UK). FFM was calculated using the equation by Deurenberg et al, which was validated in people aged over 60 year[268]: 6710 x height (m^2) ÷ resistance (Ω) + 7. FM was calculated as body weight - FFM. FM and FFM were also calculated as proportions of total body weight (% FM and % FFM). To provide a height-independent body composition measure, FM and FFM measures were normalised for height by dividing by height (m^2) to give fat mass index (FMI) and fat-free mass index (FFMI) in kg/m^2.

An alternative estimate of fat-free mass was also applied, using the equation by Janssen et al, which was validated in people aged 18-86 years[150;269]: skeletal muscle mass (kg) = [(height (m^2) ÷ resistance (Ω) x 0.401) + (1 x 3.825) + (age x -0.071)] + 5.102. Skeletal muscle was calculated as proportion of total body weight (% skeletal muscle). Skeletal

muscle mass was also normalised for height by dividing by height^2 (m) to give the skeletal muscle index (SMI) in kg/m^2.

3.3.1.3 Defining adiposity and obesity

The adiposity measures used in this thesis included markers of whole body adiposity (BMI and FMI), central adiposity (waist circumference, waist-to-hip ratio and subscapular skinfold thickness), and peripheral adiposity (triceps skinfold thickness), as introduced in section 2.4.1. Overweight and obesity based on BMI were defined in accordance with established World Health Organization cut-points ($\geq$ 25 kg/m^2 and $\geq$ 30 kg/m^2 respectively). Established sex-specific cut-points were used to define obesity for waist circumference (>102 cm) and waist-to-hip ratio ($\geq$ 1.00)[105]. Recent literature suggests using $\geq$ 0.90 as the waist-to-hip ratio cut-point for men[270]. However, since this would have classified 80.0% of participants as obese, a more stringent cut-point of $\geq$ 1.00[105] was more appropriate for this cohort (classifying 18.7% as obese).

3.3.1.4 Defining muscle mass and sarcopenia

The markers of muscle mass used within this thesis were MAMC, FFMI and SMI. Key issues influencing the definition of sarcopenia were introduced in section 2.4.6; no operational definition of sarcopenia has yet been adopted universally[17] but the European Working Group on Sarcopenia has suggested defining sarcopenia using a combination of muscle mass and function (strength and performance). However, in the BRHS cohort at the 1998-2000 re-examination, direct measures of muscle function were not available, so sarcopenia definitions are based solely on muscle mass. Sarcopenia was defined as a level of MAMC, FFMI or SMI below the second quintile of each variable. Sarcopenic obesity was defined using various combinations of sarcopenia and obesity, as described further in the subsequent results chapters (Chapter 4 and Chapter 5).

Direct measurements of muscle mass such as computerised tomography (CT), magnetic resonance imaging (MRI) or dual-energy X-ray absorptiometry (DXA) were not available in this cohort. However, the American Heart Association recognises MAMC as a proxy marker for muscle mass[102] which is strongly correlated with more accurate

dual-energy X-ray absorptiometry measures of lean mass[147]. In addition, the European Working Group on Sarcopenia has approved BIA measures as a portable alternative to dual-energy X-ray absorptiometry[17]. The implications of the specific muscle mass measurements and definitions of sarcopenia used in this thesis are discussed further within the relevant results chapters (Chapter 4 and Chapter 5) and in the chapter on implications and conclusions (Chapter 9).

3.3.2. **Dietary assessment**

At the same time period as the twenty year re-examination was carried out (1998-2000), participants also completed a separate self-administered postal food frequency questionnaire (FFQ). The FFQ was developed for use in the World Health Organization's Monitoring Trends and Determinants in Cardiovascular Disease Survey[271] and later for the Scottish Heart Health Study[272]. It has been previously validated against weighed food intake in British populations[273;274]. Participants were asked to recall their usual intake of 86 different food items. The questionnaire included a list of foods, grouped into 12 categories: (1) meat; (2) fish; (3) vegetables - fresh, tinned, dried, frozen; (4) fresh fruit; (5) cheese; (6) bread; (7) breakfast cereal; (8) biscuits, puddings and sweets; (9) egg; (10) other foods; (11) drinks and juices (non-alcoholic); (12) fats. The respondent was asked how often he/she usually ate each food per week and consumption frequencies were reported in nine categories: 1, 2, 3, 4, 5, 6, or 7 days per week, monthly, or rarely/never. Additionally, information was also collected on the specific types and quantity of fruit eaten per week, the amount and type of milk drank per week, the amount and type of fat used for cooking and for spreading on bread, the amount of salt added to food/cooking, the weekly household consumption of different types of fats, dairy products and sugar, the amounts of tea/coffee/other hot drinks consumed per day and the amount of alcohol drank per week. (See Appendix VI for further details of the questions included in the FFQ).

Total macronutrient and micronutrient intakes of all food reported as consumed in the FFQ were derived using a validated computer program. The program multiplied the food frequency of the food consumed by the standard portion sizes for each food, and by the nutrient composition of the food obtained from the UK food composition

tables[275]. This derived data on mean daily total energy intake (kcal/day), as well as mean daily intake (g/day) of fat (total, saturated and polyunsaturated), protein, carbohydrates (total, starch and sugar) and fibre (cereal and vegetable). Mean daily intake of vitamin C, vitamin E, iron and cholesterol (mg/day) were also derived. In addition, plasma vitamin C and vitamin E levels were also available from the blood sample collected at the re-examination in 1998-2000. Plasma vitamin C and vitamin E was measured with high-performance liquid chromatography that included ultraviolet and fluorescent detection[276;277]. For vitamin C, plasma extracts were treated with metaphosphoric acid at the point of collection and were then snap-frozen with dry ice. Laboratory-blinded split samples were used to ensure quality control throughout the study[278].

The distribution of total energy intakes was checked for any extreme values. However, all were within a range compatible with a normal lifestyle (500-8000 kcal/day in men[279]) so no exclusions were made on this basis. The multivariate nutrient density model was used to adjust macronutrients for energy intake; carbohydrates, fats and protein were expressed as percentages of energy (% kcal)[280]. In addition, throughout this thesis, all models including dietary patterns as exposure variables, have been adjusted for total energy intake (kcal/day)[280]. The number of participants with available data for each of the dietary variables, together with the mean intakes of macronutrients and micronutrients in this cohort will be presented in Chapter 6 (Table 6.4). Details of how dietary patterns were derived in this cohort, using *a priori* and *a posteriori* methods will be described in relevant results chapters (Chapters 6, 7 and 8).

3.3.3. **Lifestyle variables**

3.3.3.4 Smoking status

Detailed questions on cigarette smoking habits were obtained from the self-completed questionnaire completed at re-examination in 1998-2000. Participants were asked whether they had ever smoked cigarettes regularly (at least 1 a day), whether they smoke cigarettes at present and, if not, at what age they gave up smoking. From the information given, men were classified into four cigarette smoking groups (never smoked; long-term ex-smokers, >15 years; recent ex-smokers, ≤ 15 years; current smokers)[90].

3.3.3.5 Alcohol consumption

In the self-completed questionnaire at re-examination in 1998-2000, participants were asked for detailed information on their current frequency of drinking (daily/most days; weekends only; occasional; special occasions only; none) and were asked to estimate the quantity they drank on the days when they drank alcohol (None; 1-2 drinks; 3-6 drinks; >6 drinks). Based on these two questions, men were classified into five groups according to their reported weekly intake: none (0 drinks/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, which included daily 3-6 units and weekend >6 units); heavy (>42 units/week, which included >6 units daily)[281;282]. One drink was defined as half a pint of beer, a glass of wine, or a single measure of spirit (8-10gms).

3.3.3.6 Physical activity

The self-completed questionnaire at re-examination in 1998-2000, asked participants questions relating to their usual patterns of physical activity under the headings of regular walking or cycling, recreational activity and sporting (vigorous) activity. Regular walking and cycling related to weekday journeys, which included travel to and from work. Recreational activity included gardening, pleasure walking, and do-it-yourself jobs. Sporting activity included running, golf, swimming, tennis, sailing, and digging. A physical activity score was derived for each man according to the frequency and type (intensity) of physical activity[283]. Scores were assigned for each type of activity and duration on the basis of the intensity and energy demands of the activities reported[284]. The total score for each man is a relative measure of how much physical activity has been carried out. Participants were classified into six categories based on their physical activity score: inactive (score 0-2), occasional (score 3-5; regular walking or recreational activity only), light (score 6-8; more frequent recreational activities or vigorous exercise less than once a week), moderate (score 9-12; cycling or very frequent recreational activities or sporting activity once a week), moderately-vigorous (score 13-20; sporting activity at least once a week or frequent cycling, plus frequent recreational activities or walking, or frequent sporting activity only), and vigorous score ≥ 21; very

frequent sporting exercise or frequent sporting exercise plus other recreational activities). This physical activity score has been previously validated at both the baseline examination and the re-examination in 1998-2000 against heart rate and lung function (FEV_1), in men free of pre-existing CHD[283;284].

3.3.4. **Socioeconomic circumstances**

Adult socioeconomic position: The longest held occupation of participants was recorded at study entry (aged 40-59 years), via a nurse-administered questionnaire in 1978-80 (Appendix VII). The Registrar General's Classification of Occupations[285] was used to classify subjects into six occupational social class categories: I (professional occupations e.g. barristers, physicians, engineers), II (intermediate 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). Occupational social classes were dichotomised into two groups: non-manual (social classes I, II, III non-manual) and manual (social classes III manual, IV, V).

In additional to occupational social class, information was collected on other measures of socioeconomic position. The 20 years re-examination questionnaire in 1998-2000 asked participants about car and house ownership, and whether they had central heating at home. In addition, the earlier 1996 postal questionnaire provided information on education (age at leaving full-time education) and pension (what type of financial support participants have or will have on retirement - state only or state plus private pension) [Appendix VIII]. The response rate for the 1996 postal questionnaire was 88%.

Childhood socioeconomic position: In the 1992 postal questionnaire, information on childhood socioeconomic variables was collected (Appendix IX). Participants were asked for their father's longest held occupation. Registrar General's Classification of Occupations 1931[286] was used to classify participants into the following social class groups: I (professional occupations e.g. engineers, physicians, clergymen, bankers), II

(intermediate occupations e.g. farmers, coal mine owners/managers,), III (skilled occupations e.g. gardeners, farm or factory foremen), IV (partly skilled occupations e.g. shepherds, fishermen, miners, quarries) and V (unskilled occupations e.g. masons or builders' labourers, porters, messengers). The 1992 questionnaire also collected information on childhood household amenities. Participants were asked if their home had a bathroom in the house, hot water supply and family car ownership, up to 10 years old. The response rate for the 1992 postal questionnaire was 91%.

Social interaction and family circumstances: The 20 year re-examination questionnaire in 1998-2000, asked men how often they saw or spoke to their children, siblings, friends and neighbours (every week; every month; every few months; every year; rarely/never; does not apply), whether they were living alone (living alone; living with a partner/spouse; living with other family members; living with other people), and what their marital status was (single; married; widowed; divorced/separated; other).

3.3.5. **Physical measurements**

At the physical examination in 1998-2000, blood pressure was measured in duplicate in the right arm with a Dinmap 1846SX automated blood pressure monitor (Critikon Inc, Tampa, USA) with the participant seated and the arm supported[287]. Blood pressure was adjusted for observer variation[288]. Forced expiratory volume in 1 second (FEV_1) was also assessed at the re-examination as part of a spirometric lung function assessment. A Vitalograph Compact II instrument was used and this was calibrated using a precision syringe at least twice daily[289].

3.3.6. **Blood measurements**

Concentrations of 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. Serum total cholesterol and high density lipoprotein (HDL) cholesterol, and triglycerides were measured using an automated analyser Hitachi 747 (Hitachi, Tokyo, Japan)[290]. Low density lipoprotein (LDL) cholesterol was calculated using the Fredrickson-Friedewald equation[291]. Plasma glucose was measured using a glucose oxidase method with a Falcor 600 automated

analyser (A Menarini Diagnostics, Wokingham, United Kingdom). Serum insulin was measured using a Drew Hb Gold instrument (Drew Scientific Group Plc, Barrow in Furness, UK). Glucose, insulin, triglycerides and LDL cholesterol concentrations were adjusted for the period of fasting and the time of day the blood sample was taken[290].

A number of emerging cardiovascular risk markers, including haemostatic and inflammatory markers, were also measured in citrated blood plasma at the Department of Medicine, University of Glasgow[283;292]. Blood anticoagulated with K_2-EDTA (1.5 mg/ml) was used for the measurement of haematocrit, white blood cell count, and platelet count in an automated cell counter and plasma viscosity at 37°C in a semi-automated capillary viscometer (Coulter Electronics, Luton, UK)[293]. Blood was also anticoagulated with 0.109 mol/L trisodium citrate (9:1 vol:vol) for measurement of clottable fibrinogen (Clauss method). Plasma concentrations of tissue plasminogen activator (t-PA) antigen and fibrin D-dimer were measured by using enzyme-linked immunosorbent assays (Biopool AB, Umea, Sweden), as was von Willebrand factor (vWF) antigen (DAKO, High Wycombe, UK). C-reactive protein (CRP) was assayed by ultrasensitive nephelometry (Dade Behring, Milton Keynes, UK). Interleukin-6 was assayed by a high-sensitivity ELISA (R and D Systems, Oxford, UK). Serum homocysteine was measured at the Department of Pharmacology, University of Bergen, Norway. A modification of an automated assay was used, based on pre-column derivatisation with monobromobimane, followed by reverse phase high performance liquid chromatography with fluorescence detection[294].

3.3.7. **Morbidity**

The self-completed questionnaire at re-examination in 1998-2000 sought information from participants on their health status and disability. Participants were asked to rate their present state of health as excellent, good, fair or poor. Mobility limitation was determined by asking participants whether they had difficulty carrying out any of the following activities on their own as a result of a long term health problem: difficulty going up/down stairs, difficulty bending/straightening up, difficulty maintaining balance, difficulty walking for a quarter of a mile on a level surface .

3.3.8. **Prevalent disease**

The self-completed questionnaire at re-examination in 1998-2000 sought information from participants on their medical history, which provided information on the prevalent disease. Participants were asked if a doctor had ever told them that they have had a heart attack (coronary thrombosis or myocardial infarction), angina, stroke, diabetes, heart failure and cancer. Participants provided a 'yes/no' response to each question.

3.3.9. **Incident disease**

The four main outcome variables assessed in this thesis are incident CHD events, incident CVD events, CVD mortality and all-cause mortality. An incident CHD event was defined as non-fatal MI or fatal CHD (ICD-9 codes 410-414). An incident CVD event was defined as non-fatal MI, non-fatal stroke or fatal CVD (ICD-9 codes 390-459). CVD mortality was defined as all fatal CVD deaths (ICD-9 codes 390-459). All-cause mortality was defined as death from any cause. Deaths were ascertained from the NHS Central Register (as described in section 3.2.4.1). Non-fatal MIs and non-fatal strokes were ascertained from the regular review of general practice records (as described in section 3.2.4.2). This thesis uses available followed up data on cardiovascular mortality and morbidity from the twenty year re-examination, in 1998-2000, to June 2010.

3.4. Strengths of the data source for the intended analysis

The BRHS is a suitable cohort for studying the objectives set out in this thesis. The 20 year re-examination in 1998-2000 provides a detailed assessment of both a range of body composition measures (including adiposity and muscle mass) and extensive dietary data from a food frequency questionnaire, which will be used as the major exposure variables. Also, comprehensive information on cardiovascular risk factors was collected in 1998-2000. The BRHS also provides continuous follow-up over an extended period, with regular and objective measurements on CHD events, CVD events and mortality. This will enable the prospective investigation of measures of body composition and dietary patterns in relation to the risk of CVD and mortality in older men.

A major strength of the BRHS is that it is a socioeconomically and geographically representative population-based sample of middle-aged men from across Britain[264]**.** The cohort has benefited from high response rates throughout the follow-up. Data collection and recording in the BRHS have been maintained to a very high standard since baseline, with near complete follow-up (>98%) for mortality and morbidity[35]. At the start of the study (1978-80), characteristics of participants were compared to non-responders. Men who did not participate were younger, more likely to be unmarried, and more likely to be less skilled workers compared to study participants[295]. In the first three years of follow-up, non-participants also had a higher total mortality rate, but this declined to non-significant levels subsequently. Also, the death rate was similar in participants and non-participants for cardiovascular disease, suggesting that any analyses in this thesis related to this particular cause of death should not be biased by non-participation.

However, the BRHS has been limited by the restriction of the study population to men and the lack of representation from ethnic minority groups, which limits generalizability of findings to non-White British populations. The BRHS also avoided inner city populations and towns with high mobility, which has had the advantage of enabling the cohort to be stable with high response rates.

3.5. Statistical methods

All statistical analyses were carried out using Stata versions 12-13 (Stata Corp., College Station, Texas). Some of the main statistical methods used in this thesis are described below. However, specific details of statistical analyses are described in more detail in each of the relevant results chapters.

3.5.1. Generalised linear models

Generalised linear models are used to analyse the relationship between an exposure variable and an outcome variable[296]. Linear regression is used to relate a continuous outcome variable (y) to exposure variables (x) as follows:

$$y = \beta_0 + \beta_1 x$$

β_0 is the intercept (the value of y where $x = 0$) and β_1 is the regression coefficient (the increase in y for every unit increase in x).

Linear regression assumes that for any value of x, y is normally distributed and that the magnitude of the scatter of the points about the line is the same throughout the length of the line. Linear regression has been used to assess the cross-sectional associations at re-examination in 1998-2000 between continuous measures of body composition or diet in relation to cardiovascular risk factors (see chapters 4, 6 and 8).

Logistic regression is used to model the association between a binary outcome variable (y) and an exposure variable (x), fitted on a log scale.

$$Log\ (odds) = \beta_0 + \beta_1 x$$

Logistic regression thus generates the odds of the outcome event in the exposed group, the odds of the outcome event in the unexposed group, and the ratio of these two odds:

Odds = $p/1\text{-}p$ (p = probability of the outcome)

Odds ratio = Odds in exposed group/Odds in unexposed group

Logistic regression does not require a linear relationship between the exposure and outcome variables since it applies a non-linear log transformation to the predicted odds ratios. Logistic regression has been used to assess the cross-sectional associations at re-examination in 1998-2000 between categorical measures of body composition or diet in relation to cardiovascular risk factors (see chapters 4 and 7).

3.5.2. **Survival analysis and Cox proportional hazards regression analysis**

Survival analysis is used to investigate the probability of having an event when time to a binary event is the main outcomes of interest[296]. Survival time for each participant is the time from a predetermined start point e.g. entry in to the study, until the occurrence of the event of interest. For some participants the time to the event of interest may be censored, if the event has not occurred at the end of follow-up, they were lost to follow-

up after a certain date or if they die from a cause other than the event of interest. The Kaplan Meier method can be used to calculate the survival probability and to plot survival curves, when the exact follow-up time is known.

Cox proportional hazards regression analysis is used to examine the association between an exposure variable and a time to event outcome variable, and is the most commonly used approach to the regression analysis of survival data. It assumes the ratio of the hazards comparing different exposure groups is constant over time, which is known as the proportional hazards assumption. This assumption is amenable to testing, on the basis of Schoenfeld residuals[297]. The mathematical form of the Cox proportional hazards model is:

$$h(t)=h_0(t) \times exp(\beta_1 x_1 + \beta_2 x_2 + ... + \beta_p x_p)$$

where $h(t)$ is the hazard at time t, $h_0(t)$ is the baseline hazard (the hazard for an individual in whom all exposure variables = 0) at time *t*, and x_1 to x_p are the $_p$ exposure variables.

The hazard ratio comparing exposed and unexposed individuals at time *t* is:

$$HR(t) = h_0(t) \times exp(\beta_1)/h_0(t) = exp(\beta_1)$$

Survival analysis and cox proportional hazards regression analysis has been used to assess the prospective associations between measures of body composition and dietary patterns at re-examination in 1998-2000 with the risk of cardiovascular outcomes and mortality over 11 years of follow-up (see Chapters 5, 6 and 8).

3.5.3. **Principal component analysis**

Principal component analysis is a multivariate statistical technique which analyses a data table representing observations described by several exposure variables. It is a method used to find a few combinations of exposure variables, that adequately explain the total observed variation, and hence reduces the complexity of the data[296]. Principal component analysis computes new variables called principal components which are

obtained as linear combinations of the original variables[298]. The first principal component will explain the greatest variance in the data. The second component is computed under the constraint of being orthogonal to the first component and will explain the second greatest variance in the data, and so on.

Within nutritional epidemiology, principal component analysis is an exploratory approach commonly used to identify *a posteriori* dietary patterns[28] and identifies foods frequently consumed together. It aggregates food groups on the basis of the degree to which they are correlated with one another, with the aim of identifying food items/groups that account for the largest amount of variation in diet between individuals[29]. Principal component analysis is therefore useful for describing the intercorrelations between foods[299]. This thesis has used principal component analysis of food groups, derived from the FFQ at re-examination in 1998-2000, to apply *a posteriori* dietary patterns to the BRHS cohort (see Chapter 8).

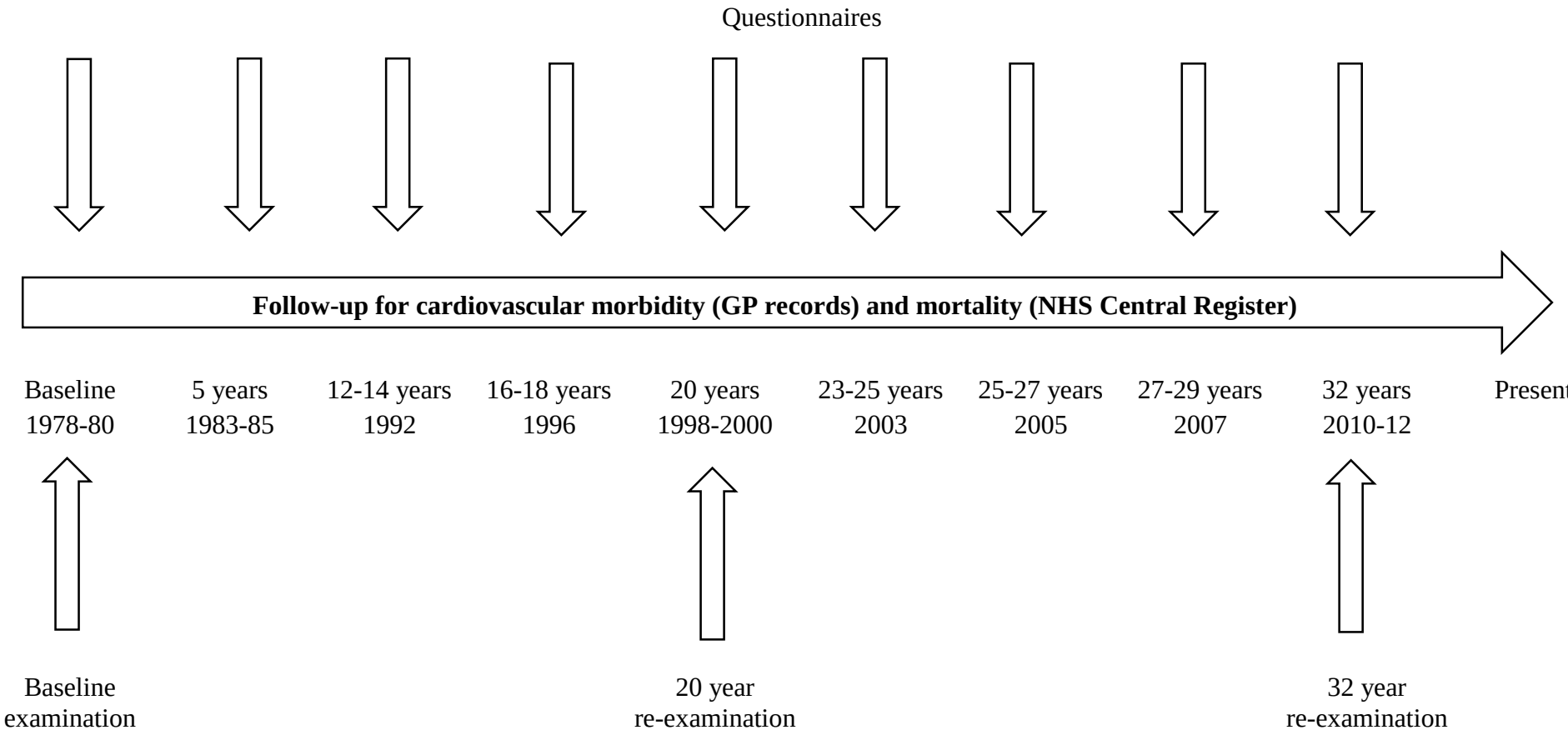
Table 3.1 Towns included in the British Regional Heart Study

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
Grimbsy	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
Scunthorpe	109	313	76
Shrewsbury	95	310	83
Southport	114	322	80
Wigan	134	337	77

Data source: Adapted from Shaper et al, 1981[34]

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

Figure 3.2 Timeline showing follow-up in the British Regional Heart Study



CHAPTER 4 Cross-sectional associations of body composition and cardiovascular risk factors in older British men

4.1. Summary

Sarcopenia has been defined as the age-associated loss of skeletal muscle mass and has been associated with metabolic impairment, cardiovascular disease (CVD) risk factors, physical disability and mortality. It has a multifactorial aetiology which is not fully understood. Sarcopenia often occurs in combination with obesity (sarcopenic obesity), and sarcopenia with obesity may synergistically increase their effect on metabolic disorders, CVD and mortality. However, whether sarcopenic obese individuals have the most adverse cardiovascular risk profile is unclear. In this chapter, the cross-sectional associations between different measures of sarcopenia, obesity, and sarcopenic obesity with cardiovascular risk factors were examined. At the 20 year re-examination in 1998-2000, 4252 men from the British Regional Heart Study (BRHS), aged 60-79 years, attended a physical examination (which included body composition assessment), provided a fasting blood sample, completed a general questionnaire on their lifestyle and medical history, and also a food frequency questionnaire. Cardiovascular risk factors were examined by quartiles of mid-arm muscle circumference (MAMC) and fat-free mass index (FFMI), by waist circumference (WC) groups and by sarcopenic obesity groups (defined by combinations of MAMC and WC, or FFMI and fat mass index [FMI]). In addition, factors associated with low muscle mass (lowest quartile of MAMC/FFMI) were analysed using multivariable logistic regression. Physical inactivity and higher levels of insulin resistance, C-reactive protein (CRP), von Willebrand Factor (vWF) and fibrinogen were associated with significantly increased odds of lower muscle mass (MAMC and FFMI) after adjustment for age, body mass index (BMI), behavioural variables and morbidity. Those with a higher percent of energy intake from carbohydrates showed lower odds of low MAMC (odds ratio [OR]: 0.73, 95% CI: 0.55-0.96) and low FFMI (OR: 0.76, 95% CI: 0.58-0.99). With participants classified into four sarcopenic obesity groups, the sarcopenic obese group (defined using combinations of MAMC and WC, and alternatively FFMI and FMI) had significantly higher levels of inflammatory and haemostatic markers (CRP, vWF and fibrinogen) than the sarcopenic alone, obese alone or non-sarcopenic, non-obese body composition groups.

4.2. Introduction

Ageing is associated with importance changes in body composition; typically visceral fat increases and muscle mass decreases, as outlined in Chapter 2 (section 2.4). Sarcopenia, the age-associated loss of muscle mass and function, is associated with increased risks of metabolic impairment, physical disability, functional impairment and mortality[137;153-155;157-159]. The aetiology of sarcopenia is multifactorial and is not fully understood. The risk of sarcopenia is increased by cardiovascular risk factors including physical inactivity and current smoking[131;138]. Diet, as well as being a major cardiovascular risk factor, may also be an important determinant of sarcopenia, with low intake of protein, total energy, vitamin D, antioxidants and omega-3 polyunsaturated fatty acids implicated in the development of sarcopenia[132;133]. Recent evidence also suggests cardiovascular and inflammatory biomarkers are important contributors to sarcopenia progression[157]. In addition, there is a suggestion from clinical studies that endothelial dysfunction may also be a determinant of sarcopenia[300] but this has been little studied in the general population. It is important to establish the contributions of a wide variety of potential determinants of low muscle mass, as well as potential mechanisms linking sarcopenia to adverse outcomes, to inform the development of specific prevention and intervention strategies in older people.

Recently, the concept of sarcopenic obesity has emerged which refers to sarcopenia coupled with high levels of adipose tissue[18-22]. The associations between adiposity and established and emerging cardiovascular risk markers are well established in the elderly, with a previous report from the cohort studied in this thesis (the BRHS) showing that adiposity (especially high BMI and high waist circumference) is an established risk factor for the metabolic syndrome and insulin resistance in older men[267]. Visceral fat and muscle mass share common metabolic and inflammatory pathways[18]. Therefore it is hypothesised that sarcopenia and obesity may act synergistically, so that sarcopenic obesity may have a greater effect on the risks of the metabolic syndrome, CVD and mortality than either obesity or sarcopenia alone[18;22]. However, as reviewed in section 2.4.7, whether sarcopenic obese individuals have a particularly adverse cardiovascular risk profile is unclear.

This chapter therefore aims to examine the cross-sectional associations between individual and combined measures of low muscle mass (sarcopenia) and obesity with established and emerging cardiovascular risk factors, including dietary factors, in older men aged 60-79 years. The association of obesity with cardiovascular risk factors has been widely studied in the elderly. However, there are gaps in the literature on the associations of sarcopenia and combined measures of sarcopenia and obesity with cardiovascular risk factors. This chapter will therefore focus particularly on measures of muscle mass and composite measures of obesity and low muscle mass in order to address these gaps in the literature.

4.3. Objectives

To examine the associations between various body composition measures (adiposity and in particular low muscle mass) and cardiovascular risk factors in older age (60-79 years). The specific aims of this chapter are:

i) To describe the patterns of body composition of a cohort of older men.
ii) To explore the correlations between different measures of body composition i.e. adiposity and muscle mass.
iii) To explore the relationships of sarcopenia measures with cardiovascular risk factors.
iv) To examine the relationships of obesity with cardiovascular risk factors.
v) To explore the relationships of combined measures of sarcopenia and obesity with cardiovascular risk factors.

4.4. Methods

4.4.1. Subjects and methods of data collection

Cross-sectional data used in this chapter are from the 20 year re-examination of BRHS participants, then aged 60-79 years, in 1998-2000. 4252 men (77% of survivors) attended a physical examination, provided a fasting blood sample, completed a general questionnaire on their lifestyle and medical history, and also a food frequency questionnaire (FFQ)[264]. The physical examination involved body composition

measurements (height, weight, waist circumference [WC], hip circumference, subscapular skinfold thickness, triceps skinfold thickness and mid-upper arm circumference) and bioelectrical impedance analysis (BIA), as described in detail in Chapter 3, section 3.3.1.

4.4.2. **Measures of adiposity**

Adiposity measures used in this chapter included markers of whole body adiposity (BMI and FMI), central adiposity (WC, waist-to-hip ratio [WHR] and subscapular skinfold thickness) and peripheral adiposity (triceps skinfold thickness). Established cut-points were used to define overweight and obesity according to BMI ($\geq$ 25 kg/m^2 and $\geq$ 30 kg/m^2 respectively) and sex-specific cut-points were used to define obesity for WC (>102 cm) and WHR ($\geq$ 1.00)[105]. Recent literature suggests using $\geq$ 0.90 as the WHR cut-point for men[270]. However, since this would have classified 80.0% of participants as obese, a more stringent cut-point of $\geq$ 1.00 was more appropriate for this cohort (classifying 18.7% as obese). Participants above the percentile point of FMI corresponding to the obesity cut-off for WC (28.7th percentile in this dataset) were also classified as obese (>11.1 kg/m^2). The measure of adiposity presented in detail in relation to cardiovascular risk factors in this chapter was WC, classified into 4 WC categories (<94, 94-102, 103-105, $\geq$ 106 cm).

4.4.3. **Measures of muscle mass**

Muscle mass measures included an anthropometric measurement (mid-arm muscle circumference [MAMC]) and BIA measurements (fat-free mass index [FFMI] and skeletal muscle index [SMI]). In this chapter, two measures of muscle mass were presented in detail in relation to cardiovascular risk factors (MAMC and FFMI), both divided by quartiles of the distribution. To assess whether sarcopenic obese individuals had the most adverse cardiovascular risk profile, participants were categorised into four non-overlapping groups (non-sarcopenic, non-obese; sarcopenic; obese; sarcopenic obese) based on the combination of anthropometric measurements (WC and MAMC) or BIA measurements (FMI and FFMI). The obesity definitions used were mentioned above (Section 4.4.2). Since no universally accepted operational definition of sarcopenia has yet been adopted[17], sarcopenia was defined as below the second quintile

of MAMC (≤ 25.9 cm) or FFMI (≤ 16.7 kg/m^2), as including only those below the lowest quartile did not yield adequate numbers in the sarcopenic obesity group.

4.4.4. Cardiovascular risk factors

4.4.4.1 Socio-demographic and behavioural risk factors

Adult occupational social class was based on the longest held occupation recorded at study entry, in 1978-80, using the Registrar General's occupational classification, as described in Chapter 3 (section 3.3.4). Participants were classified as manual, non-manual or armed forces. Behavioural risk factors (cigarette smoking, physical activity and alcohol intake) were measured at the re-examination in 1998-200 as described in Chapter 3 (section 3.3.3). Men were classified into four smoking groups (never; long-term ex; recent ex; current). Current physical activity was classified in six groups based on exercise frequency and intensity (inactive; occasional; light; moderate; moderately vigorous; vigorous). Alcohol intake was classified into five groups based on the number and frequency of alcoholic beverages consumed per week (none; occasional; light; moderate; heavy).

4.4.4.2 Dietary assessment

A self-administered postal food frequency questionnaire, completed in 1998/2000, provided dietary intake data, as described in detail in Chapter 3, section 3.3.2. Participants reported usual frequency of consumption of 86 food and drink types. Nutrient intakes were derived using a validated computer program to calculate total nutrient composition of foods consumed[301]. In addition, participants were asked to indicate how often they consumed fresh fruit and vegetables – rarely/never, monthly, or 1, 2, 3, 4, 5, 6, or 7 days per week. Daily consumption was classified as 7 days per week. The multivariate nutrient density model was used to adjust macronutrients for energy intake; carbohydrates, protein, total fat and saturated fat were expressed as percentages of energy (% kcal). Plasma vitamin C and E were also available from blood samples at the re-examination (1998-2000)[301].

4.4.4.3 Metabolic risk factors

Metabolic markers (glucose, insulin, triglyceride, high density lipoprotein [HDL] cholesterol and blood pressure) were measured by physical examination and by the

collection of fasting blood samples at re-examination in 1998-2000 as described in Chapter 3 (section 3.3.5 and 3.3.6). The homeostasis model assessment was calculated to estimate insulin resistance (HOMA-IR) = fasting glucose (mmol/L) x insulin (U/mL)]/22.5[267]. Metabolic syndrome was classified according to the National Cholesterol Education Program definition[302]; ≥ 3 metabolic risk factors as follows: 1) Central obesity: WC >102 cm; 2) Fasting plasma glucose >6.1 mmol/L; 3) Serum triglyceride >1.7 mmol/L; 4) Serum HDL cholesterol <1.04 mmol/L; and 5) Hypertension: blood pressure >130/85 mmHg or using blood pressure medication.

4.4.4.4 Inflammatory/hemostatic risk factors

Plasma concentrations of C-reactive protein (CRP), tissue plasminogen activator (t-PA), D-dimer, von Willebrand Factor (vWF), fibrinogen, interleukin 6 (IL-6) and homocysteine were measured from blood samples collected at re-examination in 1998-2000 as described in Chapter 3 (section 3.3.6).

4.4.4.5 Morbidity

Participants completed a questionnaire at the re-examination in 1998-2000, which asked: "Have you ever been told by a doctor that you have or have had any of the following conditions?" Participants provided 'yes/no' responses to the following categories: heart attack; angina; stroke; diabetes; heart failure; cancer. Prevalent CVD was defined as heart attack, angina or stroke diagnosis, and prevalent CHD as heart attack or angina diagnosis. This questionnaire also asked participants to rate their present state of health as excellent, good, fair or poor and enquired whether they had any long-standing illness or disability. Mobility limitation was determined by whether participants stated they had difficulty either going up/down stairs or walking for a quarter of a mile on a level surface[303]. Lung function was assessed at the re-examination in 1998-2000, providing measurements of forced expiratory volume in 1 second (FEV_1). FEV_1 was height-standardised to the mean height in this study (1.72m)[289]. Additionally, at the re-examination participants were asked to report whether their weight had changed in the previous 3 years (weight loss; no change; gain or fluctuation). A dichotomous weight loss variable was created: yes (weight loss) and no (no change; gain or fluctuation).

4.4.5. Statistical methods

Pearson correlation coefficients were used to assess the relationships between various measures of body composition. The distributions of HOMA-IR, CRP, D-dimer, IL-6 and homocysteine were highly skewed and were log transformed. Descriptive characteristics of participants were presented by quartiles of the distribution of MAMC and FFMI and by the four WC groups, and p values for trend were obtained fitting MAMC/FFMI/WC continuously using regression analyses, adjusting for age and BMI, fitted as continuous variables. Descriptive characteristics of participants were also presented by four sarcopenic obesity groups (as defined in section 4.4.3) and p values for differences between groups were obtained using chi squared tests for proportions and analysis of variance (ANOVA) for means.

Multiple logistic regression was used to provide odds ratios, and 95% CIs, for the associations between low muscle mass (the lowest quartile of MAMC/FFMI compared to the reference group of the highest three quartiles combined) and cardiovascular risk factors. Continuous dietary, metabolic and inflammatory risk factors were divided into quartiles and odds ratios for low muscle mass were presented for the highest versus the lowest quartile. Models were adjusted for potential confounders, which are related to muscle mass, in a sequential manner including age (model 1), adding BMI and behavioural risk factors (model 2) and adding morbidity variables (model 3). In addition, to adjust for total energy intake this variable was included in the models for all dietary variables assessed by the FFQ[280]. Age, BMI, FEV_1 and energy intake were fitted as continuous variables. Smoking, physical activity, alcohol, social class, CVD, diabetes, cancer and poor/fair health were fitted as categorical variables.

4.5. Results

Among 4252 men aged 60-79 years who attended the 20 year re-examination, the mean age was 69 years. A small proportion of the cohort were current smokers (12.8%), heavy drinkers (3.0%) or physically inactive (11.5%). Just over half of the men had a manual occupational social class (51.0%).

4.5.1. **Body composition characteristics of the study population**

The mean body composition measures of the cohort are presented in Table 4.1. Of the 4252 men attending the physical examination, 4204 had MAMC data, 4114 had FFMI data and 4225 had WC data for analysis. Defining adiposity using BMI, over two-thirds of the participant were overweight (BMI $\geq$ 25 kg/m^2, n = 2944, 69.6%) and almost one in five were obese (BMI $\geq$ 30 kg/m^2, n = 735, 17.4%). The proportion of participants classified as obese was higher when measures of central adiposity were used. Using the established sex-specific WC definition (WC >102cm), 29.4% of participants were classified as obese and using the established sex-specific WHR definition (WHR $\geq$ 0.90 cm) 80.0% were classified as obese. However, when a more stringent WHR definition was applied (WHR $\geq$ 1.00 cm), only 18.7% of participants were classified as obese. Using bioelectrical impedance-based measures of body composition, just over a third of the mean body weight of participants (80.1kg) was fat mass (FM = 35.1 %) and almost two-thirds was lean mass (FFM = 64.9 %). Using an alternative fat-free mass estimate[150], skeletal mass (SM) contributed a mean of 39.0% of the total mass of participants.

4.5.2. **Correlations between body composition measures**

The Pearson correlation coefficients between various body composition measures are shown in Table 4.2. Strong positive correlations was found between key measures of adiposity, including BMI and WC (r = 0.87, p <0.01), BMI and FMI (r = 0.81, p <0.01) and WC and FMI (r = 0.76, p <0.01). A moderate positive correlation was found between BMI and WHR (r = 0.55, p <0.01). Only modest positive correlations were found between BMI, WC or WHR with subscapular or triceps skinfold measures (r = 0.29 to 0.63, p <0.01). FFMI and SMI, two measures of muscle mass derived from BIA but using different formulae, showed a near perfect positive correlation (r = 0.99, p <0.01). MAMC, a measure of regional muscle mass, showed weak to moderate correlations with FFMI (r = 0.41, p <0.01) and SMI (r = 0.36, p <0.01). Observed correlations between measures of adiposity and measures of muscle mass varied, ranging from a weak negative association (FMI and FFMI, r = -0.07, p <0.01) to a moderate positive correlation (BMI and MAMC, r = 0.61, p <0.01).

4.5.3. Muscle mass and cardiovascular risk factors

In this chapter, results are presented for two markers of muscle mass (MAMC and FFMI) in relation to cardiovascular risk factors. Results are only presented for FFMI, and not SMI, since these two BIA-derived measures of muscle mass were highly correlated (Table 4.2) and showed virtually identical results in relation to cardiovascular risk factors.

4.5.3.1 Mid-arm muscle circumference and cardiovascular risk factors

Cardiovascular risk factors in relation to quartiles of MAMC are presented in Table 4.3. MAMC showed a strong inverse association with age and a strong positive association with BMI. After adjustment for age and BMI, MAMC was inversely associated with smoking, heavy drinking, physical inactivity and manual occupational social class. Several dietary variables, including intakes of energy, fibre, vitamin C, iron, daily fruit intake, daily vegetable intake and plasma vitamin E showed significant positive linear trends with MAMC. In contrast, the percent of energy intake from fat showed a significant inverse linear trend with MAMC, but no significant association was seen with percent of energy from saturated fat. Central obesity showed a significant positive linear trend with MAMC in age-adjusted analysis. HOMA-IR and high glucose were inversely associated with MAMC, after adjustment for age and BMI, while hypertension, high triglycerides, low HDL and the metabolic syndrome showed no associations. MAMC showed inverse graded associations with all of the inflammatory/hemostatic markers (CRP, t-PA, D-dimer, vWF, fibrinogen, IL-6 and homocysteine) after age and BMI adjustment. MAMC showed a significant positive association with FEV_1 and a significant inverse association with prevalent CVD, CHD, heart failure, poor/fair self-rated health, long-standing illness/disability, mobility limitation and weight loss in the past 3 years, after age and BMI adjustment ($p<0.01$).

Table 4.4 shows the relationships between low muscle mass and cardiovascular risk factors, with age-adjusted odds ratios for the lowest quartile of MAMC compared to the reference group of the other three quartiles combined. Current smoking and heavy drinking were initially associated with increased odds of low muscle mass in the age-adjusted model. However, these associations were attenuated after additional adjustment

for BMI, and behavioural variables. In the fully adjusted model (further adjusted for morbidity variables), the only socio-demographic/behavioural variables significantly associated with increased odds of low MAMC were physical inactivity and manual social class. Men in the highest quartile (compared to the lowest) of percent of energy from protein, vitamin C intake, plasma vitamin E, and daily fruit consumers, were at significantly lower odds of low MAMC, adjusting for age. However, after additional adjustments for BMI, behavioural and morbidity variables, these associations were markedly attenuated and became statistically non-significant. Men with high energy intake and high percentage energy from carbohydrates had lower odds of low MAMC even after adjustment for age, BMI, behavioural and morbidity variables. In contrast, men with a high percentage energy from fat showed higher odds of low MAMC. High HOMA-IR and blood glucose were associated with increased odds of low MAMC after full adjustment. No independent association was seen with other metabolic risk factors. HOMA-IR was strongly correlated with obesity ($r = 0.45$, $p<0.001$), which explains why the direction of association changed after BMI adjustment. High levels of CRP, vWF and fibrinogen were associated with increased odds of low MAMC after adjustment for BMI, behavioural and morbidity variables. However, D-dimer, t-PA, IL-6 and homocysteine were not significantly associated with low MAMC.

4.5.3.2 Fat-free mass index and cardiovascular risk factors

Cardiovascular risk factors are presented by quartiles of FFMI in Table 4.5. Similar linear trends were observed between variables and FFMI quartiles, compared to MAMC quartiles. Table 4.6 shows the relationships between low muscle mass and cardiovascular risk factors, with odds ratios for the lowest quartile of FFMI compared to the reference group of the other three quartiles combined. As for the MAMC-based analyses, consistent statistically significant associations were also observed, with those in the lowest FFMI quartile having an increased odds of physical inactivity, a lower percent of energy from carbohydrates, and higher levels of HOMA-IR, CRP, vWF and fibrinogen after adjustment for age, BMI, behavioural and morbidity variables. However, in contrast to MAMC-based analyses, low plasma vitamin C, and higher levels of central obesity, high triglycerides, t-PA and the metabolic syndrome were also statistically significantly associated with low FFMI.

4.5.4. Adiposity and cardiovascular risk factors

As highlighted in section 4.2, the associations between adiposity and established and emerging cardiovascular risk markers are well established in the elderly, with a previous report from the BRHS already presenting the associations between adiposity (including BMI, WC, WHR and FM) and metabolic abnormalities and insulin resistance[267]. In this chapter, results are presented for one measure of adiposity (WC) in relation to cardiovascular risk factors, which will extend previous work in this cohort[267] to also include emerging cardiovascular risk factors. WC was chosen as a valid marker of visceral adiposity[304], which is strongly associated with CVD and mortality in older subjects[13;79;122;125-127].

4.5.4.1 Waist circumference and cardiovascular risk factors

Cardiovascular risk factors in relation to WC groups are presented in Table 4.7. After adjustment for age and BMI, WC showed a strong inverse trend with current smoking and a strong positive trend with heavy drinking and physical inactivity. Several dietary variables were related to WC, with inverse trends seen with percent of energy from carbohydrate, percent of energy from protein, fibre, vitamin C intake, daily fruit intake and plasma vitamin C, and a positive linear trend with percent of energy from fat and percent of energy from saturated fat. Several metabolic variables were associated with WC, with significant positive trends seen with increasing mean HOMA-IR levels, and the proportion of participants with high triglycerides, low HDL, high glucose and the metabolic syndrome. Strong positive linear trends were also seen between WC and all of the inflammatory/hemostatic markers (CRP, t-PA, D-dimer, vWF, fibrinogen, IL-6 and homocysteine) after adjustment for age and BMI.

4.5.5. Combined measures of adiposity and muscle mass and cardiovascular risk factors

4.5.5.1 Waist circumference, mid-arm muscle circumference and cardiovascular risk factors

Both WC and MAMC measurements were available for 4178 of the 4252 participants attending the re-examination in 1998 to 2000. Using these anthropometric measures to classify participants into sarcopenic obesity groups, 36.1% of men were defined as non-sarcopenic, non-obese, 35.1% were sarcopenic only, 24.1% were obese only and 4.7% had sarcopenic obesity. Cardiovascular risk factors in the four sarcopenic obesity groups (defined by MAMC and WC) are presented in Table 4.8. Mean age was highest in the sarcopenic obese group, with a significant difference between groups. All cardiovascular risk factors, apart from two dietary variables (vitamin E and iron), showed significant differences between sarcopenic obesity groups ($p \leq 0.05$).

The non-sarcopenic, non-obese group was generally associated with the lowest levels of many cardiovascular risk factors. The sarcopenic only group displayed the greatest proportion of current smokers and self-reported weight loss, the lowest percent of energy intake from protein, the lowest vitamin C intake, the lowest proportion of daily fruit and vegetable intake and the highest percent of energy intake from carbohydrates. The obese only group showed the highest proportion of heavy drinkers, the lowest mean fibre intake, the highest levels of HOMA-IR, the highest proportion of the metabolic syndrome (and the highest proportion of each individual component of the metabolic syndrome) and the highest levels of D-dimer and t-PA. The sarcopenic obesity group had the highest proportion of physically inactive individuals, the highest proportion of manual social class, the highest total energy intake, the highest percent of energy from fat and saturated fat, the lowest plasma vitamin C and plasma vitamin E levels, the lowest mean FEV_1, and the highest mean levels of several inflammatory/hemostatic markers (CRP, vWF, fibrinogen, IL-6 and homocycsteine).

4.5.5.1 Fat mass index, fat-free mass index and cardiovascular risk factors

Both FMI and FFMI measurements were available for 4111 of the 4252 participants attending the re-examination between 1998 and 2000. Using these BIA-derived

measures to classify participants into sarcopenic obesity groups, 41.2% of men were defined as non-sarcopenic, non-obese, 29.5% were sarcopenic only, 18.8% were obese only and 10.6% were sarcopenic obese. The prevalence of sarcopenic obesity defined using BIA derived measures was more than double the prevalence compared to the definition using MAMC and WC (Section 4.5.5.1). Cardiovascular risk factors in relation to four sarcopenic obesity groups, defined by FMI and FFMI, are presented in Table 4.9.

Broadly similar results were observed defining sarcopenic obesity groups using FMI and FFMI to those obtained using MAMC and WC measurements (Section 4.5.5.1). However, there were no significant differences between sarcopenic obesity groups in the proportion of heavy drinkers, mean percent of energy intake from saturated fat, proportion consuming fruit intake daily, mean D-dimer levels, mean homocysteine levels and the proportion with weight loss in the past three years. In contrast to the MAMC and WC definition of sarcopenic obesity groups, BIA derived measured showed that the obese only group had the highest proportion of physically inactive individuals, the highest proportion of manual social class, the highest percent of energy intake from fat and saturated fat, and the highest mean levels of IL-6, and the sarcopenic obese group had the lowest proportion consuming vegetables daily and the highest mean t-PA levels.

4.6. Discussion

4.6.1. Summary of main findings

This chapter has examined the cross-sectional associations between measures of low muscle mass and obesity, combined measures of these body composition components and cardiovascular risk factors. Several established and emerging cardiovascular risk factors in this study of older British men were related to low muscle mass, based on consistent associations with both MAMC and FFMI. Individuals with lower muscle mass had a higher prevalence of physical inactivity, lower percent of energy intake from carbohydrates, higher mean levels of insulin resistance and higher levels of inflammatory and hemostatic markers including CRP, fibrinogen and vWF, which were

all independent of the effects of age, BMI, behavioural and morbidity variables. Classifying participants into four sarcopenic obesity groups, the sarcopenic obese group (defined using combinations of MAMC and WC, and also FFMI and FMI) had significantly higher levels of inflammatory and haemostatic markers (CRP, vWF and fibrinogen) than the sarcopenic only, obese only or non-sarcopenic, non-obese groups.

4.6.2. **Comparison with previous studies**

4.6.2.1 Body composition and socio-demographic/behavioural variables

Physical inactivity was the behavioural risk factor most strongly associated with low MAMC and FFMI. Levels of physical inactivity were elevated in the sarcopenic, obese and sarcopenic obese groups, compared to the non-sarcopenic, non-obese group, and physical inactivity was highest in the sarcopenic obese group when defined using MAMC and WC. This is consistent with previous literature showing that physical inactivity is an important contributor to loss of muscle mass and strength at all ages[131;138;305;306].

Men with low muscle mass (whether defined using MAMC or FFMI) had the highest proportion of current smokers. However, after adjustment for age, BMI and behavioural variables, this association was attenuated. A recent meta-analysis of studies examining the associations between smoking and sarcopenia reported a modest association between smoking and sarcopenia in men (OR: 1.20, 95% CI: 1.06 - 1.35)[307]. However, there were inconsistencies in results of the 12 individual studies included, which may have reflected different approaches to measuring both smoking status and sarcopenia. In the present study, the proportion of men with heavy alcohol intake differed between sarcopenic obesity groups, when defined by MAMC and WC, with the highest proportion of heavy drinkers in the obese only group. However, in the present study, heavy alcohol intake was not significantly associated with low muscle mass, which is consistent with previous literature[131;305]. The proportion of men from a manual occupational social class was highest in the sarcopenic obese and obese groups respectively for MAMC and WC, and FFMI and FMI definitions. The odds of low MAMC were significantly increased in men from a manual occupational social class. This finding conflicts with the results of a previous study, which reported that average

forearm muscle cross-sectional area was higher among men of manual social class, but these analyses were unadjusted for physical activity as an important confounder[308].

4.6.2.2 Body composition and dietary risk factors

A high percentage energy intake from carbohydrates was associated with lower odds of both low MAMC and FFMI, after adjustment for confounders. To my knowledge, this is the first suggestion that high percentage energy intake of this macronutrient may be associated with low muscle mass. There was an association between low energy intake and low MAMC, emphasising the need for an adequate calorie intake in older adults. This is consistent with previous literature suggesting that energy intake is important for the prevention of low muscle mass[132]. Men with a higher percentage energy from fat showed higher odds of low MAMC. This result is consistent with a British study of women aged 18-79 years, which showed inverse associations between FFM and percentage energy from fat, saturated fatty acids, monounsaturated fatty acids, and trans-unsaturated fatty acids and a positive association with the polyunsaturated-to-saturated fatty acid ratio[309]. No other dietary variables were significantly associated with low MAMC or FFMI, contrasting with previous studies showing independent relationships between sarcopenia and dietary variables, in particular protein and antioxidant nutrients vitamin C and vitamin E[132;133;309]. However, looking at dietary intake by sarcopenic obesity groups (using both the MAMC/WC definitions and the FFMI/FMI definition) the sarcopenia group had the lowest percent of energy intake from protein and the lowest mean vitamin C intake. The relationship between overall diet quality and sarcopenia will be explored in Chapter 6 and Chapter 8.

4.6.2.3 Body composition and metabolic variables

Insulin resistance was the only metabolic risk factor significantly associated with both low MAMC and FFMI, after adjustment for age, BMI, behavioural and morbidity variables. This is consistent with the findings of earlier research showing that insulin resistance is inversely associated with low muscle mass, independent of obesity, and may explain why diabetics are prone to sarcopenia[153;169;310]. High triglycerides were significantly associated with increased odds of low muscle mass (defined using FFMI

only) which supports previous research in an elderly Korean cohort which showed an association between sarcopenia and dyslipidemia[154].

However, in conflict with the above results, when examining metabolic risk factors by sarcopenic obesity groups (defined using MAMC/WC and FFMI/FMI), levels of insulin resistance and the prevalence of the metabolic syndrome, were higher in the obese group, followed by the sarcopenic-obese group. This result was contrary to expectations based on previous studies which have found that the sarcopenic obese group have the highest risk of metabolic variables[154;155;160-167;169]. However, results found here are consistent with a study of older adults from the New Mexico Aging Process Study, aged 60 years or over, which reported that the prevalence of MetS and hypertension was highest in the non-sarcopenic obese group, followed by the sarcopenic obese group (assessed using DXA measurements)[170].

4.6.2.4 Body composition and inflammatory/hemostatic variables

Three inflammatory/hemostatic markers (CRP, vWF and fibrinogen) were significantly associated with both low MAMC and FFMI. This is consistent with the results of some other studies and a review suggesting sarcopenia is a low-level inflammatory state driven by cytokines and oxidative stress[157-159;174]. The association described in this chapter between vWF and low muscle mass was novel and consistent with a review suggesting that endothelial dysfunction may contribute to sarcopenia development[300]. The lack of association between D-dimer, IL-6, homocysteine and low MAMC or FFMI supports evidence showing no consistent association between high IL-6 and sarcopenia[158], but is contrary to research showing associations between these three biomarkers and sarcopenia[159;174].

When examining levels of inflammatory and hemostatic markers by sarcopenia and obesity groups, the sarcopenic obese group (defined using MAMC/WC and FFMI/FMI) had the highest levels of CRP, vWF and fibrinogen compared to the sarcopenic only, obese only and non-obese non-sarcopenic groups. The sarcopenic obese group also had the highest IL-6 levels, when using the WC/MAMC definition only. Previous literature

has shown conflicting results regarding the relationship between inflammatory and haemostatic markers and sarcopenic obesity. These results are comparable to those from the InCHIANTI study, in participants aged 65 years and older, which showed that sarcopenic obesity (based on grip strength and WC measurements) was associated with increased levels of CRP and IL-6[173] and a study of Korean adults which showed that sarcopenic obese women had the highest CRP levels[167]. However, these results conflict with those from baseline data from the Trial of Angiotensin Converting Enzyme Inhibition and Novel Cardiovascular Risk Factors study, which found no significant interactions between sarcopenia and obesity with CRP or IL-6[174], while another study found that CRP levels did not differ significantly between sarcopenic obese and non-sarcopenic, non-obese postmenopausal women[172].

4.6.3. **Strengths and limitations**

A major strength of the results presented in this chapter is that data are from a moderately large population-based, geographically and socioeconomically representative, cohort of older British men[35;264]. Also, two different measures of muscle mass and two different sarcopenic obesity definitions have been compared in relation to an extensive range of established and emerging cardiovascular risk factors. Gold standard measurements of adiposity or muscle mass such as computerised tomography (CT) scanning or magnetic resonance imaging (MRI) were not available in this cohort, but such expensive, time-consuming measures are rarely available in non-clinical settings and the anthropometric and BIA measures used represent a practical alternative. The American Heart Association recognises mid-upper arm circumference (MUAC) as a muscle mass proxy[102] and MAMC has been shown to correlate strongly with more accurate DXA measures of lean body mass[147]. Also WC has been shown to be the anthropometric variable, which best correlates with adiposity stores in men, as measured by MRI[304]. The possibility of using imprecise measurements of adiposity and muscle mass is likely to have underestimated, rather than overestimated, the strength of associations observed with cardiovascular risk factors.

Since no universally accepted operational definition of sarcopenia has yet been adopted[17], a standard statistical approach was used to define low muscle mass, including

participants in the first and second quintile of the distribution of MAMC or FFMI. The cut-off used for the lowest two fifths of MAMC (≤ 25.9cm) was comparable to another population-based study of slightly older men (aged ≥ 80 years), which used a cut-off for the lowest tertile of 21.1cm[179]. Similarly, the cut-point for the lowest two fifths of FFMI (16.7 kg/m^2) was comparable to a study in men and women aged 65 years and over[181], where the lowest quartile cut-point was 14.6 kg/m^2. Some differences were observed in the associations between cardiovascular risk factors with MAMC and FFMI as measures of muscle mass and in the different sarcopenic obesity definitions. These differences could be explained by the greater inaccuracy of BIA in assessment of FFMI in older people, predominantly due to fat-free mass hydration variability[311;312].

The European Working Group on Sarcopenia in Older People has suggested defining sarcopenia using both muscle mass and function (strength and performance)[17] and it has been suggested that the age-related loss of muscle mass does not necessary equate to the age-related loss of muscle strength[313]. However, direct measures of muscle function (e.g. grip strength) were not available in this cohort and only markers of muscle mass have been used. Therefore findings are applicable to sarcopenia and sarcopenic obesity as defined by muscle mass, but not muscle strength.

A limitation of the results is that the BRHS comprises older male participants, predominantly of white European ethnic origin, so the findings may not be generalisable to women and non-white ethnic groups. All analyses were cross-sectional in nature so causality of associations between components of body composition and cardiovascular risk factors cannot be established and findings should therefore be interpreted with caution. For example, the observed associations between emerging cardiovascular risk factors (CRP, vWF and fibrinogen) and sarcopenia and sarcopenic obesity, could suggest that inflammatory and heamostatic markers could causally contribute to the development of sarcopenia or conversely that a sarcopenic state could lead to increased levels of inflammatory and heamostatic markers. Therefore further prospective research is needed to explore the causal mechanistic pathways leading to sarcopenia.

Another limitation of results presented here is that measures of body composition and cardiovascular risk factors were assessed at one time point only. Bias from non-participation is also possible, as men too unwell to attend the physical examination would have been excluded, potentially eliminating men with extremely low muscle mass and underestimating observed associations. This may explain why some variables previously reported to be associated with low muscle mass, e.g. protein intake[132;133], were not related in this study. However, the response rate was high and BMI did not differ between respondents and non-respondents[266], suggesting the extent of this bias is limited.

Self-reported variables (smoking status, alcohol intake, physical activity, occupational social class, weight loss and morbidity variables) may have been subject to misclassification. In particular, although the physical activity score used here has been validated by the use of heart rate and lung function[283;284], the measure was self-reported and objective measures would have more accurately captured the exact physical activity level. Previous studies have shown only moderate agreement between self-reported and accelerometry-based estimates, with self-reports tending to overestimate physical activity intensity and total time[314]. Self-reported physical activity can be subject to measurement error. This can be a particular problem in older age groups due to the light intensities of activity and vast variability in duration of activity in these age groups, which makes accurate recall especially difficult[315-317]. However, a validation study in older men within the BRHS has shown self-reported physical activity questions used within this cohort are associated with a graded increase in objectively measured physical activity[318]. This reduces the risk of measurement error and any possible misclassification of physical activity is likely to have been non-differential between body composition groups, with a previous study showing that the correlation between self-reported and objective measures of physical activity is not affected by BMI[319]. Therefore any non-differential misclassification of physical activity level may have led to some residual confounding, but this is only likely to have attenuated relative risk estimates[320].

Self-reported assessment of dietary intake is prone to error through misreporting, which can affect the estimation of energy intake and micronutrient intake[321;322]. In this study,

dietary intake was assessed using a FFQ which is more prone to measurement error and social desirability bias than other self-reported measures such as weighted food records or 24-hour dietary recall[198-200]. In elderly populations in particular non-response to questions could have increased the chance of underreporting of intake[198;323]. However the FFQ used in this study has previously been validated against weighed food intakes in British populations[273;274]. In addition, to reduce the risk of bias in dietary assessment, established minimum and maximum cut-offs for total energy intake were applied to the data (<500 or > 8000 kcal[279]) to exclude under and over-reporters, and all statistical models were adjusted for total energy intake[280]. It is possible, however, that some bias remains, with evidence that underreporting may be greater with increasing BMI[321;324]. Differential misclassification of energy and micronutrient intake could therefore have been possible between different body composition groups, but this is only likely to have under estimated the size of the relative risk estimates.

4.6.4. **Conclusions**

Chapter 4 has shown that both established and emerging cardiovascular risk factors are related to both sarcopenia and sarcopenic obesity. Physical inactivity and higher levels of insulin resistance, CRP, vWF and fibrinogen were significantly associated with increased odds of lower muscle mass (MAMC and FFMI) and a higher percent of energy intake from carbohydrates was significantly associated with decreased odds of low muscle mass after adjustment for age, BMI, behavioural variables and morbidity. With participants classified into four sarcopenic obesity groups, it was apparent that sarcopenic obese individuals had the highest levels of inflammatory and haemostatic markers including CRP, vWF and fibrinogen. However, the cross-sectional nature of the analyses in this chapter means that the causality of associations between components of body composition and cardiovascular risk factors cannot be established. Chapter 5 will examine the prospective associations between components of body composition and the risk of CVD and mortality in older age. In addition, the contribution of established and emerging cardiovascular risk factors, including inflammatory and haemostatic markers, to associations between body composition and CVD risk, will be evaluated.

Table 4.1 Body composition measures of men aged 60-79 years in 1998-2000

Body composition measure	n	Mean (SD)	Range
Weight (kg)	4240	80.1 (12.6)	36.7 - 148.1
Height (cm)	4235	172.3 (6.5)	148.6 - 199.0
Body mass index (kg/m^2)	4232	26.9 (3.7)	14.5 - 47.6
Waist circumference (cm)	4225	97.3 (10.5)	56.8 - 149.1
Hip circumference (cm)	4234	102.5 (7.2)	50.6 - 150.8
Waist-to-hip ratio (cm)	4222	0.9 (0.1)	0.7 - 1.4
Subscapular skinfold (mm)	4167	19.6 (6.3)	1.7 - 47.9
Triceps skinfold (mm)	4208	12.2 (4.5)	2.2 - 39.7
Fat mass (kg)	4111	28.6 (9.6)	0.4 - 82.1
Fat mass (%)	4111	35.1 (8.2)	0.5-66.6
Fat mass index (kg/m^2)	4111	9.6 (3.2)	0.1 - 28.4
Fat-free mass (kg)	4114	51.5 (7.6)	28.4 - 116.6
Fat-free mass (%)	4111	64.9 (8.2)	33.4 - 99.5
Fat-free mass index (kg/m^2)	4114	17.3 (2.2)	9.6 - 35.5
Skeletal muscle (kg)	4164	31.0 (5.4)	17.1 - 79.7
Skeletal muscle (%)	4161	39.0 (6.0)	20.2 - 99.0
Skeletal muscle index (kg/m^2)	4164	10.4 (1.6)	5.8 - 27.2
Mid-upper arm circumference (cm)	4246	30.4 (2.8)	20.0 - 47.3
Mid-arm muscle circumference (cm)	4204	26.5 (2.3)	18.0 - 38.6

SD, standard deviation.

Table 4.2 Correlations between body composition measures in men aged 60-79 years in 1998-2000

Body composition measure	Pearson correlation coefficients*								
	BMI	WC	HC	WHR	Subscapular skinfold	Triceps skinfold	FMI	FFMI	SMI
BMI									
WC	0.87								
HC	0.81	0.81							
WHR	0.55	0.76	0.23						
Subscapular skinfold	0.63	0.61	0.54	0.41					
Triceps skinfold	0.54	0.51	0.50	0.29	0.59				
FMI	0.81	0.76	0.68	0.51	0.55	0.49			
FFMI	0.53	0.38	0.40	0.20	0.26	0.21	-0.07		
SMI	0.44	0.31	0.31	0.16	0.22	0.16	-0.06	0.99	
MAMC	0.61	0.52	0.51	0.30	0.33	0.05	0.42	0.41	0.36

BMI, body mass index; FMI, fat mass index; FFMI, fat-free mass index; HC, hip circumference; MAMC, mid-arm muscle circumference; SMI, skeletal muscle index; WC, waist circumference; WHR, waist-to-hip ratio.

*For all: $p < 0.01$.

Table 4.3 Cardiovascular risk factors by quartiles of mid-arm muscle circumference in men aged 60-79 years in 1998-2000

	MAMC Quartiles (cm)				p-trend (age adjusted)	p-trend (age & BMI adjusted)
	≤ 24.95	24.95-26.45	26.45-27.97	≥ 27.97		
n	1051	1051	1051	1051		
Socio-demographic/Behavioural variables						
Age (years)	70.2 (5.7)	69.3 (5.5)	68.4 (5.3)	67.0 (5.0)	<0.001*	<0.001†
Obesity (BMI ≥ 30 kg/m^2) (%)	2.9	7.7	17.1	39.4	<0.001	n/a
Current smokers (%)	17.9	14.1	9.8	9.4	<0.001	<0.001
Heavy drinkers (%)	3.8	3	2.5	2.4	0.29	0.03
Physically inactive (%)	15.1	9.4	10.2	10.8	0.09	<0.001
Manual social class (%)	53.2	49.1	50.1	50.8	0.3	<0.001
Dietary variables						
Energy intake (kcal)	2125.7 (524.4)	2125.6 (528.6)	2100.4 (524.3)	2103.0 (542.4)	0.41	0.02
Carbohydrates (% kcal)	53.1 (6.9)	52.8 (6.9)	52.5 (6.9)	52.1 (7.1)	<0.001	0.06
Protein (% kcal)	15.4 (2.3)	15.7 (2.4)	15.8 (2.3)	15.8 (2.3)	0.001	0.10
Fat (% kcal)	30.5 (6.1)	30.1 (6.2)	29.9 (6.3)	30.0 (6.3)	0.99	0.04
Saturated fat (% kcal)	12.5 (3.6)	12.2 (3.5)	12.1 (3.7)	12.3 (3.6)	0.96	0.16
Fibre (g/day)	25.6 (9.0)	26.1 (8.6)	25.8 (8.5)	26.2 (8.9)	0.25	<0.001
Vitamin C (mg/day)	79.2 (36.3)	82.8 (36.3)	83.7 (36.2)	87.1 (39.5)	<0.001	0.001
Vitamin E (mg/day)	8.4 (4.8)	8.4 (4.8)	8.5 (4.7)	8.5 (5.0)	0.31	0.08
Iron (mg/day)	14.0 (5.1)	14.4 (5.5)	14.1 (5.0)	14.2 (5.3)	0.26	<0.001
Daily fruit intake (%)	40.5	42.8	44.7	44.2	0.002	0.01
Daily vegetable intake (%)	30.9	32.9	33.2	35.1	0.002	<0.001
Plasma vitamin C (µmol/L)	30.1 (28.9)	30.1 (28.6)	31.0 (27.9)	29.5 (23.5)	0.39	0.26
Plasma vitamin E (µmol/L)	32.1 (11.4)	33.8 (12.0)	34.3 (11.8)	33.8 (12.2)	0.001	0.01

Table 4.3 *Continued*. Cardiovascular risk factors by quartiles of mid-arm muscle circumference in men aged 60-79 years in 1998-2000

	MAMC Quartiles (cm)				p-trend (age adjusted)	p-trend (age & BMI adjusted)
	≤ 24.95	24.95-26.45	26.45-27.97	≥ 27.97		
Metabolic variables						
HOMA-IR‡	1.9 (1.1-2.7)	2.1 (1.4-3.0)	2.3 (1.5-3.2)	2.7 (1.7-4.0)	<0.001	0.002
Central obesity (%)	9	19.5	31.9	54.7	<0.001	n/a
Hypertension (%)	53.8	56.1	62.9	63.4	<0.001	0.32
High triglycerides (%)	33.4	42.4	46.8	56.9	<0.001	0.08
Low HDL (%)	15.2	18.7	21.3	27.9	<0.001	0.77
High glucose (%)	25	24.2	23.5	27.3	0.001	0.006
Metabolic Syndrome (%)	13.5	20.8	29.7	42.9	<0.001	0.57
Inflammatory/hemostatic markers						
CRP (mg/L) ‡	1.8 (0.8-3.8)	1.7 (0.8-3.5)	1.7 (0.8-3.3)	1.7 (0.9-3.4)	0.09	<0.001
t-PA (ng/mL)	10.5 (4.6)	10.9 (4.4)	11.2 (4.5)	11.6 (4.2)	<0.001	0.01
D-dimer (ng/mL) ‡	94.2 (52.0-145.0)	88.4 (50.0-134.0)	83.5 (47.0-128.0)	72.8 (46.0-105.0)	0.002	<0.001
vWF (IU/dL)	147.3 (48.6)	141.2 (46.1)	136.6 (44.1)	134.0 (44.4)	<0.001	<0.001
Fibrinogen (g/L)	3.4 (0.8)	3.3 (0.8)	3.3 (0.7)	3.2 (0.7)	<0.001	<0.001
IL-6 (pg/mL) ‡	2.6 (1.6-3.8)	2.5 (1.6-3.4)	2.6 (1.5-3.4)	2.4 (1.6-3.3)	0.53	<0.001
Homocysteine (μmol/L) ‡	13.2 (10.4-16.0)	12.7 (10.3-14.9)	12.6 (10.3-14.7)	12.2 (10.0-14.2)	0.002	<0.001
Morbidity						
CVD (%)	24.7	22.4	22.5	21.2	0.98	<0.001
CHD (%)	20.7	18.5	19.3	18.2	0.91	<0.001
Stroke (%)	6.9	5.7	5.3	5.6	0.28	0.24
Diabetes (%)	5.9	6.7	6.7	7.8	0.01	0.1
Heart failure (%)	1.8	2.2	1.9	1.3	0.71	0.003
Cancer (%)	7.5	6.6	5.1	5.2	0.19	0.05
Poor/fair self-rated health (%)	30.7	25.5	22.4	25.2	0.007	<0.001

Table 4.3 *Continued*. Cardiovascular risk factors by quartiles of mid-arm muscle circumference in men aged 60-79 years in 1998-2000

		MAMC Quartiles (cm)				p-trend (age adjusted)	p-trend (age & BMI adjusted)
		≤ 24.95	24.95-26.45	26.45-27.97	≥ 27.97		
Disability							
	Long-standing illness/disability (%)	36.2	33.9	31.5	34	0.26	<0.001
	Mobility limitation (%)	23.9	18.6	20.1	21.3	0.68	<0.001
Other							
	FEV_1 (L)	2.4 (0.7)	2.6 (0.7)	2.6 (0.6)	2.7 (0.6)	<0.001	<0.001
	Weight loss in past 3 years (%)	21.3	13.3	14.7	13.5	<0.001	0.001

Values presented as mean (SD) unless otherwise stated.
BMI, body mass index; CHD, coronary heart disease; CRP, C-reactive protein; CVD, cardiovascular disease; FEV_1, forced expiratory volume in 1 second; HOMA-IR, homeostasis model assessment insulin resistance; IL-6, interleukin 6; MAMC, mid-arm muscle circumference; t-PA, tissue plasminogen activator; vWF, von Willebrand factor.
*Unadjusted.
†Adjusted for BMI only.
‡Log-transformed values - geometric mean (interquartile range).

Table 4.4 Odds ratios (95% CI) for low mid-arm muscle circumference by cardiovascular risk factors in men aged 60-79 years in 1998-2000

	Low MAMC (OR, 95% CI)		
	Model 1	**Model 2**	**Model 3**
Socio-demographic/Behavioural variables			
Current smokers	1.87 (1.54-2.28)**	1.12 (0.87-1.44)	1.01 (0.78-1.32)
Heavy drinkers	1.55 (1.04-2.30)*	1.52 (0.93-2.49)	1.54 (0.92-2.56)
Physically inactive	1.43 (1.15-1.76)**	1.97 (1.50-2.59)**	1.69 (1.26-2.27)**
Manual social class	1.14 (0.99-1.31)	1.31 (1.10-1.56)**	1.31 (1.09-1.57)**
Dietary variables			
Energy intake†	0.99 (0.80-1.22)	0.74 (0.57-0.95)*	0.73 (0.56-0.95)*
Carbohydrates (% kcal) †‡	1.17 (0.95-1.43)	0.72 (0.56-0.94)*	0.73 (0.55-0.96)*
Protein (% kcal) †‡	0.78 (0.62-0.96)*	1.21 (0.93-1.59)	1.16 (0.88-1.54)
Fat (% kcal) †‡	1.18 (0.95-1.46)	1.33 (1.03-1.72)*	1.31 (1.00-1.71)*
Saturated fat (% kcal) †‡	1.14 (0.92-1.41)	1.23 (0.95-1.59)	1.24 (0.94-1.62)
Fibre†‡	0.81 (0.65-1.00)	0.93 (0.70-1.22)	0.97 (0.73-1.30)
Vitamin C†‡	0.65 (0.53-0.80)**	0.94 (0.73-1.22)	0.92 (0.70-1.21)
Vitamin E†‡	0.86 (0.69-1.05)	0.95 (0.73-1.25)	0.91 (0.69-1.21)
Iron†‡	0.84 (0.65-1.08)	1.03 (0.75-1.42)	1.01 (0.72-1.41)
Daily fruit intake‡	0.85 (0.73-0.99)*	1.01 (0.84-1.21)	0.98 (0.81-1.18)
Daily vegetable intake‡	0.86 (0.74-1.01)	0.94 (0.78-1.13)	0.94 (0.78-1.14)
Plasma vitamin C†	0.84 (0.69-1.04)	0.77 (0.60-1.00)*	0.82 (0.63-1.07)
Plasma vitamin E†	0.71 (0.57-0.88)**	0.87 (0.67-1.13)	0.88 (0.67-1.15)

Table 4.4 *Continued*. Odds ratios (95% CI) for low mid-arm muscle circumference by cardiovascular risk factors in men aged 60-79 years in 1998-2000

	Low MAMC (OR, 95% CI)		
	Model 1	**Model 2**	**Model 3**
Metabolic variables			
HOMA-IR†	0.37 (0.30-0.46)**	1.64 (1.25-2.17)**	1.60 (1.19-2.17)**
Central obesity	0.18 (0.14-0.22)**	1.07 (0.79-1.44)	0.95 (0.70-1.30)
Hypertension	0.72 (0.63-0.84)**	0.96 (0.81-1.15)	0.94 (0.78-1.12)
High triglycerides	0.54 (0.47-0.63)‡	0.93 (0.77-1.11)	0.86 (0.71-1.04)
Low HDL	0.62 (0.51-0.75)**	1.02 (0.81-1.30)	1.00 (0.78-1.28)
High glucose	0.96 (0.81-1.13)	1.37 (1.11-1.68)**	1.34 (1.07-1.69)*
Metabolic Syndrome	0.34 (0.28-0.42)‡	0.99 (0.77-1.27)	0.89 (0.69-1.16)
Inflammatory/hemostatic markers			
CRP†	0.89 (0.73-1.10)	1.66 (1.28-2.15)**	1.44 (1.09-1.89)*
t-PA†	0.46 (0.40-0.61)**	1.11 (0.85-1.45)	1.01 (0.76-1.33)
D-dimer†	1.15 (0.93-1.43)	1.14 (0.88-1.48)	1.03 (0.79-1.36)
vWF†	1.49 (1.21-1.83)**	1.74 (1.36-2.23)**	1.67 (1.29-2.17)**
Fibrinogen†	1.52 (1.24-1.87)**	1.63 (1.26-2.11)**	1.48 (1.13-1.95)**
IL-6†	1.10 (0.90-1.36)	1.33 (1.02-1.73)*	1.23 (0.94-1.63)
Homocysteine†	1.23 (1.00-1.51)	1.22 (0.95-1.58)	1.20 (0.92-1.57)

Low MAMC = lowest quartile of MAMC (≤ 24.95 cm). Model 1: adjusted for age; Model 2: adjusted for model 1 + BMI, smoking, physical activity, alcohol, social class; Model 3: adjusted for model 2 + morbidity (CVD, diabetes, cancer, FEV_1, poor/fair health).
CRP, C-reactive protein; HOMA-IR, homeostasis model assessment insulin resistance; IL-6, interleukin 6; MAMC, mid-arm muscle circumference; t-PA, tissue plasminogen activator; vWF, von Willebrand factor.
* $p<0.05$ ** $p<0.01$
†Highest vs. lowest quartile
‡Additionally adjusted for energy intake in all models.

Table 4.5 Cardiovascular risk factors by quartiles of fat-free mass index in men aged 60-79 years in 1998-2000

	FFMI Quartiles (kg/m^2)				p-trend (age adjusted)	p-trend (age & BMI adjusted)
	≤ 15.96	15.96-17.09	17.09-18.36	≥ 18.36		
n	1029	1028	1029	1028		
Socio-demographic/Behavioural variables						
Age (years)	69.0 (5.5)	68.8 (5.5)	68.3 (5.5)	68.7 (5.5)	0.19*	0.07†
Obesity (BMI ≥ 30 kg/m^2) (%)	2.7	9.1	16.4	42.0	<0.001	n/a
Current smokers (%)	16.4	12.8	11.4	10.2	<0.001	0.12
Heavy drinkers (%)	3.0	3.2	2.8	3.3	0.77	0.52
Physically inactive (%)	13.4	10.8	9.1	12.6	0.28	<0.001
Manual social class (%)	51.6	49.4	51.7	52.2	0.37	<0.001
Dietary variables						
Energy intake (kcal)	2140.0 (523.6)	2108.4 (514.4)	2107.6 (529.7)	2097.5 (552.2)	0.24	0.2
Carbohydrates (% kcal)	52.9 (6.9)	52.7 (7.0)	52.7 (7.0)	51.9 (6.8)	<0.001	0.13
Protein (% kcal)	15.4 (2.4)	15.6 (2.2)	15.7 (2.3)	16.0 (2.3)	<0.001	0.02
Fat (% kcal)	30.4 (6.2)	30.0 (6.0)	29.9 (6.4)	30.3 (6.1)	0.41	0.27
Saturated fat (% kcal)	12.4 (3.6)	12.2 (3.5)	12.2 (3.8)	12.3 (3.5)	0.67	0.06
Fibre (g/day)	25.6 (8.9)	25.8 (8.5)	26.1 (8.6)	26.3 (9.1)	0.08	<0.001
Vitamin C (mg/day)	80.5 (37.5)	82.1 (35.7)	83.3 (36.2)	86.3 (39.3)	0.002	0.21
Vitamin E (mg/day)	8.6 (5.0)	8.4 (4.7)	8.3 (4.7)	8.6 (4.9)	0.05	0.03
Iron (mg/day)	14.1 (5.3)	14.2 (5.1)	14.1 (5.3)	14.3 (5.1)	0.49	0.01
Daily fruit intake (%)	39.5	44.2	41.7	47.3	<0.001	0.001
Daily vegetable intake (%)	30.0	33.9	32.7	35.0	0.02	0.002
Plasma vitamin C (µmol/L)	28.7 (24.8)	31.2 (30.4)	31.0 (27.9)	29.4 (22.6)	0.59	0.02
Plasma vitamin E (µmol/L)	32.6 (11.5)	33.8 (12.2)	33.6 (12.2)	34.3 (11.8)	0.002	0.03

Table 4.5 *Continued.* Cardiovascular risk factors by quartiles of fat-free mass index in men aged 60-79 years in 1998-2000

	FFMI Quartiles (kg/m^2)				p-trend (age adjusted)	p-trend (age & BMI adjusted)
	≤ 15.96	15.96-17.09	17.09-18.36	≥ 18.36		
Metabolic variables						
HOMA-IR‡	2.0 (1.2-2.9)	2.2 (1.4-3.0)	2.3 (1.4-3.2)	2.7 (1.6-4.0)	<0.001	<0.001
Central obesity (%)	14.6	23.1	31.5	49.6	<0.001	n/a
Hypertension (%)	54.4	60.5	58.4	64.3	0.001	0.02
High triglycerides (%)	40	44.3	46.5	50.5	<0.001	<0.001
Low HDL (%)	15.5	17.6	22.8	27.7	<0.001	0.47
High glucose (%)	23.7	25.6	23.0	29.2	0.004	0.04
Metabolic Syndrome (%)	17.5	23.8	28.6	39.7	<0.001	<0.001
Inflammatory/hemostatic markers						
CRP (mg/L) ‡	1.8 (0.8-3.8)	1.8 (0.8-3.6)	1.7 (0.8-3.3)	1.7 (0.9-3.3)	0.77	<0.001
t-PA (ng/mL)	11.2 (4.7)	11.1 (4.4)	10.7 (4.3)	11.5 (4.4)	0.01	<0.001
D-dimer (ng/mL) ‡	85.1 (49.0-133.0)	83.1 (49.0-123.0)	83.6 (47.0-133.5)	83.9 (50.0-127.0)	0.66	0.71
vWF (IU/dL)	144.6 (48.2)	140.0 (45.7)	136.6 (43.2)	138.6 (47.1)	0.23	<0.001
Fibrinogen (g/L)	3.4 (0.8)	3.3 (0.8)	3.2 (0.7)	3.2 (0.7)	<0.001	<0.001
IL-6 (pg/mL) ‡	2.4 (1.6-3.5)	2.4 (1.6-3.4)	2.4 (1.6-3.4)	2.5 (1.6-3.7)	0.05	<0.001
Homocysteine (µmol/L) ‡	12.9 (10.2-15.5)	12.5 (10.1-14.7)	12.5 (10.1-14.3)	12.8 (10.4-14.8)	0.5	0.11
Morbidity						
CVD (%)	22.7	22.6	21.7	22.8	0.92	<0.001
CHD (%)	18.7	19.1	19.1	19.1	0.78	0.004
Stroke (%)	6.1	5.6	4.8	6.5	0.54	0.19
Diabetes (%)	5.3	5.1	7.4	9.8	<0.001	0.08
Heart failure (%)	2.6	1.3	1.2	1.9	0.48	0.005
Cancer (%)	7.4	5.7	5.9	5.5	0.3	0.18
Poor/fair self-rated health (%)	29.0	23.8	23.5	27.6	0.9	<0.001

Table 4.5 *Continued.* Cardiovascular risk factors by quartiles of fat-free mass index in men aged 60-79 years in 1998-2000

		FFMI Quartiles (kg/m^2)				p-trend (age adjusted)	p-trend (age & BMI adjusted)
		≤ 15.96	15.96-17.09	17.09-18.36	≥ 18.36		
Disability							
	Long-standing illness/disability (%)	33.0	33.5	31.6	36.4	0.12	0.1
	Mobility limitation (%)	21.0	19.9	19.3	23.2	0.09	<0.001
Other							
	FEV_1 (L)	2.5 (0.7)	2.5 (0.6)	2.6 (0.6)	2.6 (0.6)	<0.001	<0.001
	Weight loss in past 3 years (%)	17.0	14.8	14.7	15.3	0.22	0.58

Values presented as mean (SD) unless otherwise stated.
BMI, body mass index; CHD, coronary heart disease; CRP, C-reactive protein; CVD, cardiovascular disease; FEV_1, forced expiratory volume in 1 second; FFMI, fat-free mass index; HOMA-IR, homeostasis model assessment insulin resistance; IL-6, interleukin 6; t-PA, tissue plasminogen activator; vWF, von Willebrand factor.
*Unadjusted.
†Adjusted for BMI only.
‡Log-transformed values - geometric mean (interquartile range).

Table 4.6 Odds ratios (95% CI) for low fat-free mass index by cardiovascular risk factors in men aged 60-79 years in 1998-2000

	Lowest FFMI quartile (OR, 95% CI)		
	Model 1	**Model 2**	**Model 3**
Socio-demographic/Behavioural variables			
Current smokers	1.53 (1.25-1.87)**	1.06 (0.83-1.35)	0.94 (0.73-1.22)
Heavy drinkers	0.99 (0.65-1.50)	0.85 (0.51-1.41)	0.80 (0.47-1.36)
Physically inactive	1.25 (1.00-1.55)*	1.67 (1.28-2.18)**	1.43 (1.07-1.90)*
Manual social class	1.02 (0.89-1.18)	1.09 (0.92-1.30)	1.04 (0.87-1.24)
Dietary variables			
Energy intake†	1.19 (0.97-1.45)	1.05 (0.83-1.35)	1.03 (0.81-1.33)
Carbohydrates (% kcal) †‡	1.19 (0.97-1.46)	0.77 (0.59-0.99)*	0.76 (0.58-0.99)*
Protein (% kcal) †‡	0.66 (0.53-0.82)**	0.89 (0.69-1.14)	0.89 (0.68-1.16)
Fat (% kcal) †‡	1.07 (0.86-1.32)	1.21 (0.95-1.56)	1.24 (0.96-1.60)
Saturated fat (% kcal) †‡	1.06 (0.86-1.31)	1.13 (0.88-1.45)	1.17 (0.91-1.52)
Fibre†‡	0.77 (0.62-0.96)*	0.84 (0.65-1.10)	0.85 (0.64-1.12)
Vitamin C†‡	0.73 (0.59-0.90)**	1.00 (0.78-1.28)	0.98 (0.76-1.28)
Vitamin E†‡	0.93 (0.75-1.16)	1.11 (0.85-1.44)	1.05 (0.80-1.37)
Iron†‡	0.71 (0.55-0.91)**	0.77 (0.57-1.04)	0.77 (0.56-1.06)
Daily fruit intake‡	0.82 (0.70-0.95)**	0.92 (0.77-1.09)	0.89 (0.75-1.07)
Daily vegetable intake‡	0.82 (0.70-0.96)**	0.85 (0.71-1.01)	0.83 (0.69-1.00)
Plasma vitamin C†	0.78 (0.63-0.96)*	0.70 (0.54-0.89)**	0.71 (0.55-0.92)*
Plasma vitamin E†	0.79 (0.64-0.98)*	0.89 (0.69-1.14)	0.93 (0.72-1.20)

Table 4.6 *Continued*. Odds ratios (95% CI) for low fat-free mass index by cardiovascular risk factors in men aged 60-79 years in 1998-2000

	Lowest FFMI quartile (OR, 95% CI)		
	Model 1	**Model 2**	**Model 3**
Metabolic variables			
HOMA-IR†	0.52 (0.43-0.65)**	2.14 (1.63-2.81)**	2.22 (1.65-2.98)**
Central obesity	0.32 (0.27-0.39)**	2.21 (1.69-2.90)**	2.01 (1.52-2.67)**
Hypertension	0.75 (0.65-0.87)**	1.04 (0.88-1.23)	1.00 (0.84-1.19)
High triglycerides	0.76 (0.65-0.88)**	1.35 (1.13-1.61)**	1.32 (1.10-1.59)**
Low HDL	0.63 (0.52-0.76)**	0.97 (0.77-1.22)	0.98 (0.77-1.24)
High glucose	0.89 (0.75-1.05)	1.20 (0.99-1.47)	1.20 (0.96-1.49)
Metabolic Syndrome	0.48 (0.40-0.58)**	1.38 (1.09-1.73)**	1.30 (1.02-1.66)*
Inflammatory/hemostatic markers			
CRP†	1.05 (0.86-1.29)	2.04 (1.58-2.64)**	1.94 (1.48-2.54)**
t-PA†	0.91 (0.74-1.11)	2.46 (1.90-3.18)**	2.33 (1.78-3.04)**
D-dimer†	0.99 (0.80-1.22)	0.97 (0.76-1.25)	0.91 (0.70-1.19)
vWF†	1.36 (1.10-1.66)**	1.48 (1.17-1.88)**	1.57 (1.22-2.02)**
Fibrinogen†	1.47 (1.20-1.80)**	1.55 (1.21-1.98)**	1.52 (1.17-1.96)**
IL-6†	0.93 (0.75-1.14)	1.19 (0.92-1.53)	1.13 (0.86-1.47)
Homocysteine†	1.15 (0.94-1.42)	1.12 (0.87-1.43)	1.09 (0.84-1.41)

Low FFMI = lowest quartile of FFMI ($\leq$ 15.96 kg/m^2). Model 1: adjusted for age; Model 2: adjusted for model 1 + BMI, smoking, physical activity, alcohol, social class; Model 3: adjusted for model 2 + morbidity (CVD, diabetes, cancer, FEV_1, poor/fair health).

CRP, C-reactive protein; FFMI, fat-free mass index; HOMA-IR, homeostasis model assessment insulin resistance; IL-6, interleukin 6; t-PA, tissue plasminogen activator; vWF, von Willebrand factor.

* $p<0.05$ ** $p<0.01$

†Highest vs. lowest quartile

‡Additionally adjusted for energy intake in all models.

Table 4.7 Cardiovascular risk factors by waist circumference groups in men aged 60-79 years in 1998-2000

	WC (cm)				p-trend (age adjusted)	p-trend (age & BMI adjusted)
	<94	**94-102**	**103-105**	**≥ 106**		
n	1593	1390	467	775		
Socio-demographic/Behavioural variables						
Age (years)	68.8 (5.7)	68.7 (5.4)	68.5 (5.3)	68.6 (5.3)	0.07*	<0.001†
Obesity (BMI ≥ 30 kg/m^2) (%)	0.1	4.9	24.1	29.2	<0.001	n/a
Current smokers (%)	14.8	12.0	10.9	10.4	<0.001	<0.001
Heavy drinkers (%)	2.3	3.0	3.3	4.4	0.001	<0.001
Physically inactive (%)	8.7	8.9	12.2	20.6	<0.001	0.006
Manual social class (%)	48.0	49.4	52.7	59.0	<0.001	0.47
Dietary variables						
Energy intake (kcal)	2139.7 (515.4)	2111.7 (539.9)	2097.3 (511.3)	2076.4 (551.4)	0.004	0.06
Carbohydrates (% kcal)	53.6 (6.6)	52.6 (7.0)	51.6 (7.3)	51.1 (7.0)	<0.001	0.006
Protein (% kcal)	15.5 (2.3)	15.7 (2.3)	15.8 (2.3)	16.0 (2.5)	<0.001	<0.001
Fat (% kcal)	29.8 (6.0)	30.1 (6.3)	30.2 (6.3)	30.8 (6.5)	<0.001	0.04
Saturated fat (% kcal)	12.1 (3.5)	12.3 (3.6)	12.3 (3.7)	12.6 (3.8)	0.001	0.005
Fibre (g/day)	26.7 (8.9)	25.8 (8.8)	25.3 (9.1)	25.1 (8.5)	<0.001	0.001
Vitamin C (mg/day)	83.0 (36.8)	81.1 (35.6)	85.9 (38.5)	86.2 (40.7)	0.04	0.01
Vitamin E (mg/day)	8.5 (4.7)	8.5 (5.1)	8.3 (4.5)	8.5 (4.8)	0.73	0.23
Iron (mg/day)	14.3 (5.3)	14.2 (5.2)	13.9 (5.1)	13.9 (5.1)	0.008	0.69
Daily fruit intake (%)	44.0	41.5	43.2	44.3	0.67	0.03
Daily vegetable intake (%)	35.2	31.1	32.9	32	0.20	0.15
Plasma vitamin C (µmol/L)	32.2 (28.0)	29.3 (26.3)	29.8 (29.8)	27.2 (24.1)	<0.001	0.002
Plasma vitamin E (µmol/L)	33.3 (12.0)	33.6 (11.8)	34.0 (11.8)	33.9 (12.2)	0.10	0.38

Table 4.7 *Continued.* Cardiovascular risk factors by waist circumference groups in men aged 60-79 years in 1998-2000

	WC (cm)				p-trend (age adjusted)	p-trend (age & BMI adjusted)
	<94	94-102	103-105	≥ 106		
Metabolic variables						
HOMA-IR‡	1.6 (1.1-2.3)	2.3 (1.5-3.1)	2.7 (1.8-3.8)	2.0 (2.3-5.6)	<0.001	<0.001
Hypertension (%)	53.0	58.8	65.4	68.9	<0.001	0.60
High triglycerides (%)	28.7	51.3	55.7	62.7	<0.001	<0.001
Low HDL (%)	12.1	22.8	26.4	32.3	<0.001	0.01
High glucose (%)	19.3	24.4	28.3	36.5	<0.001	<0.001
Metabolic Syndrome (%)	8.2	18.9	55.8	66.2	<0.001	<0.001
Inflammatory/hemostatic markers						
CRP (mg/L) ‡	1.3 (0.6-2.6)	1.8 (0.8-3.4)	2.1 (1.1-3.9)	2.6 (1.3-4.9)	<0.001	<0.001
t-PA (ng/mL)	9.6 (4.2)	11.4 (4.2)	12.0 (4.5)	13.1 (4.4)	<0.001	<0.001
D-dimer (ng/mL) ‡	81.5 (47.0-128.0)	85.0 (49.0-130.0)	83.1 (50.0-125.0)	88.5 (52.0-130.0)	0.003	0.001
vWF (IU/dL)	137.0 (45.5)	138.7 (45.3)	139.8 (44.7)	148.1 (49.0)	<0.001	<0.001
Fibrinogen (g/L)	3.2 (0.7)	3.3 (0.7)	3.3 (0.7)	3.4 (0.7)	<0.001	<0.001
IL-6 (pg/mL) ‡	2.4 (1.4-3.2)	2.4 (1.5-3.3)	2.6 (1.7-3.6)	3.0 (2.0-4.3)	<0.001	<0.001
Homocysteine (µmol/L) ‡	12.4 (10.0-14.7)	12.8 (10.3-14.9)	12.7 (10.4-14.5)	13.6 (10.4-15.2)	0.008	0.001

Values presented as mean (SD) unless otherwise stated.
BMI, body mass index; CRP, C-reactive protein; HOMA-IR, homeostasis model assessment insulin resistance; IL-6, interleukin 6; t-PA, tissue plasminogen activator; vWF, von Willebrand factor; WC, waist circumference.
*Unadjusted.
†Adjusted for BMI only.
‡Log-transformed values - geometric mean (interquartile range).

Table 4.8 Cardiovascular risk factors by sarcopenic obesity groups (defined by mid-arm muscle circumference and waist circumference) in men aged 60-79 years in 1998-2000

	Sarcopenic Obesity Groups (MAMC lowest 2 fifths; WC >102cm)*				p†
	Non-sarcopenic, non-obese	Sarcopenic	Obese	Sarcopenic obese	
Total (%)	1507 (36.1)	1467 (35.1)	1006 (24.1)	198 (4.7)	
Socio-demographic/Behavioural variables					
Age (years)	67.6 (5.3)	70.0 (5.6)	68.2 (5.3)	70.3 (5.5)	<0.001
Obesity (BMI ≥ 30 kg/m^2) (%)	3.9	0.6	56.8	29.8	<0.001
Current smokers (%)	10.6	16.7	10.1	13.3	<0.001
Heavy drinkers (%)	1.9	3.3	4.0	3.1	0.02
Physically inactive (%)	6.2	11.5	16.4	21.0	<0.001
Manual social class (%)	46.6	50.6	55.7	58.1	<0.001
Dietary variables					
Energy intake (kcal)	2129.7 (532.9)	2124.3 (521.6)	2064.6 (522.61)	2179.8 (581.9)	0.005
Carbohydrates (% kcal)	53.1 (6.6)	53.2 (7.0)	51.2 (7.1)	51.4 (7.0)	<0.001
Protein (% kcal)	15.7 (2.2)	15.5 (2.3)	15.9 (2.4)	15.7 (2.5)	<0.001
Fat (% kcal)	29.7 (6.2)	30.2 (6.1)	30.4 (6.4)	31.1 (6.5)	0.004
Saturated fat (% kcal)	12.1 (3.6)	12.4 (3.6)	12.4 (3.7)	13.0 (3.8)	0.01
Fibre (g/day)	26.6 (8.6)	25.9 (9.1)	25.1 (8.7)	25.6 (8.8)	<0.001
Vitamin C (mg/day)	84.6 (36.3)	79.6 (36.1)	85.6 (39.5)	87.8 (39.4)	<0.001
Vitamin E (mg/day)	8.5 (4.8)	8.5 (5.0)	8.4 (4.7)	8.0 (4.1)	0.59
Iron (mg/day)	14.4 (5.2)	14.1 (5.3)	13.8 (5.0)	14.4 (5.8)	0.06
Daily fruit intake (%)	45.5	40.0	43.7	44.0	0.03
Daily vegetable intake (%)	35.8	30.7	32.7	32.3	0.03
Plasma vitamin C (µmol/L)	31.2 (24.6)	30.5 (29.8)	28.3 (26.3)	26.8 (25.6)	0.03
Plasma vitamin E (µmol/L)	34.0 (12.0)	32.8 (11.6)	34.2 (12.0)	31.9 (10.9)	0.004

Table 4.8 *Continued.* Cardiovascular risk factors by sarcopenic obesity groups (defined by mid-arm muscle circumference and waist circumference) in men aged 60-79 years in 1998-2000

	Sarcopenic Obesity Groups (MAMC lowest 2 fifths; WC >102cm)*				p†
	Non-sarcopenic, non-obese	Sarcopenic	Obese	Sarcopenic obese	
Metabolic variables					
HOMA-IR‡	2.0 (1.4-2.8)	1.8 (1.1-2.6)	3.3 (2.1-4.8)	3.2 (2.0-4.2)	<0.001
Hypertension (%)	58.2	52.9	68.2	62.9	<0.001
High triglycerides (%)	43.5	34.9	61.3	50.3	<0.001
Low HDL (%)	19.1	15	31.7	21.7	<0.001
High glucose (%)	20.1	23.4	33.7	33.3	<0.001
Metabolic Syndrome (%)	15.3	11.1	63.7	52.6	<0.001
Inflammatory/hemostatic markers					
CRP (mg/L) ‡	1.4 (0.7-2.7)	1.7 (0.7-3.4)	2.3 (1.2-4.1)	4.8 (1.4-5.5)	<0.001
t-PA (ng/mL)	10.5 (4.2)	10.4 (4.4)	12.7 (4.5)	12.3 (4.4)	<0.001
D-dimer (ng/mL) ‡	76.4 (45.0-116.0)	83.6 (51.0-139.0)	103.4 (50.0-123.0)	101.0 (59.0-152.0)	<0.001
vWF (IU/dL)	132.4 (43.4)	143.1 (46.7)	142.1 (45.8)	156.7 (53.0)	<0.001
Fibrinogen (g/L)	3.2 (0.7)	3.3 (0.7)	3.3 (0.7)	3.4 (0.8)	<0.001
IL-6 (pg/mL) ‡	2.2 (1.4-3.0)	2.5(1.6-3.4)	2.8 (1.8-3.9)	3.1 (2.0-4.3)	<0.001
Homocysteine (µmol/L) ‡	12.3 (10.0-14.2)	13.0 (10.3-15.6)	12.7 (10.3-14.9)	13.4 (10.5-15.65)	<0.001
Other					
FEV_1 (L)	2.8 (0.6)	2.4 (0.7)	2.6 (0.7)	2.3 (0.7)	<0.001
Weight loss in past 3 years (%)	13.7	17.7	15.0	16.1	0.03

Values presented as mean (SD) unless otherwise stated. CRP, C-reactive protein; FEV_1, forced expiratory volume in 1 second; HOMA-IR, homeostasis model assessment insulin resistance; IL-6, interleukin 6; MAMC, mid-arm muscle circumference; t-PA, tissue plasminogen activator; WC, waist circumference; vWF, von Willebrand factor.

*Non-sarcopenic, non-obese (WC ≤ 102 cm, MAMC >25.9cm); sarcopenic (WC ≤ 102 cm, MAMC ≤ 25.9 cm); obese (WC >102 cm, MAMC >25.9 cm); sarcopenic obese (WC >102 cm, MAMC ≤ 25.9 cm).

†p value for difference between groups (x^2 for percentages; ANOVA for means).

‡Log-transformed values - geometric mean (interquartile range).

Table 4.9 Cardiovascular risk factors by sarcopenic obesity groups (defined by fat-free mass index and fat mass index) in men aged 60-79 years in 1998-2000

	Sarcopenic Obesity Groups (FFMI lowest 2 fifths; FMI highest 29.4%)*				p†
	Non-sarcopenic, non-obese	Sarcopenic	Obese	Sarcopenic obese	
n (%)	1692 (41.2)	1211 (29.5)	773 (18.8)	435 (10.6)	
Socio-demographic/Behavioural variables					
Age (years)	68.7 (5.6)	69.2 (5.5)	68.0 (5.3)	68.6 (5.3)	0.0001
Obesity (BMI ≥ 30 kg/m^2) (%)	5.4	0	71.5	17.5	<0.001
Current smokers (%)	11.8	16.8	9.5	10.6	<0.001
Heavy drinkers (%)	2.8	3.2	2.8	4.3	0.43
Physically inactive (%)	8.1	11.1	17.1	15.9	<0.001
Manual social class (%)	48.2	48.3	59.8	55.9	<0.001
Dietary variables					
Energy intake (kcal)	2118.9 (526.6)	2143.8 (519.8)	2061.9 (565.0)	2095.2 (503.1)	0.009
Carbohydrates (% kcal)	52.9 (6.8)	53.2 (6.7)	51.1 (7.1)	51.9 (7.1)	<0.001
Protein (% kcal)	15.7 (2.2)	15.4 (2.3)	16.1 (2.4)	15.5 (2.3)	<0.001
Fat (% kcal)	29.9 (6.1)	30.1 (5.9)	30.6 (6.7)	30.5 (6.3)	0.05
Saturated fat (% kcal)	12.2 (3.6)	12.3 (3.5)	12.5 (3.9)	12.4 (3.5)	0.20
Fibre (g/day)	26.6 (8.9)	25.8 (8.6)	25.3 (8.6)	24.9 (8.7)	<0.001
Vitamin C (mg/day)	83.6 (36.3)	80.8 (35.3)	86.2 (41.1)	81.7 (38.9)	0.01
Vitamin E (mg/day)	8.5 (4.8)	8.5 (4.8)	8.4 (4.8)	8.5 (4.9)	0.98
Iron (mg/day)	14.3 (5.3)	14.2 (5.1)	13.8 (5.1)	13.9 (5.3)	0.13
Daily fruit intake (%)	44.7	41.2	44.5	40.1	0.13
Daily vegetable intake (%)	35.3	32.28	30.72	28.8	0.02
Plasma vitamin C (µmol/L)	31.4 (26.0)	29.8 (27.2)	28.9 (27.7)	27.5 (25.4)	0.03
Plasma vitamin E (µmol/L)	34.1 (12.3)	32.8 (11.3)	33.7 (12.2)	33.2 (12.0)	0.04

Table 4.9 *Continued.* Cardiovascular risk factors by sarcopenic obesity groups (defined by fat-free mass index and fat mass index) in men aged 60-79 years in 1998-2000

	Sarcopenic Obesity Groups (FFMI lowest 2 fifths; FMI highest 29.4%)*				p†
	Non-sarcopenic, non-obese	Sarcopenic	Obese	Sarcopenic obese	
Metabolic variables					
HOMA-IR‡	2.0 (1.3-2.8)	1.8 (1.2-2.5)	3.6 (2.2-5.2)	3.0 (1.9-4.0)	<0.001
Central obesity (%)	16.6	3.3	84	57.1	<0.001
Hypertension (%)	58.1	52.5	68.5	67.5	<0.001
High triglycerides (%)	41	35.4	64.7	56.3	<0.001
Low HDL (%)	20.5	13.3	32.7	23.5	<0.001
High glucose (%)	22.8	21.7	34.1	30.2	<0.001
Metabolic Syndrome (%)	20.7	10.8	61.1	42.6	<0.001
Inflammatory/hemostatic markers					
CRP (mg/L) ‡	1.5 (0.7-2.9)	1.6 (0.7-3.1)	2.4 (1.2-4.6)	2.6 (1.4-5.0)	<0.001
t-PA (ng/mL)	10.3 (4.1)	10.5 (4.5)	12.8 (4.2)	12.9 (4.7)	<0.001
D-dimer (ng/mL) ‡	84.4 (48.0-130.5)	82.4 (49.0-131.0)	83.5 (49.0-125.0)	96.5 (51.0-120.5)	0.92
vWF (IU/dL)	135.5 (44.9)	141.7 (46.4)	142.9 (45.8)	147.1 (49.5)	<0.001
Fibrinogen (g/L)	3.2 (0.7)	3.3 (0.8)	3.3 (0.7)	3.4 (0.8)	<0.001
IL-6 (pg/mL) ‡	2.3 (1.5-3.3)	2.3 (1.5-3.3)	2.8 (1.8-4.0)	2.7 (1.8-3.8)	<0.001
Homocysteine (µmol/L) ‡	12.6 (10.3-14.6)	12.6 (10.1-15.0)	12.5 (10.2-14.7)	13.0 (10.3-15.6)	0.39
Other					
FEV_1 (L)	2.7 (0.7)	2.5 (0.7)	2.5 (0.7)	2.5 (0.7)	<0.001
Weight loss in past 3 years (%)	15.3	16.5	13.7	16.1	0.40

Values presented as mean (SD) unless otherwise stated. CRP, C-reactive protein; FEV_1, forced expiratory volume in 1 second; FMI, fat mass index; FFMI, fat-free mass index; HOMA-IR, homeostasis model assessment insulin resistance; IL-6, interleukin 6; t-PA, tissue plasminogen activator; vWF, von Willebrand factor.

*Non-sarcopenic, non-obese (FMI ≤ 11.1cm, FFMI >16.7cm); sarcopenic (FMI ≤ 11.1cm, FFMI ≤ 16.7cm); obese (FMI >11.1cm, FFMI >16.7cm); sarcopenic obese (FMI >11.1cm, FFMI ≤ 16.7cm).

†p value for difference between groups (x^2 for percentages; ANOVA for means).

‡Log-transformed values - geometric mean (interquartile range).

CHAPTER 5 Prospective associations between body composition and risk of cardiovascular disease and mortality in older British men

5.1. Summary

Important changes to body composition occur with age – typically visceral fat increases and muscle mass decreases (sarcopenia). Sarcopenic obesity refers to the age-associated loss of muscle mass coupled with high adiposity levels. Both obesity and low muscle mass (sarcopenia) have been linked to increased all-cause mortality and morbidity. However, whether sarcopenia is associated with cardiovascular disease (CVD) is not well established and the combined effects of sarcopenia and obesity on the risk of CVD and mortality remain unclear. In this chapter, the prospective associations between various measures of sarcopenia and obesity with the risk of CVD and mortality were examined. 4182 men, aged 60-79 years, from the British Regional Heart Study (BRHS) were followed up from physical examination in 1998-2000 until 2010 for cardiovascular mortality and morbidity. Participants were classified as either non-sarcopenic non-obese, sarcopenic only, obese only, or sarcopenic obese, using baseline anthropometric or bioelectrical impedance analysis (BIA) measurements to define them. Cox proportional hazards regression was used to assess associations with coronary heart disease (CHD) events, CVD events, CVD mortality and all-cause mortality. 1340 deaths, 528 cardiovascular deaths, 865 CVD events and 466 CHD events occurred during a mean follow-up of 11.3 years. Defining sarcopenic obesity groups using waist circumference (WC), as a measure of obesity, and mid-arm muscle circumference (MAMC), as a measure of low muscle mass, the sarcopenic group and the obese group were each significantly associated with increased cardiovascular mortality and all-cause mortality, after adjustment for behavioural variables. Men with both sarcopenia and obesity showed the highest risk of all-cause mortality (hazard ratio [HR]: 1.72, 95% CI: 1.35-2.18) and also an increased risk of cardiovascular mortality, although non-significant (HR: 1.38, 95% CI: 0.91-2.08). Broadly similar associations were observed when defining sarcopenic obesity groups using waist-to-hip ratio (WHR) and MAMC measurements, and using body mass index (BMI) and MAMC showed slightly weaker associations. However, no significant associations with outcomes were observed when using BIA measures for the classification of sarcopenia. Moreover, no association was seen

between sarcopenia or obesity with incident CHD events or CVD events. It is therefore important to consider both muscle mass and adiposity as determinants of CVD mortality and all-cause mortality in older adults. A combination of anthropometric measures of central adiposity (WC or WHR) and muscle mass (MAMC) appear to be the strongest predictors of cardiovascular mortality and all-cause mortality in older men.

5.2. Introduction

Body mass index (BMI) is commonly used to assess obesity, but the relationship between BMI and all-cause mortality is controversial in the elderly. A systematic review and meta-analysis of men and women aged ≥ 65 years found that BMI in the overweight range is not associated with a significantly increased risk of all-cause mortality, while BMI in the moderately obese range is only associated with a modest increase in mortality risk[14]. Important changes to body composition occur with age; typically fat (particularly visceral fat) increases and muscle mass decreases, meaning that overall body weight and BMI may remain relatively unchanged[3]. Since BMI combines both fat and muscle mass, the validity of the use of BMI in measuring the impact of obesity in the elderly may therefore be limited. However, in recent years there has been a focus on visceral/abdominal obesity as a potentially better measure of adiposity than BMI, and meta-analyses have supported this possibility; analysis of 29 cohorts of older men and women aged 65 to 74 years, showed positive associations between WC and all-cause and cardiovascular mortality risks, which was consistent across BMI categories[127].

In contrast, muscle mass has opposing effects on mortality to those of obesity. Prospective studies have shown consistent associations between low muscle mass (sarcopenia), as measured by dual energy X-ray absorptiometry (DXA), BIA, and anthropometric measures, and an increased risk of mortality[178;179;181;183;191]. However, whether sarcopenia is associated with CVD risk is not clearly established. Since adiposity is positively associated with risk of CVD and mortality and muscle mass is inversely associated with mortality, there is a need to combine both these component measures of body composition in the elderly to fully understand the associations of body composition with both CVD risk and

all-cause mortality. Recently the concept of sarcopenic obesity has been developed, which refers to the age-associated loss of muscle mass coupled with high levels of adiposity[18;22]. However, to date no universally accepted operational definition or classification of sarcopenic obesity exists[17] so that prevalence estimates, obtained using differing measurement methods in different study populations, have ranged widely, between about 1% and 15% in men[138].

The combined effects of sarcopenia and obesity on CVD and all-cause mortality have been sparsely studied. The majority of studies examining the associations between sarcopenic obesity and health outcomes have focused on functional capacity or disability or have been cross-sectional rather than longitudinal[152]; there is a paucity of prospective studies examining the concept of sarcopenic obesity on CVD outcomes and mortality. The small number of studies so far reported show that sarcopenic obesity has been linked prospectively to an increased risk of all-cause mortality in study populations with specific prevalent diseases[190;325]. Also, a large longitudinal study, the Cardiovascular Health Study, found that sarcopenic obesity, with the definition of sarcopenia based on muscle strength, was associated with a 23% increased risk of CVD. However, risks were not significantly increased in either the sarcopenic or obese groups alone[177]. A previous report from this cohort examined anthropometric indexes of body composition and found that high WC and low muscle mass, as measured by MAMC, were both associated with all-cause mortality[191]. However the influence of low muscle mass on CVD risk was not explored and the concept of sarcopenic obesity was not examined.

The aim of this chapter is therefore to examine the prospective associations between individual and combined measures of obesity and low muscle mass (sarcopenia) with the risk of CHD events, CVD events, CVD mortality and all-cause mortality in older men (60-79 years). The association of obesity with CVD and mortality has been widely studied in the elderly. However, little is known about the extent to which sarcopenia and the combination of sarcopenia and obesity are associated with risks of CVD and all-cause mortality. This chapter will therefore specifically focus on measures of muscle mass and

composite measures of obesity and low muscle mass in order to address these gaps in research.

5.3. Objectives

The specific objectives of this chapter are:

i) To explore the relationships between a range of adiposity measures and the risk of CHD events, CVD events, CVD mortality and all-cause mortality in older age (60-79 years).
ii) To explore the relationships between a range of muscle mass measures and the risk of CHD events, CVD events, CVD mortality and all-cause mortality in older age.
iii) To examine the combined effects of obesity and low muscle mass (sarcopenia) on the risk of CHD events, CVD events, CVD mortality and all-cause mortality, and to investigate the contribution of established and emerging CVD risk factors to these relationships in older age.

5.4. Methods

5.4.1. Subjects and methods of data collection

Data for this chapter are based on the 20 year re-examination of BRHS participants in 1998-2000, then aged 60-79 years. 4252 men (77% of survivors) completed a mailed questionnaire answering questions on their lifestyle and medical history, attended a physical examination and provided a fasting blood sample[264]. Participants were followed prospectively for cardiovascular mortality and morbidity from re-examination (1998-2000) through to June 2010 and follow-up was achieved for 98% of the cohort participants[35]. Information on deaths was collected through the National Health Service Central Register (death certificates coded using International Classification of Diseases, ninth revision [ICD-9]). Evidence regarding non-fatal events was obtained by on-going reports from general practitioners and by biennial reviews of the patients' medical records[264]. The four outcome measures examined were: CHD events (diagnosis of non-fatal myocardial infarction [MI] or fatal CHD [ICD-9 codes 410-414]); CVD events (diagnosis of non-fatal MI, non-fatal

stroke or fatal CVD [ICD-9 codes 390-459]); CVD mortality (ICD-9 codes 390-459) and all-cause mortality. Two additional outcomes were also considered in further exploratory analysis: non-CVD mortality (all deaths excluding ICD-9 codes 390-459) and cancer mortality (ICD-9 codes 140-209). Participants were censored at date of death or at the end of the study period (June 2010) if still alive.

Of the 4252 men attending the physical examination, 70 men with prevalent heart failure were excluded from the analyses because of their exceptionally high mortality rates, due to the strong association between heart failure and weight loss, and because of the established inverse relationship between BMI and mortality in this group[326]. This left 4182 participants for analyses.

5.4.2. **Measures of adiposity and muscle mass**

Anthropometric measurements at the 20 year re-examination included height, weight, waist circumference, hip circumference, mid-upper arm circumference, triceps skinfold thickness, subscapular skinfold thickness, and also bioelectrical impedance analysis (BIA) as described in detail in Chapter 3 (Section 3.3.1). Adiposity measures included whole body adiposity (BMI and fat mass index [FMI], assessed using BIA), central adiposity (WC, WHR and subscapular skinfold thickness) and peripheral adiposity (triceps skinfold thickness). Muscle mass measures included an anthropometric measurement (MAMC) and BIA measurements (fat-free mass index [FFMI] and skeletal muscle mass index [SMI]). Participants were classified into 5 BMI categories (<18.5, 18.5-24.9, 25-27.4, 27.5-29, ≥ 30 kg/m^2) and 4 WC categories (<94, 94-102, 103-105, ≥ 106 cm). For all other measures of adiposity (FMI, WHR, triceps skinfold thickness, subscapular skinfold thickness) and muscle mass (MAMC, FFMI, SMI) men were divided by quintiles of the distribution. Obesity was defined using established cut-points for BMI (≥ 30 kg/m^2) and cut-points specific for men for WC (>102 cm) and WHR (≥ 1.00 cm)[105]. Recent literature suggests using ≥ 0.90 cm as the WHR cut-point for men[270]. However, since this would have classified 79.8% of participants as obese, a more stringent cut-point of ≥ 1.00 cm was used for this cohort (classifying 18.6% of men as obese). Participants above the percentile point

of FMI corresponding to the obesity cut-off for WC (28.7th percentile in this dataset) were also classified as obese (>11.1 kg/m^2). Since no universally accepted operational definition of sarcopenia has yet been adopted[17], low muscle mass (sarcopenia) was defined as below the second quintile of MAMC (≤ 25.9 cm), FFMI (≤ 16.7 kg/m^2) or SMI (≤ 9.2 kg/m^2); an alternative definition, including only those in the lowest quartile of muscle mass, did not yield adequate numbers in the sarcopenic obesity group and was therefore rejected.

To assess the combined effects of sarcopenia and obesity on the risk of the relevant outcomes, participants were categorised into four non-overlapping groups (non-sarcopenic non-obese, sarcopenic only, obese only and sarcopenic obese), according to different combinations of obesity and sarcopenia classifications.

5.4.3. **Cardiovascular risk factors**

Established and emerging cardiovascular risk factors were measured at the re-examination in 1998-2000, as described in detail in Chapter 3, section 3.3. Cigarette smoking, physical activity and alcohol intake were assessed by a self-administered questionnaire. Participants were classified into four cigarette smoking groups (never smoked; long-term ex-smokers, >15 years; recent ex-smokers, ≤ 15 years; current smokers)[90]. Current physical activity was classified into six groups based on intensity and frequency of exercise (inactive; occasional; light; moderate; moderately vigorous and vigorous)[283]. Alcohol intake was classified into five groups based on the number and frequency of alcoholic drinks consumed per week (none; occasional; light; moderate; heavy)[282]. Social class was measured using the baseline questionnaire in 1978-80, as described in Chapter 3, section 3.3.4. Social class was based on the longest held occupation coded using the Registrar General's occupational classification[285] and participants were classified as manual, non-manual or armed forces.

Systolic blood pressure (SBP) and forced expiratory volume in one second (FEV_1) were assessed by physical examination at the twenty year re-examination in 1998-2000 (see section 3.3.5). FEV_1 was height-standardised to the mean height of this cohort (1.72m)[289]. Plasma concentrations of high density lipoprotein [HDL], C-reactive protein (CRP), D-

dimer and von Willebrand factor (vWF) were measured from fasting blood samples collected at re-examination in 1998-2000 as described in Chapter 3 (section 3.3.6). In addition, at the 20th year examination, participants were classified as having prevalent MI and prevalent stroke, if they had a previous diagnosis, according to self-report. Additionally, at the re-examination participants were asked to report whether their weight had changed in the previous 3 years (weight loss; no change; weight gain or weight fluctuation). A dichotomous weight loss variable was created: yes (weight loss) and no (no change; gain or fluctuation).

5.4.4. **Statistical methods**

Cox proportional hazards regression models were used to calculate age-adjusted hazard ratios (HRs) with 95% CIs for the risk of CHD events, CVD events, CVD mortality and all-cause mortality according to different measures of adiposity and muscle mass. For adiposity measures, the reference categories used were normal BMI (18.5-24.9 kg/m^2), normal WC (<94cm) and the lowest fifths of the distribution of FMI, WHR, triceps skinfold thickness and subscapular skinfold thickness. For muscle mass measures, the reference categories used were the lowest fifths of the distribution of MAMC, FFMI and SMI. A linear trend was tested for by fitting adiposity or muscle mass variables continuously. In addition, a non-linear trend was tested for by adding a quadratic term to the model (the square of the continuous adiposity or muscle mass variable).

Survival analysis was carried out and Kaplan Meier curves were plotted to examine the survival probability of the cohort for all-cause mortality, CVD mortality, CVD events and CHD events, by sarcopenic obesity groups. Cox proportional hazards regression models were also used to calculate adjusted HRs with 95% CIs for the risk of outcomes by sarcopenic obesity groups (defined used various combinations of adiposity and muscle mass). Sarcopenic, obese and sarcopenic obese groups were compared to the non-sarcopenic non-obese group as the reference category. Models were adjusted for potential confounders in a sequential manner based on the risk factors identified as being associated with adiposity or muscle mass in this cohort (see Chapter 4) and in previous literature (see

Chapter 2). Specific confounding variables adjusted for were age (model 1), adding smoking status, alcohol intake, social class and physical activity (model 2), adding prevalent MI, prevalent stroke, HDL, SBP and FEV_1 (model 3), adding CRP, D-dimer, vWF (model 4), and finally weight loss (model 5). Smoking status, alcohol intake, social class, physical activity, prevalent MI, prevalent stroke and weight loss were fitted as categorical variables and age, HDL, SBP, FEV_1, CRP, D-dimer and vWF were fitted as continuous variables. The distributions of CRP and D-dimer were highly skewed so log transformation was used. In addition, the possibility of a sarcopenia x obesity interaction was formally examined, using a Cox proportional hazards model with an interaction term between obesity and sarcopenia (each fitted as binary variables using the cut-points described earlier), adjusting for confounders. Further sensitivity analysis examined the interaction between sarcopenia and obesity, fitting muscle mass as a continuous variable. All Cox models were tested for the proportional-hazards assumption, on the basis of Schoenfeld residuals, which was not found to be violated.

For the Cox regression analysis of sarcopenic obesity groups and outcomes, sensitivity analyses were carried out excluding men with prevalent MI or stroke (n = 653). However, this made no difference to the direction or magnitude of observed associations. Prevalent cases of MI or stroke were therefore included in the analysis and prevalent MI and prevalent stroke was added as covariates to the models (Model 3).

5.5. Results

Analyses were based on 4182 men, aged 60-79 years, who attended the 20 year re-examination. The body composition characteristics of the study population and relationships between cardiovascular risk factors and various measures of adiposity and muscle mass were presented in Chapter 4. Participants were followed up for a mean period of 11.3 years (range: 10.3-12.3 years). During this follow-up period, 1340 men died from all causes; 528 (39.4%) of these deaths were attributed to CVD. Also, 466 men had an incident non-fatal or fatal CHD event, and 865 men had an incident non-fatal or fatal CVD event. The rate of all-cause mortality was 33.4 per 1000 person years, the rate of CVD

mortality was 13.2 per 1000 person years, the rate of CVD events was 22.6 per 1000 person years and the rate of CHD events was 11.9 per 1000 person years.

5.5.1. Adiposity and risk of all-cause mortality, CVD mortality, CVD events and CHD events

The crude incidence and mortality rates for all-cause mortality, CVD mortality, CVD events and CHD events by the different measures of adiposity are presented in Figures 5.1 to 5.6 and the age-adjusted HRs for the risk of outcomes by adiposity measures can be found in Table 5.1. Measures of whole body adiposity (BMI and FMI) and central adiposity (WC) showed statistically significant quadratic relationships with all-cause mortality, but only BMI and WC showed a significant quadratic relationship with cardiovascular mortality. These quadratic relationships may be explained by the high correlation observed between these adiposity measures and measures of muscle mass (see section 4.5.2). Despite a high correlation between BMI and WC, WC showed a stronger positive relationship with all-cause mortality, CVD mortality and CVD events. WHR (an alternative measure of central adiposity) showed a significant positive linear trend with all-cause mortality, CVD mortality and CVD events. Subscapular skinfold thickness showed a slight inverse relationship with all-cause mortality, but no trend with CVD mortality or CVD events. Triceps skinfold thickness did not show any significant trends with all-cause mortality, CVD mortality or CVD events. No significant relationships were seen between any of the adiposity variables and CHD events. Overall, the impact of obesity was best seen for central adiposity measures (WC and WHR) as these were most strongly associated with CVD events, CVD mortality and all-cause mortality. Skinfold thickness measurements were not strongly associated with CVD and all-cause mortality and hence were excluded from further analysis of combined adiposity and muscle mass measures.

5.5.2. Muscle mass and risk of all-cause mortality, CVD mortality, CVD events and CHD events

The crude incidence rates of all-cause mortality, CVD mortality, CVD events, and CHD events by measures of muscle mass are presented in Figures 5.7 to 5.9; age-adjusted HRs for the risk of outcomes by muscle mass measures can be found in Table 5.2. The risks of these outcomes tended to decrease with increasing muscle mass, but with a slight upturn in risk in the highest muscle mass quintile. A significant quadratic trend was observed between MAMC and three of the outcomes, with the lowest risks of all-cause mortality (age-adjusted HR: 0.62, 95% CI: 0.52-0.73), CVD mortality (age-adjusted HR: 0.79, 95% CI: 0.60-1.03) and CHD events (age-adjusted HR: 0.82, 95% CI: 0.62-1.10) in the fourth quintile of MAMC (27.0-28.3 cm). However, these quadratic trends could be explained by the highest muscle mass group having the highest mean BMI; when obese participants were excluded (BMI >30 kg/m^2), there were significant inverse linear trends between MAMC and all-cause mortality (HR: 0.89, 95% CI:0.86-0.91), CVD mortality (HR: 0.91, 95% CI: 0.87-0.95) and CHD events (HR: 0.95, 95% CI: 0.90-0.99), with no evidence of appreciable quadratic trends. No significant quadratic or linear trend was found between MAMC and CVD events, either before or after exclusion of obese individuals. Both FFMI and SMI showed similar initial significant quadratic relationships with all-cause mortality and CVD mortality. SMI showed a significant linear trend with CVD events. No significant trend was found between either FFMI or SMI with CHD events. In overall age-adjusted analysis, MAMC was the strongest predictor of both CVD and all-cause mortality.

5.5.3. Combined measures of adiposity and muscle mass and risk of all-cause mortality, CVD mortality, CVD events and CHD events

As outlined in Chapter 2 (section 2.4), since adiposity is positively associated and muscle mass is inversely associated with risk of CVD and mortality, there is a need to combine both measures to fully understand risk. Different classifications of sarcopenic obesity were explored, starting with obesity and muscle mass variables which emerged as strongly associated with CVD and mortality: WC and MAMC (n = 4111), WHR and MAMC (n =

4108), BMI and MAMC (n = 4118), WC and SMI (n = 4078) and FFMI and FMI (n = 4045).

5.5.3.1 Waist circumference and mid-arm muscle circumference

Defining sarcopenic obesity using WC as a measure of central obesity and MAMC as a measure of low muscle mass (sarcopenia), 1490 (36.2%) men were classified as non-sarcopenic non-obese, 1443 (35.1%) were classified as sarcopenic only, 983 (23.9%) were classified as obese only and 195 (4.7%) were classified as sarcopenic obese. Kaplan Meier survival curves for all-cause mortality, CVD mortality, CVD events and CHD events calculated for each sarcopenic obesity group showed that the survival probabilities for all outcomes were highest in the non-sarcopenic non-obese group and lowest in the sarcopenic obesity group (Figures 5.10 to 5.13).

Table 5.3 shows adjusted HRs for outcomes by sarcopenic obesity groups. Sarcopenic and obese men both had a significantly increased risk of all-cause mortality after adjustment for smoking, alcohol, social class and physical activity (model 2) with the highest risk seen in sarcopenic obese men, compared to non-sarcopenic non-obese (sarcopenic, HR: 1.41, 95% CI: 1.22-1.63; obese, HR: 1.21, 95% CI: 1.03-1.42; sarcopenic obese, HR: 1.72, 95% CI: 1.35-2.18). The increased mortality associated with sarcopenia and sarcopenic obesity (but not obesity) remained after adjustment for prevalent MI, prevalent stroke, HDL, SBP, FEV_1, CRP, D-dimer, vWF and weight loss (model 5) although the HRs were slightly attenuated; 1.34 (1.15-1.57) for sarcopenia and 1.44 (1.10-1.90) for sarcopenic obesity.

Further exploratory analysis, examining non-CVD mortality, showed that risks were significantly increased in sarcopenic men (HR: 1.39, 95% CI: 1.14-1.70) and sarcopenic obese men (HR: 1.73, 95% CI: 1.23-2.42) compared to the non-sarcopenic non-obese group, in the maximally adjusted model. However, a significantly increased risk in non-CVD mortality was not apparent in the obese group. When examining cancer mortality, the

risk was significantly higher in the sarcopenic obese group compared to the non-sarcopenic non-obese group (HR: 1.64, 95% CI: 1.05-2.57), but was not significantly higher in the sarcopenic group or the obese group.

The risk of CVD mortality was significantly increased in sarcopenic men (HR: 1.35, 95% CI: 1.07-1.70) and obese men (HR: 1.39, 95% CI: 1.07-1.80) compared to the non-sarcopenic non-obese group after adjusting for behavioural variables. This risk was also elevated in sarcopenic obese men (HR: 1.38, 95% CI: 0.91-2.08), but the association was non-significant, possibly due to small numbers in this group. Additional adjustment for morbidity and CVD risk factors attenuated the HR for the obese group but the risk of CVD mortality remained significantly higher in the sarcopenic group. However, further adjustment for CRP, D-dimer and vWF in the sarcopenic group attenuated the associations which became non-significant. The risk of CVD events and CHD events was not significantly increased in any of the body composition groups after adjusting for smoking status, alcohol intake, physical activity and social class.

In addition, the possibility of a sarcopenia x obesity interaction (both fitted as binary variables) was formally examined in relation to the risk of all-cause mortality, CVD mortality, CVD events and CHD events (see Table 5.3). However, there was no evidence of interaction between sarcopenia and obesity for any of the outcomes. In further sensitivity analysis, fitting MAMC as a continuous variable and waist circumference as a binary variable, results were essentially unchanged and there was still no significant interaction between sarcopenia and obesity in relation to the outcomes (results not presented).

5.5.3.2 Alternative sarcopenic obesity definitions

Using MAMC and WHR to define sarcopenic obesity groups (instead of WC as a measure of central adiposity) resulted in broadly similar associations, with the highest risk of all-cause mortality in the sarcopenic obese group (HR: 1.61, 95% CI: 1.27-2.03), after

adjustment for behavioural variables (Table 5.4). However, WHR appeared to be a slightly stronger predictor of CVD mortality than WC, with a significant increase in risk in the sarcopenic obese group (HR: 1.48, 95% CI: 1.02-2.16). Similar, although weaker, associations were observed when defining sarcopenic obesity groups using BMI (reflecting whole body adiposity) and MAMC measurements (Table 5.5). Also, the observed association between sarcopenic obesity and all-cause mortality became non-significant after adjustment for morbidity and cardiovascular risk factors. This may be explained by the small number of participants classified as sarcopenic obese, based on BMI and MAMC measurements, (n=68, 1.7%) compared to the larger proportion identified when using the WC-MAMC classification (n=195, 4.7%).

In additional exploratory analysis, in order to maximise the number of participants identified as sarcopenic obese, classifications were also explored defining obesity using any one of the three criteria for BMI, WC and WHR, together with MAMC. By increasing the numbers in the sarcopenic obesity group (n = 294, 7.1%), associations with all-cause mortality were strengthened in men with sarcopenia only (HR: 1.45, 95% CI: 1.24-1.69), obesity only (HR: 1.26, 95% CI: 1.07-1.49) and sarcopenic obese (HR: 1.74, 95% CI: 1.41-2.16) groups, after adjustment for behavioural variables. Similarly, associations with CVD mortality were also stronger in the sarcopenic (HR: 1.36, 95% CI: 1.06-1.75), obese (HR: 1.51, 95% CI: 1.16-1.96) and sarcopenic obese (HR: 1.80, 95% CI: 1.27-2.53) groups. However, after additional adjustment for morbidity, cardiovascular risk factors and inflammation, hazard ratios were attenuated to similar levels to those observed when using a single measure of obesity in the definition.

Other composite measures of obesity and muscle mass, using BIA measurements, showed no significant associations with outcomes. The risks of CHD events, CVD events, CVD mortality and all-cause mortality were not significantly elevated when using WC and SMI measurements (Table 5.6) or when using FFMI and FMI measurements (Table 5.7), after adjustment for behavioural risk factors. Overall, central adiposity (WC or WHR) and

MAMC seem to be the best composite measures to predict cardiovascular mortality and all-cause mortality in the older adults.

5.6. Discussion

5.6.1. Summary of main findings

This chapter has examined the relationship between sarcopenia, obesity and sarcopenic obesity and the risk of CHD events, CVD events, CVD mortality and all-cause mortality in a prospective cohort of older men, aged 60-79 years. Few studies have looked at composite measures of sarcopenia and obesity in relation to CVD and mortality and these findings add to the limited literature in this area. Sarcopenia (defined as below the second quintile of MAMC; ≤ 25.9cm) and abdominal obesity (defined as WC >102cm) were associated with increased all-cause mortality risks compared to non-sarcopenic non-obese, with sarcopenic obese men showing the highest all-cause mortality risk. For sarcopenia and sarcopenic obesity, this association could not be explained by established CV risk factors or inflammation. Sarcopenia and obesity were not associated with CHD events or CVD events after adjustment for behavioural characteristics but both were associated with increased CVD mortality and this was to a large extent explained by their influence on CV risk factors (blood pressure, blood lipids and inflammation). Sarcopenic obese men also had an increased risk of cardiovascular mortality, although this was not statistically significant. Broadly similar associations were observed when defining sarcopenic obesity groups using WHR and MAMC. Weaker associations were found using BMI and MAMC, but no associations were observed when using BIA measurements to define sarcopenia. Overall, a combination of anthropometric measures of central adiposity (WC or WHR) and muscle mass (MAMC) appeared to be most strongly associated with cardiovascular mortality and all-cause mortality in older men.

5.6.2. Comparison with previous studies

5.6.2.1 Individual measures of adiposity and muscle mass and risk of outcomes

Many measures of adiposity have previously been explored to assess the impact of obesity on the risk of CVD and mortality in healthy adults. Most studies on BMI and CVD and mortality tend to show either U-shaped, flat or even inverse relationships because of opposing effects of muscle mass and adiposity[76;78;128]. This is in keeping with findings from this analysis, which showed a significant quadratic trend between BMI and FMI (an alternative measure of whole body adiposity) with CVD and all-cause mortality. The general consensus in the literature is that central adiposity is best in predicting CVD and mortality[79;126;128;327] which again fits with analysis reported here, showing significant trends between higher WC and WHR and an increased risk of CVD mortality and all-cause mortality. Analysis of other UK cohorts have previously found an association between individual skinfold thickness measurements and CHD but not with all-cause mortality[328]. In comparison, the only significant association observed here was a slight inverse relationship between subscapular skinfold thickness and all-cause mortality. Overall, of the adiposity measures explored, central adiposity (WC or WHR) were the best indicators of mortality, consistent with the results of a recent meta-analysis of elderly cohorts showing a strong positive association between WC and mortality risk[127].

A range of markers of muscle mass were explored, including anthropometric (MAMC) and BIA measures (FFMI and SMI). All measures showed significant trends with CVD mortality and all-cause mortality, adjusting for age only. In addition, SMI showed a significant trend with CVD events and MAMC showed a significant trend with CHD events. Similarly, previous prospective studies have reported an inverse J-shaped or U-shaped associations between all-cause mortality and a range of muscle mass measurements, including appendicular skeletal muscle mass (measured by DXA), lean mass (measured by BIA) and arm circumference measurements[178;179;181;183;191]. Few previous studies have investigated the prospective associations between sarcopenia and CVD risk, but cross-sectional studies have shown associations between sarcopenia and CVD risk factors[161;168;175;329]. Overall, MAMC was the measure which best described muscle mass in

this cohort, suggesting that a simple anthropometric measure of measure mass is better than alternative BIA measures in predicting risk of CVD and mortality in older adults. The exclusion of participants with a BMI above 30 kg/m^2 resulted in significant inverse linear trends between muscle mass and outcomes, stressing the fact that composite measures of muscle mass and adiposity provide a clearer picture.

5.6.2.2 Combined measures of adiposity and muscle mass and risk of all-cause mortality

A composite measure of central adiposity (WC or WHR) and MAMC best described body composition in terms of all-cause mortality risk. Using WC and MAMC to define sarcopenic obesity groups, sarcopenia was associated with increased all-cause mortality, which was independent of behavioural and cardiovascular risk markers. This is consistent with previous prospective studies in older adults which have shown associations between various measures of low muscle mass and an increased mortality risk[178;179;181;183;330]. Although inflammation is strongly related to sarcopenia and all-cause mortality these previous studies did not assess the contributing role of CRP[82;157]; this study showed that the sarcopenia-mortality association could only partially be explained by inflammation. Obesity was associated with increased all-cause mortality, independent of behavioural variables, but the association disappeared after adjustment for established cardiovascular risk factors. Despite obesity being a strong risk factor for mortality in middle age[76], some previous studies have shown that overweight/obesity is not as adverse in elderly populations[13;14;331;332]. Sarcopenic obese older men were at the highest risk of all-cause mortality compared to the non-sarcopenic non-obese group, after adjustment for behavioural variables, but there was no evidence of an interaction between sarcopenia and obesity. This lack of interaction suggests that the relationship between sarcopenia and all-cause mortality was consistent across obese and non-obese body composition groups. The observed association between sarcopenic obesity and mortality diminished slightly after adjustment for potential mediators (blood pressure, blood lipids and inflammation) but a significant increase in risk remained. This suggests that cardiovascular and inflammatory risk markers only partially explain the relationship between sarcopenic obesity and mortality.

These findings confirm initial work carried out in this cohort suggesting that the combined use of WC and MAMC provides anthropometric body composition measures which are associated with the risk of mortality in older men[191]. This current analysis had almost double the length of follow-up of previous analyses (follow-up period extended from 6 to 11 years) and included additional outcomes (CHD events, CVD events and CVD mortality). Previous prospective studies of the association between sarcopenic obesity and mortality are limited. However, these findings support previous research which has shown an association between sarcopenic obesity and a greater mortality risk in cohorts with end-stage renal disease and cancer[190;325] and demonstrates that this association holds true in a population-based cohort. This study showed a similar direction of association between sarcopenic obesity and all-cause mortality as a previous study with 30 years of follow-up in which overweight men in the lowest grip strength tertile had about a 40% higher mortality risk compared to normal weight men in the highest tertile[194].

As expected, very similar results were observed when defining sarcopenic obesity using MAMC and WHR (an alternative measure of central adiposity standardised for hip circumference). The use of this alternative central adiposity measure added little in terms of risk prediction for all-cause mortality beyond that of WC. Since WC would be quicker and easier to measure than WHR in a clinical setting, the use of WHR instead of WC offers no real additional advantages. Sarcopenic obesity (defined by BMI and MAMC) resulted in a similar, but weaker, pattern of association to those seen for WC and MAMC. BMI reflects both fat and muscle mass; therefore taking muscle mass into account strengthened the impact of obesity, as measured by BMI, on all-cause mortality risk. However, the significant association initially observed between sarcopenic obesity and all-cause mortality disappeared after adjustment for CVD risk factors. This observation was consistent with the findings of a recent meta-analysis in the elderly, which highlighted the limitations of BMI as a measure of adiposity in older people and suggested that WC may be a stronger risk factor for mortality[128].

5.6.2.3 Combined measures of adiposity and muscle mass and risk of cardiovascular outcomes

Using WC and MAMC to define sarcopenic and obesity groups, sarcopenia was not associated with CHD events or CVD events after adjustment for behavioural variables. However, sarcopenia was associated with CVD mortality even after adjustment for blood pressure and blood lipids, but this association was no longer significant after adjustment for CRP, D-dimer and vWF. This attenuated association between sarcopenia and CVD mortality after adjusting for CRP, D-dimer and vWF in multivariable models suggests a plausible mechanism by which chronic inflammation and hemostatic dysfunction may in part mediate the relationship between low muscle mass and cardiovascular mortality. This would be consistent with the finding that CRP is more strongly associated with the risk of fatal vascular events than non-fatal vascular events[333]. Obesity was not associated with CHD events or CVD events but was associated with an increased risk of CVD mortality, which was largely due to its associations with established cardiovascular risk factors. The observed association between obesity and an increased risk of CVD mortality is consistent with a previous meta-analysis in the elderly[127]. Cross-sectionally, sarcopenic obese men have an especially adverse cardiovascular risk profile, as observed in both previous literature (Section 2.4.7) and in this study population (Section 4.5.5). Prospective analyses in this chapter have shown that sarcopenic obese men also have an elevated risk of CVD mortality, after adjustment for behavioural variables. This association was significant using WHR and MAMC measurements but not when using WC and MAMC measurements, perhaps due to the small numbers in the sarcopenic obesity group. WHR therefore seemed to be a slightly stronger predictor of CVD mortality than WC, consistent with findings from a meta-regression analysis of prospective studies[126].

Chapter 2 established that previous research investigating prospective associations between sarcopenia or sarcopenic obesity and CVD outcomes is extremely limited (see Table 2.2), with the few studies available mostly cross-sectionally examining CV risk factors (see Table 2.1). The findings from this chapter are broadly consistent with one published

prospective study of community-dwelling older men and women (≥ 65 years) which showed that the risk of CHD events and CVD events was not significantly elevated within the sarcopenic, obese or sarcopenic obese groups (as determined by WC and BIA-measured muscle mass) compared to the non-sarcopenic non-obese group, after adjustment for behavioural variables and cognitive function[177]. However, this previous study did not specifically look at CVD mortality, which did show an association with both sarcopenia and obesity in this study, after adjustment for behavioural variables. The authors of this aforementioned study did however imply that muscle strength rather than muscle mass may be more important, since sarcopenic obesity (defined using grip strength) was predictive of increased risk of CVD events[177].

Using BIA measurements to define sarcopenic obesity (FMI and FFMI or WC and SMI) no significant associations were observed with any of the outcomes. This is consistent with previous research in this cohort, suggesting that a composite measure of MAMC and WC is more effective in predicting all-cause mortality than measures of FFMI and FMI. These results are also consistent with those of a prospective study of older adults from NHANES III, which found that the risk of mortality in sarcopenic obese men (based on BIA measurements) was not significantly increased[192]. This lack of observed associations between sarcopenic obesity, defined using BIA measures, and outcomes may be explained by the imprecision of BIA in assessment of muscle mass in older people, principally due to the variability that exists in fat-free mass hydration[311;312], as referred to in section 4.6.3.

5.6.3. **Strengths and limitations**

A major strength of the results presented in this chapter is that data are from a moderately large population-based, geographically and socioeconomically representative, cohort of older British men with very high follow-up rates[35;264]. However, since the study comprised older male participants, predominantly of white European ethnic origin, the findings may not be generalisable to women and non-white ethnic groups. Moreover, results may not be applicable to men with prevalent heart failure since such participants were excluded from

analyses. Although all mortality and morbidity outcomes were based on objective measurements, self-reported variables (e.g. smoking status, alcohol intake, and physical activity) may have been subject to misclassification which could lead to residual confounding. In particular, self-reported measures of physical activity can be a particular problem in older age groups due to the light intensities of activity and vast variability in duration of activity in these age groups which make accurate recall especially difficult[315-317] (as discussed in Chapter 4, Section 4.6.3). However, a validation study in older men within the BRHS has shown self-reported physical activity questions used within this cohort are associated with a graded increase in objectively measured physical activity[318]. This reduces the risk of measurement error, and any possible misclassification of physical activity is likely to have been non-differential between body composition groups and is only likely to have attenuated relative risk estimates between body composition groups and outcomes[320].

An additional strength of this study is the wide range of body composition measures used to assess adiposity and muscle mass. Although this study did not have direct measurements of adiposity or muscle mass such as computerised tomography (CT), magnetic resonance imaging (MRI) or dual-energy X-ray absorptiometry (DXA), these expensive, time-consuming measures are rarely available in non-clinical settings and the anthropometric and BIA measures used represent a practical alternative (as discussed in section 4.6.3). The American Heart Association recognises MAMC as a proxy marker for muscle mass[102] which is strongly correlated with more accurate dual-energy X-ray absorptiometry measures of lean mass[147]. In addition, the European Working Group on Sarcopenia has approved BIA measures as a portable alternative to dual-energy X-ray absorptiometry[17]. Also, WC has been shown to be the anthropometric variable which best correlates with adiposity stores in men, as measured by MRI[304]. Any imprecision in the assessment of adiposity and muscle mass may have weakened (rather than strengthened) the estimates of the strength of associations observed in this chapter between sarcopenic obesity groups and disease outcomes and mortality.

Since no universally accepted operational definition of sarcopenia has yet been adopted[17], a statistical approach was used to define low muscle mass as participants below the second quintile of the distribution of MAMC, FFMI or SMI. However, as discussed in Chapter 4 (section 4.6.3), the cut-offs used in this study for MAMC and FFMI were comparable to those used in previous studies[179;181]. In addition, the cut-point used for the lowest two fifths of SMI (9.9 kg/m^2) was very similar to the definition of low muscle mass used previously in NHANES III in men aged 70 years and over (lower two fifths of SMI: <9.12 kg/m^2)[334].

As outlined in Chapter 2 (Section 2.4.6) the European Working Group on Sarcopenia in Older People proposed a definition of sarcopenia which included the presence of both low muscle mass and low muscle function[17]. However, measures of muscle function were not available in this study population and only markers of muscle mass were used. Findings from this chapter are therefore applicable to sarcopenia and sarcopenic obesity as defined by muscle mass, but not muscle strength. Another consideration is that the body composition measures used within this chapter were assessed at one time point only, so information was unavailable on whether participant's sarcopenia and obesity status changed over time.

5.6.4. **Conclusions**

The results of this chapter show that both muscle mass and adiposity are associated with risks of CVD mortality and all-cause mortality in older adults. A combination of anthropometric measures of central adiposity (WC or WHR) and muscle mass (MAMC) appear to be the strongest predictors of cardiovascular mortality and all-cause mortality in older men. Using these combined measures, sarcopenia and abdominal obesity are both associated with increased all-cause mortality with the highest risk in sarcopenic obese men. Sarcopenia and sarcopenic obesity, but not obesity on its own, were associated with increased all-cause mortality independent of CVD risk factors, inflammation and weight loss. No association was seen between sarcopenia and obesity with CHD events or CVD

events, but sarcopenia and obesity were both associated with increased CVD mortality largely due to their associations with blood pressure, blood lipids and inflammation.

Table 5.1 Hazard ratios (95% CI) for risk of all-cause mortality, CVD mortality, CVD events and CHD events by measures of adiposity and in men aged 60-79 years in 1998-2000

	n	All-cause mortality	CVD mortality	CVD events	CHD events
		Age-adjusted HR (95% CI)			
BMI (kg/m^2)					
<18.5	25	2.93 (1.80-4.75)*	2.70 (1.20-6.10)	1.99 (0.94-4.21)	2.72 (1.11-6.64)
18.5-24.9	1,249	1.00	1.00	1.00	1.00
25-27.4	1,248	0.81 (0.70-0.93)*	0.87 (0.69-1.09)	0.99 (0.83-1.18)	1.12 (0.88-1.42)
27.5-29.9	928	0.89 (0.76-1.03)	0.96 (0.76-1.23)	1.10 (0.91-1.32)	1.08 (0.84-1.40)
≥ 30	713	1.11 (0.95-1.30)	1.39 (1.09-1.78)*	1.23 (1.01-1.51)*	1.23 (0.93-1.62)
p for linear trend		0.88	0.02	0.02	0.44
p for quadratic trend		<0.001	0.01	0.44	0.34
FMI (kg/m$^{2)}$					
Q1 (≤ 7.19)	809	1.00	1.00	1.00	1.00
Q2 (7.19-8.70)	809	0.93 (0.78-1.10)	0.94 (0.71-1.24))	0.93 (0.75-1.16)	0.94 (0.71-1.23)
Q3 (8.70-10.24)	809	0.88 (0.74-1.05)	0.82 (0.61-1.09)	0.98 (0.79-1.22)	0.86 (0.64-1.16)
Q4 (10.24-12.04)	809	0.92 (0.77-1.09)	0.96 (0.73-1.27)	0.99 (0.79-1.22)	0.96 (0.72-1.28)
Q5 (≥ 12.04)	809	1.15 (0.97-1.36)	1.34 (1.03-1.74)*	1.20 (0.97-1.48)	1.15 (0.87-1.53)
p for linear trend		0.27	0.05	0.13	0.48
p for quadratic trend		0.007	0.07	0.18	0.30
WC (cm)					
<94	1,573	1.00	1.00	1.00	1.00
94-102	1,369	0.95 (0.83-1.08)	0.96 (0.77-1.18)	1.04 (0.89-1.23)	1.00 (0.80-1.24)
103-105	457	1.06 (0.89-1.28)	0.97 (0.71-1.32)	1.02 (0.81-1.29)	1.16 (0.86-1.58)
≥ 106	758	1.24 (1.07-1.44)*	1.46 (1.16-1.83)*	1.32 (1.10-1.59)*	1.20 (0.93-1.54)
p for linear trend		0.04	0.006	0.009	0.32
p for quadratic trend		<0.001	0.01	0.46	0.73
WHR (cm)					
Q1 (≤ 0.90)	831	1.00	1.00	1.00	1.00
Q2 (0.90-0.93)	831	1.00 (0.84-1.19)	0.99 (0.75-1.30)	0.94 (0.75-1.17)	1.06 (0.79-1.44)
Q3 (0.93-0.96)	831	1.00 (0.84-1.20)	0.87 (0.65-1.16)	0.98 (0.79-1.22)	1.04 (0.76-1.41)
Q4 (0.96-1.00)	831	1.11 (0.93-1.31)	1.06 (0.81-1.40)	1.12 (0.91-1.39)	1.33 (0.99-1.78)
Q5 (≥ 1.00)	830	1.26 (1.07-1.49)*	1.30 (1.01-1.69)*	1.27 (1.03-1.560*	1.36 (1.02-1.82)*
p for linear trend		0.002	0.04	0.01	0.05
p for quadratic trend		0.14	0.59	0.66	0.73

Table 5.1 *Continued*. Hazard ratios (95% CI) for risk of all-cause mortality, CVD mortality, CVD events and CHD events by measures of adiposity and in men aged 60-79 years in 1998-2000

	n	All-cause mortality	CVD mortality	CVD events	CHD events
		Age-adjusted HR (95% CI)			
Subscapular skinfold (mm)					
Q1 (≤ 14.40)	822	1.00	1.00	1.00	1.00
Q2 (14.40-17.27)	820	0.76 (0.64-0.89)*	1.06 (0.82-1.39)	0.98 (0.79-1.20)	1.15 (0.87-1.52)
Q3 (17.27-20.50)	820	0.80 (0.68-0.94)*	0.93 (0.71-1.23)	0.92 (0.74-1.14)	0.94 (0.70-1.27)
Q4 (20.50-24.65)	820	0.74 (0.63-0.88)*	0.95 (0.72-1.25)	0.94 (0.76-1.16)	0.93 (0.69-1.25)
Q5 (≥ 24.65)	819	0.81 (0.68-0.95)*	1.01 (0.76-1.33)	0.99 (0.80-1.22)	0.99 (0.73-1.33)
p for linear trend		0.03	0.98	0.99	0.64
p for quadratic trend		<0.001	0.09	0.23	0.08
Triceps Skinfold (mm)					
Q1 (≤ 8.76)	828	1.00	1.00	1.00	1.00
Q2 (8.76-10.49)	828	0.88 (0.74-1.04)	0.83 (0.62-1.11)	0.92 (0.74-1.15)	0.95 (0.72-1.27)
Q3 (10.49-12.39)	828	0.83 (0.70-0.98)*	1.02 (0.78-1.33)	1.08 (0.88-1.34)	0.88 (0.66-1.18)
Q4 (12.39-15.15)	828	0.95 (0.80-1.12)	1.09 (0.83-1.43)	1.07 (0.86-1.32)	1.00 (0.66-1.18)
Q5 (≥ 15.15)	827	1.09 (0.93-1.29)	1.26 (0.97-1.64)	1.16 (0.94-1.43)	1.04 (0.78-1.38)
p for linear trend		0.42	0.11	0.18	0.75
p for quadratic trend		0.38	0.14	0.26	0.99

BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; FMI, fat mass index; WC, waist circumference; WHR, wait-to-hip ratio. P-value for quadratic trend adjusted for linear trend.
* $p<0.05$

Table 5.2 Hazard ratios (95% CI) for risk of all-cause mortality, CVD mortality, CVD events and CHD events by measures of muscle mass and in men aged 60-79 years in 1998-2000

	n	All-cause mortality	CVD mortality	CVD events	CHD events
		Age-adjusted HR (95% CI)			
MAMC (cm)					
Q1 (≤ 24.54)	827	1.00	1.00	1.00	1.00
Q2 (24.54-25.90)	827	0.79 (0.68-0.92)*	0.99 (0.78-1.26)	1.05 (0.86-1.28)	0.85 (0.65-1.12)
Q3 (25.90-27.00)	827	0.65 (0.55-0.77)*	0.81 (0.62-1.06)	0.90 (0.73-1.11)	0.83 (0.63-1.10)
Q4 (27.00-28.33)	827	0.62 (0.52-0.73)*	0.79 (0.60-1.03)	0.94 (0.76-1.16)	0.82 (0.62-1.10)
Q5 (≥ 28.33)	827	0.67 (0.57-0.80)*	0.85 (0.64-1.13)	1.03 (0.82-1.27)	0.90 (0.68-1.21)
p for linear trend		<0.001	0.12	0.93	0.48
p for quadratic trend		<0.001	0.03	0.13	0.004
FFMI (kg/m^2)					
Q1 (≤ 15.71)	810	1.00	1.00	1.00	1.00
Q2 (15.71-16.66)	810	0.88 (0.74-1.04)	0.89 (0.68-1.17)	1.09 (0.88-1.34)	1.19 (0.90-1.58)
Q3 (16.66-17.55)	809	0.77 (0.65-0.92)*	0.72 (0.54-0.96)*	0.85 (0.68-1.07)	0.86 (0.64-1.72)
Q4 (17.55-18.70)	810	0.86 (0.73-1.02)	0.79 (0.60-1.05)	0.89 (0.71-1.11)	0.93 (0.69-1.25)
Q5 (≥ 18.70)	809	0.91 (0.77-1.07)	1.07 (0.82-1.38)	1.21 (0.98-1.48)	1.03 (0.77-1.37
p for linear trend		0.38	0.16	0.06	0.75
p for quadratic trend		<0.001	0.002	0.23	0.19
SMI (kg/m^2)					
Q1 (≤ 9.35)	820	1.00	1.00	1.00	1.00
Q2 (9.35-9.92)	820	0.80 (0.68-0.94)*	0.73 (0.56-0.96)	1.04 (0.84-1.28)	1.16 (0.88-1.53)
Q3 (9.92-10.48)	819	0.81 (0.68-0.95)*	0.80 (0.61-1.04)	0.91 (0.73-1.13)	0.93 (0.69-1.25)
Q4 (10.48-11.18)	820	0.80 (0.67-0.94)*	0.76 (0.58-1.00)	0.95 (0.76-1.17)	0.95 (0.71-1.27)
Q5 (≥ 11.18)	819	0.93 (0.78-1.09)	1.11 (0.87-1.43)	1.24 (1.01-1.52)*	1.09 (0.81-1.45)
p for linear trend		0.74	0.03	0.01	0.75
p for quadratic trend		0.001	0.05	0.46	0.63

CHD, coronary heart disease; CVD, cardiovascular disease; FFMI, fat-free mass index; MAMC, mid-arm muscle circumference; SMI, skeletal muscle index. P-value for quadratic trend adjusted for linear trend.
* $p<0.05$

Table 5.3 Hazard ratios (95% CI) for risk of all-cause mortality, CVD mortality, CVD events and CHD events by sarcopenic obesity groups (as defined by mid-arm muscle circumference and waist circumference) in men aged 60-79 years in 1998-2000

		Sarcopenic Obesity Groups (MAMC lowest 2 quintiles; WC >102cm)				p value (sarcopenia*obesity interaction)
		Non-sarcopenic non-obese	Sarcopenic	Obese	Sarcopenic obese	
Total (%)		1 490 (36.2)	1 443 (35.1)	983 (23.9)	195 (4.7)	
CHD events	Model 1	1.00	1.22 (0.97-1.53)	1.33 (1.04-1.70)*	1.37 (0.90-2.08)	0.50
	Model 2	1.00	1.09 (0.86-1.38)	1.19 (0.92-1.55)	1.11 (0.71-1.75)	0.55
CVD events	Model 1	1.00	1.19* (1.01-1.41)	1.30* (1.08-1.56)	1.39* (1.02-1.89)	0.55
	Model 2	1.00	1.11 (0.93-1.32)	1.18 (0.98-1.43)	1.08 (0.77-1.52)	0.31
CVD mortality	Model 1	1.00	1.48 (1.19-1.85)*	1.60 (1.25-2.03)*	1.79 (1.19-1.85)*	0.21
	Model 2	1.00	1.35 (1.07-1.70)*	1.39 (1.07-1.80)*	1.38 (0.91-2.08)	0.20
	Model 3	1.00	1.33 (1.04-1.70)*	1.18 (0.89-1.55)	1.29 (0.83-2.00)	0.44
	Model 4	1.00	1.26 (0.98-1.61)	1.12 (0.84-1.48)	1.14 (0.73-1.79)	0.42
All-cause mortality	Model 1	1.00	1.54 (1.34-1.76)*	1.41 (1.21-1.64)*	2.09 (1.67-2.62)*	0.78
	Model 2	1.00	1.41 (1.22-1.63)*	1.21 (1.03-1.42)*	1.72 (1.35-2.18)*	0.95
	Model 3	1.00	1.37 (1.18-1.59)*	1.11 (0.93-1.32)	1.61 (1.25-2.08)*	0.70
	Model 4	1.00	1.34 (1.15-1.56)*	1.07 (0.90-1.28)	1.49 (1.15-1.93)*	0.81
	Model 5	1.00	1.34 (1.15-1.57)*	1.07 (0.89-1.28)	1.44 (1.10-1.90)*	0.96

CHD, coronary heart disease; CVD, cardiovascular disease; MAMC, mid-arm muscle circumference; WC, waist circumference.
Model 1: adjusted for age; Model 2: adjusted for model 1 + smoking, alcohol, social class, physical activity; Model 3: adjusted for model 2 + prevalent MI, prevalent stroke, HDL, SBP, FEV_1; Model 4: adjusted for model 3 + CRP, D-dimer, vWF; Model 5: adjusted for model 4 + weight loss.
* $p<0.05$

Table 5.4 Hazard ratios (95% CI) for risk of all-cause mortality, CVD mortality, CVD events and CHD events by sarcopenic obesity groups (as defined by mid-arm muscle circumference and waist-to-hip ratio) in men aged 60-79 years in 1998-2000

		Sarcopenic Obesity Groups (MAMC lowest 2 quintiles; WHR >1.00 cm)				p value (sarcopenia*obesity interaction)
		Non-sarcopenic non-obese	Sarcopenic	Obese	Sarcopenic obese	
Total (%)		1921 (46.8)	1440 (35.1)	550 (13.4)	197 (4.8)	
CHD events	Model 1	1.00	1.16 (0.94-1.43)	1.38 (1.05-1.81)*	1.35 (0.90-2.02)	0.49
	Model 2	1.00	1.05 (0.84-1.31)	1.21 (0.91-1.61)	1.09 (0.70-1.70)	0.55
CVD events	Model 1	1.00	1.11 (0.95-1.30)	1.28 (1.05-1.58)*	1.49 (1.13-1.98)*	0.80
	Model 2	1.00	1.05 (0.90-1.24)	1.19 (0.96-1.48)	1.25 (0.92-1.71)	0.99
CVD mortality	Model 1	1.00	1.33 (1.09-1.62)*	1.53 (1.18-1.99)*	1.74 (1.23-2.47)*	0.49
	Model 2	1.00	1.23 (0.99-1.52)	1.32 (0.99-1.74)	1.48 (1.02-2.16)*	0.72
	Model 3	1.00	1.26 (1.00-1.58)	1.18 (0.88-1.59)	1.49 (1.01-2.21)*	0.99
	Model 4	1.00	1.19 (0.95-1.50)	1.12 (0.83-1.51)	1.41 (0.95-2.09)	0.83
All-cause mortality	Model 1	1.00	1.46 (1.29- 1.65)*	1.42 (1.29-1.65)*	1.87 (1.50-2.34)*	0.48
	Model 2	1.00	1.36 (1.19-1.55)*	1.19 (0.99-1.42)	1.61 (1.27-2.03)*	0.98
	Model 3	1.00	1.35 (1.17-1.55)*	1.12 (0.92-1.35)	1.57 (1.23-2.00)*	0.81
	Model 4	1.00	1.32 (1.15-1.52)*	1.08 (0.89-1.31)	1.47 (1.15-1.89)*	0.83
	Model 5	1.00	1.31 (1.14-1.52)*	1.08 (0.89-1.32)	1.54 (1.19-1.99)*	0.62

CHD, coronary heart disease; CVD, cardiovascular disease; MAMC, mid-arm muscle circumference; WHR, waist-to-hip ratio.
Model 1: adjusted for age; Model 2: adjusted for model 1 + smoking, alcohol, social class, physical activity; Model 3: adjusted for model 2 + prevalent MI, prevalent stroke, HDL, SBP, FEV_1; Model 4: adjusted for model 3 + CRP, D-dimer, vWF; Model 5: adjusted for model 4 + weight loss.
* $p<0.05$

Table 5.5 Hazard ratios (95% CI) for risk of all-cause mortality, CVD mortality, CVD events and CHD events by sarcopenic obesity groups (as defined by mid-arm muscle circumference and body mass index) in men aged 60-79 years in 1998-2000

		Sarcopenic Obesity Groups (MAMC lowest 2 quintiles; BMI ≥ 30				p value (sarcopenia*obesity interaction)
		Non-sarcopenic non-obese	Sarcopenic	Obese	Sarcopenic obese	
Total (%)		1858 (45.1)	1579 (38.3)	613 (14.9)	68 (1.7)	
CHD events	Model 1	1.00	1.15 (0.93-1.41)	1.25 (0.96-1.55)	1.06 (0.50-2.26)	0.44
	Model 2	1.00	1.04 (0.84-1.29)	1.13 (0.85-1.50)	0.79 (0.35-1.80)	0.34
CVD events	Model 1	1.00	1.13 (0.97-1.32)	1.26 (1.04-1.54)*	1.58 (1.00-2.52)	0.69
	Model 2	1.00	1.06 (0.90-1.24)	1.14 (0.93-1.41)	1.22 (0.74-1.99)	0.98
CVD mortality	Model 1	1.00	1.41 (1.16-1.72)*	1.73 (1.35-2.24)*	2.06 (1.17-3.63)*	0.57
	Model 2	1.00	1.31 (1.06-1.62)*	1.52 (1.16-2.00)*	1.62 (0.89-2.94)	0.52
	Model 3	1.00	1.29 (1.03-1.61)*	1.23 (0.92-1.65)	1.49 (0.77-2.85)	0.85
	Model 4	1.00	1.23 (0.98-1.54)	1.17 (0.87-1.57)	1.28 (0.66-2.47)	0.75
All-cause mortality	Model 1	1.00	1.52 (1.35-1.72)*	1.46 (1.24-1.73)*	1.92 (1.33-2.78)*	0.46
	Model 2	1.00	1.42 (1.25-1.62)*	1.26 (1.06-1.50)*	1.59 (1.09-2.33)*	0.57
	Model 3	1.00	1.39 (1.21-1.60)*	1.17 (0.97-1.41)	1.40 (0.92-2.15)	0.53
	Model 4	1.00	1.37 (1.19-1.57)*	1.14 (0.94-1.37)	1.26 (0.82-1.94)	0.36
	Model 5	1.00	1.37 (1.19-1.58)*	1.14 (0.94-1.39)	1.18 (0.75-1.87)	0.24

BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; MAMC, mid-arm muscle circumference.
Model 1: adjusted for age; Model 2: adjusted for model 1 + smoking, alcohol, social class, physical activity; Model 3: adjusted for model 2 + prevalent MI, prevalent stroke, HDL, SBP, FEV_1; Model 4: adjusted for model 3 + CRP, D-dimer, vWF; Model 5: adjusted for model 4 + weight loss.
* $p<0.05$

Table 5.6 Hazard ratios (95% CI) for risk of all-cause mortality, CVD mortality, CVD events and CHD events by sarcopenic obesity groups (as defined by skeletal muscle index and waist circumference) in men aged 60-79 years in 1998-2000

		Sarcopenic Obesity Groups (SMI lowest 2 quintiles; WC >102cm)				p value (sarcopenia*obesity interaction)
		Non-sarcopenic non-obese	Sarcopenic	Obese	Sarcopenic obese	
Total (%)		1540 (37.8)	1338 (32.8)	902 (22.1)	297 (7.3)	
CHD events	Model 1	1.00	1.14 (0.91-1.43)	1.21 (0.94-1.56)	1.38 (0.98-1.94)	0.98
	Model 2	1.00	1.12 (0.88-1.41)	1.14 (0.87-1.48)	1.20 (0.83-1.73)	0.80
CVD events	Model 1	1.00	1.08 (0.92-1.27)	1.26 (1.05-1.51)*	1.17 (0.90-1.52)	0.34
	Model 2	1.00	1.06 (0.89-1.26)	1.17 (0.96-1.41)	0.96 (0.72-1.29)	0.15
CVD mortality	Model 1	1.00	1.08 (0.87-1.34)	1.34 (1.06-1.69)*	1.35 (0.97-1.86)	0.72
	Model 2	1.00	1.03 (0.82-1.29)	1.18 (0.92-1.52)	1.04 (0.72-1.49)	0.46
All-cause mortality	Model 1	1.00	1.18 (1.03-1.35)*	1.31 (1.13-1.52)*	1.33 (1.08-1.64)*	0.25
	Model 2	1.00	1.08 (0.94-1.24)	1.12 (0.96-1.32)	1.07 (0.86-1.33)	0.34

CHD, coronary heart disease; CVD, cardiovascular disease; SMI, skeletal muscle index; WC, waist circumference.
Model 1: adjusted for age; Model 2: adjusted for model 1 + smoking, alcohol, social class, physical activity; Model 3: adjusted for model 2 + prevalent MI, prevalent stroke, HDL, SBP, FEV_1; Model 4: adjusted for model 3 + CRP, D-dimer, vWF; Model 5: adjusted for model 4 + weight loss.
* $p<0.05$

Table 5.7 Hazard ratios (95% CI) for risk of all-cause mortality, CVD mortality, CVD events and CHD events by sarcopenic obesity groups (as defined by fat-free mass index and fat mass index) in men aged 60-79 years in 1998-2000

		Sarcopenic Obesity Groups (FFMI lowest 2 quintiles; FMI highest 28.7%)				p value (sarcopenia*obesity interaction)
		Non-sarcopenic non-obese	Sarcopenic	Obese	Sarcopenic obese	
Total (%)		1670 (41.3)	1190 (29.4)	756 (18.7)	429 (10.6)	
CHD events	Model 1	1.00	1.17 (0.94-1.46)	1.13 (0.87-1.48)	1.35 (1.00-1.83)*	0.92
	Model 2	1.00	1.15 (0.91-1.45)	1.04 (0.79-1.38)	1.13 (0.82-1.56)	0.79
CVD events	Model 1	1.00	1.05 (0.89-1.24)	1.10 (0.90-1.33)	1.21 (0.97-1.51)	0.77
	Model 2	1.00	1.03 (0.87-1.22)	1.01 (0.82-1.24)	1.01 (0.79-1.29)	0.85
CVD mortality	Model 1	1.00	1.18 (0.95-1.46)	1.43 (1.12-1.82)*	1.37 (1.02-1.82)*	0.29
	Model 2	1.00	1.11 (0.89-1.39)	1.25 (0.96-1.62)	1.11 (0.81-1.53)	0.30
All-cause mortality	Model 1	1.00	1.19 (1.05-1.36)*	1.26 (1.08-1.47)*	1.18 (0.98-1.42)	0.05
	Model 2	1.00	1.08 (0.94-1.24)	1.09 (0.92-1.27)	0.98 (0.80-1.20)	0.19

CHD, coronary heart disease; CVD, cardiovascular disease; FFMI, fat-free mass index; FMI fat mass index.
Model 1: adjusted for age; Model 2: adjusted for model 1 + smoking, alcohol, social class, physical activity. Cut-off for obesity (FMI >28.7th percentile) corresponds to the WC >102cm cut-off.
*p<0.05

Figure 5.1 Rate of CHD events, CVD events, CVD mortality and all-cause mortality by body mass index in men aged 60-79 years in 1998-2000

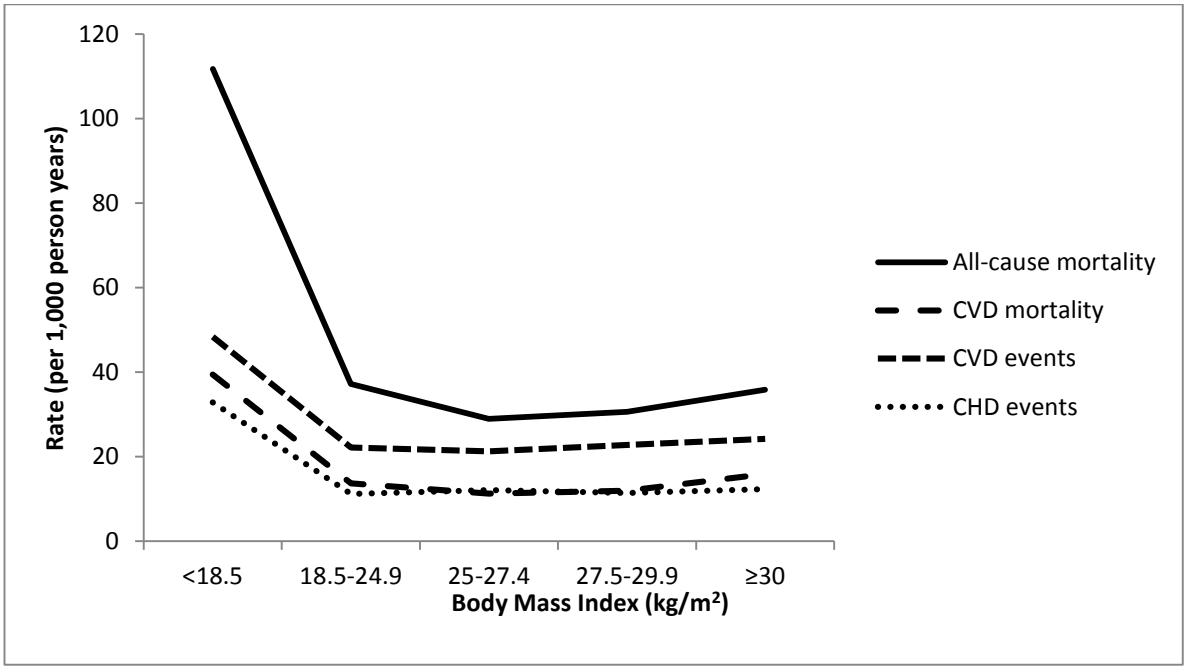


Figure 5.2 Rate of CHD events, CVD events, CVD mortality and all-cause mortality by fat mass index in men aged 60-79 years in 1998-2000

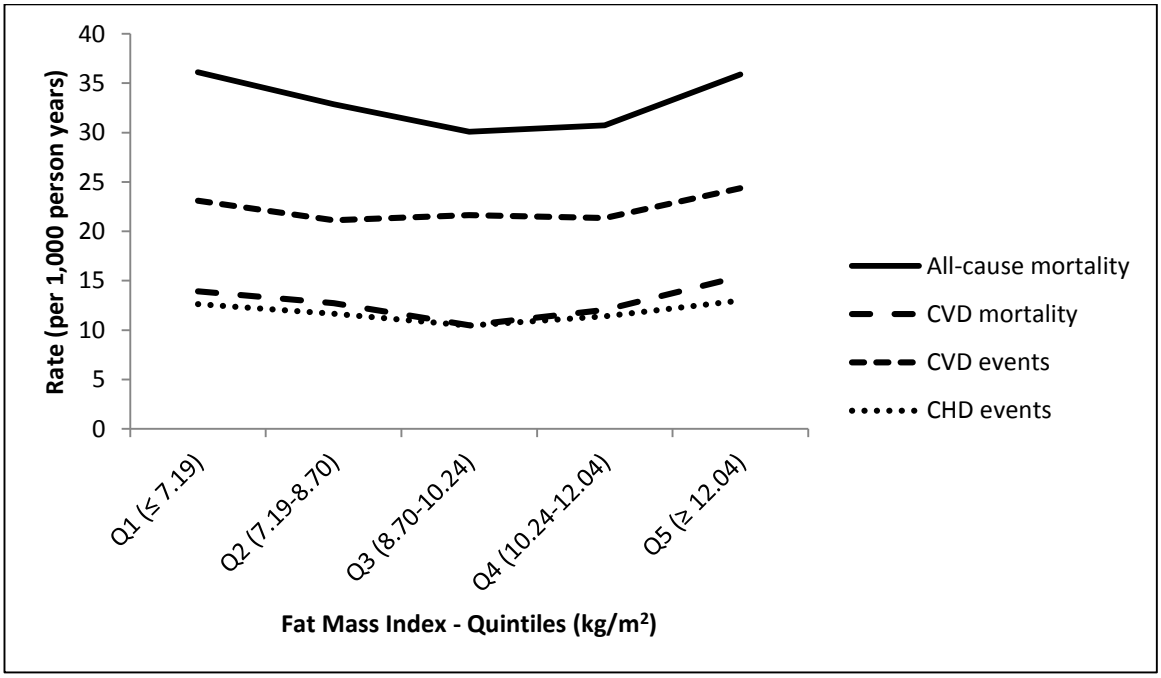


Figure 5.3 Rate of CHD events, CVD events, CVD mortality and all-cause mortality by waist circumference in men aged 60-79 years in 1998-2000

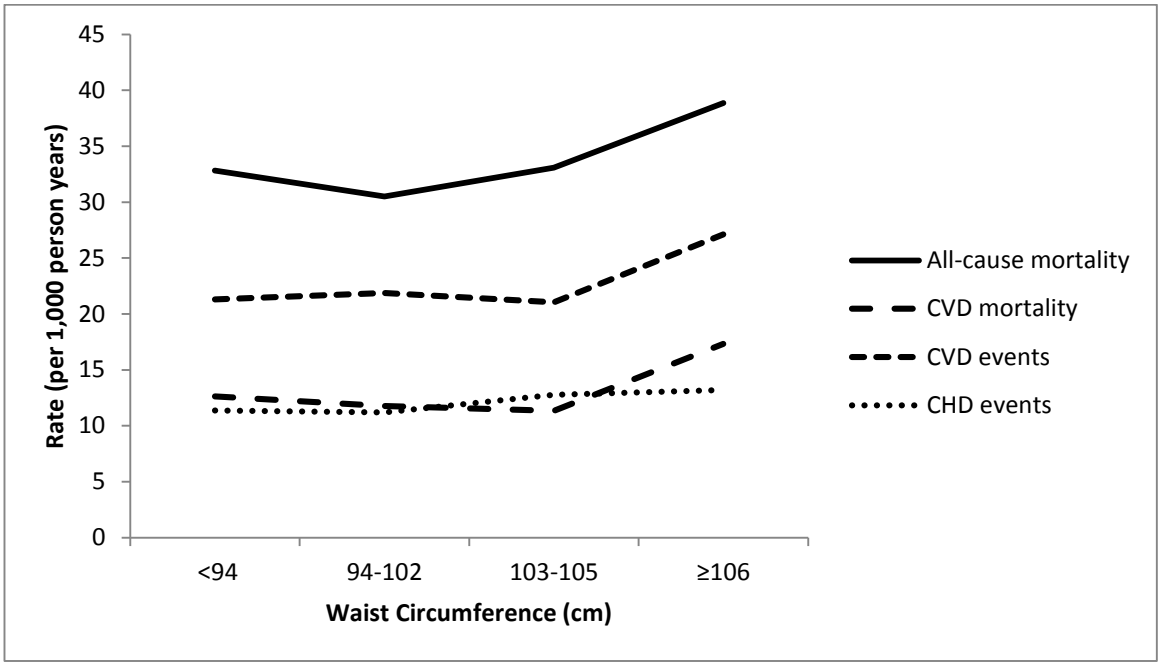


Figure 5.4 Rate of CHD events, CVD events, CVD mortality and all-cause mortality by waist-to-hip ratio in men aged 60-79 years in 1998-2000

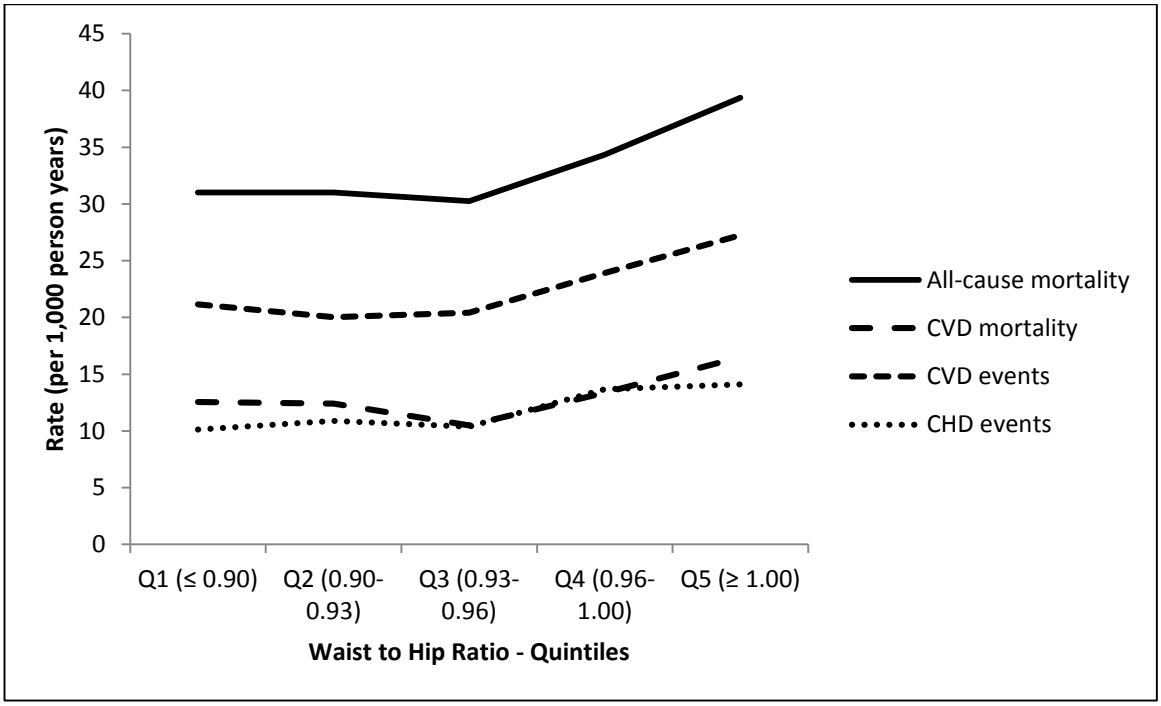


Figure 5.5 Rate of CHD events, CVD events, CVD mortality and all-cause mortality by subscapular skinfold thickness in men aged 60-79 years in 1998-2000

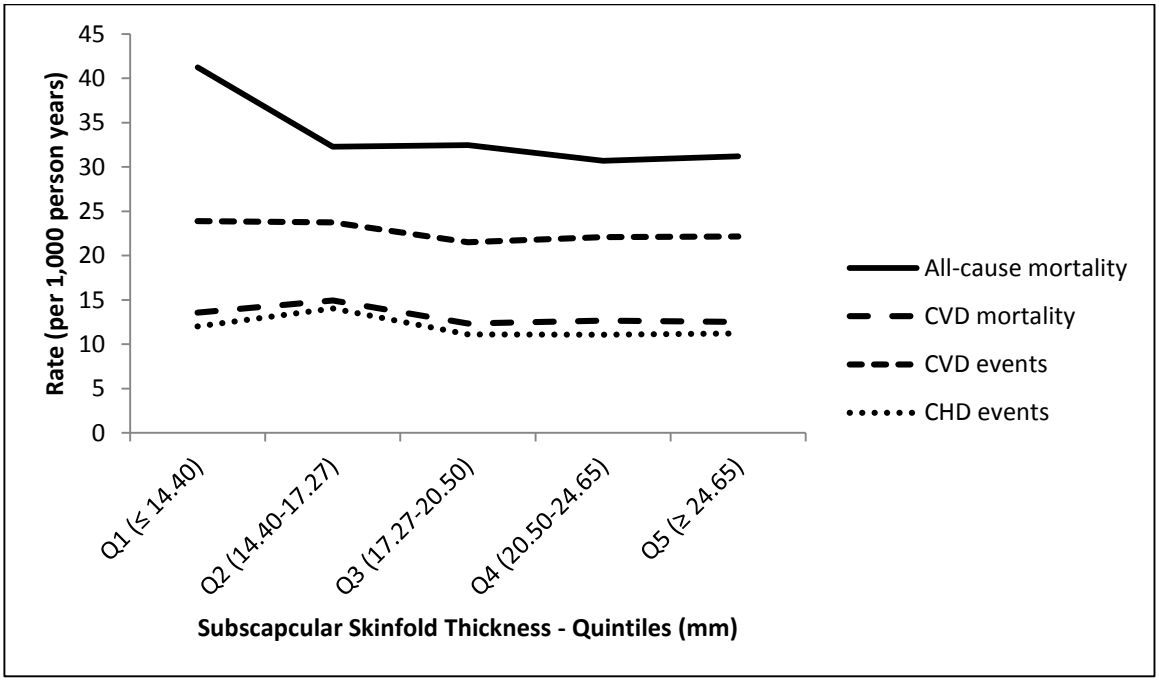


Figure 5.6 Rate of CHD events, CVD events, CVD mortality and all-cause mortality by triceps skinfold thickness in men aged 60-79 years in 1998-2000

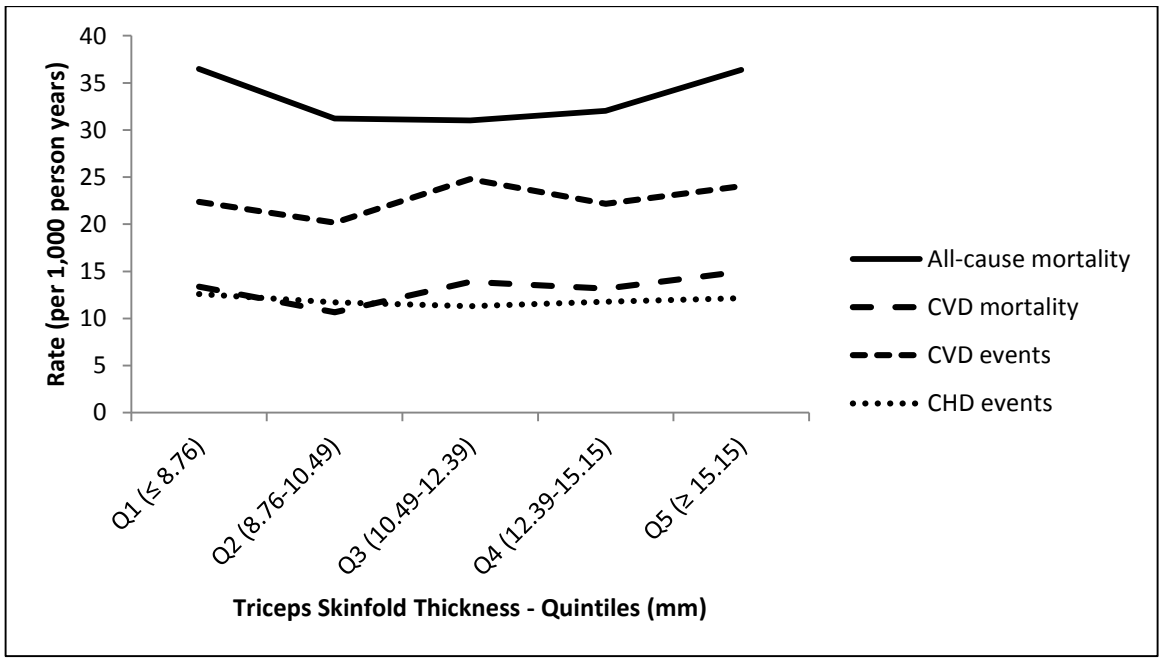


Figure 5.7 Rate of CHD events, CVD events, CVD mortality and all-cause mortality by mid-arm muscle circumference in men aged 60-79 years in 1998-2000

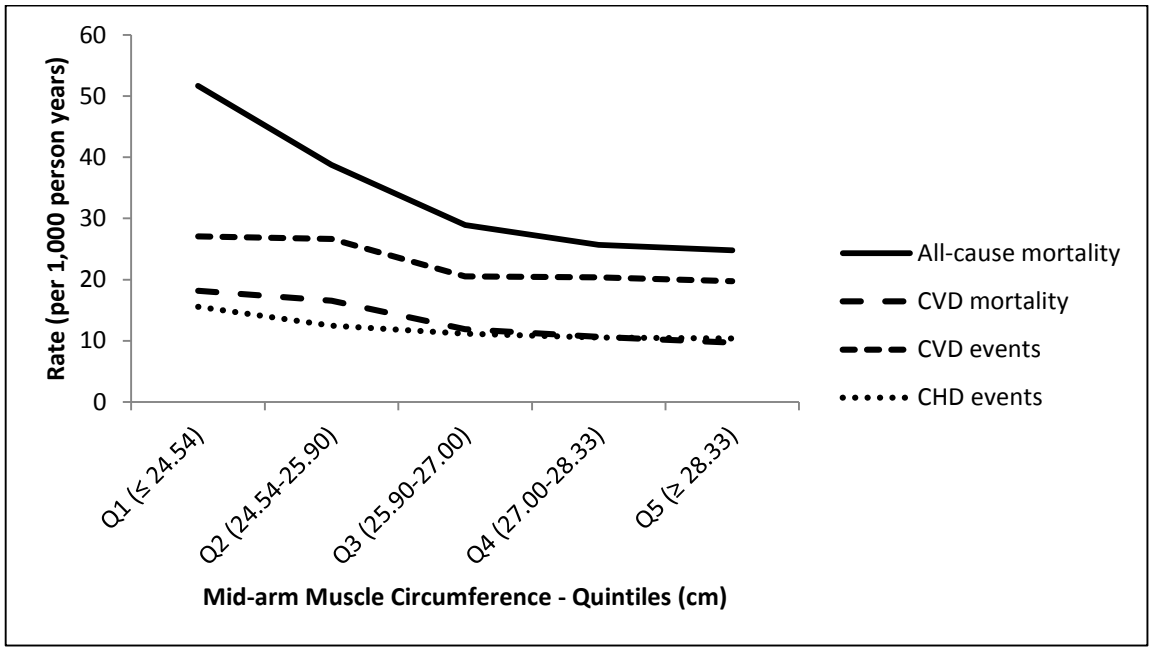


Figure 5.8 Rate of CHD events, CVD events, CVD mortality and all-cause mortality by fat-free mass index in men aged 60-79 years in 1998-2000

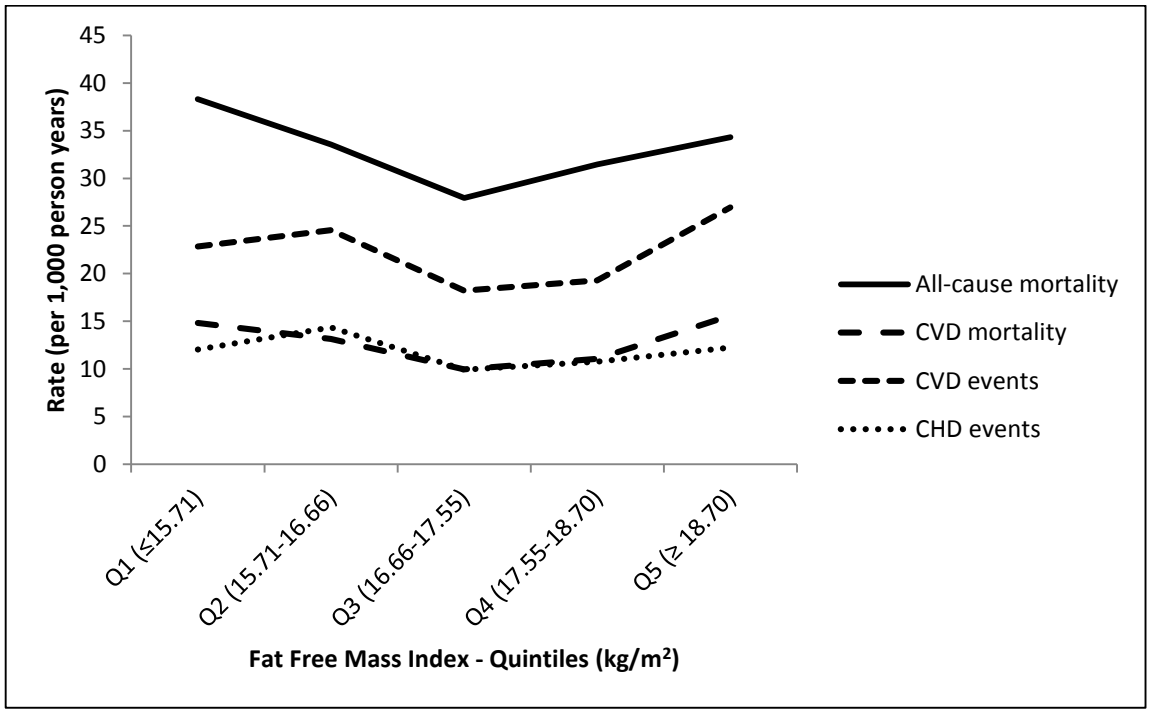


Figure 5.9 Rate of CHD events, CVD events, CVD mortality and all-cause mortality by skeletal muscle index in men aged 60-79 years in 1998-2000

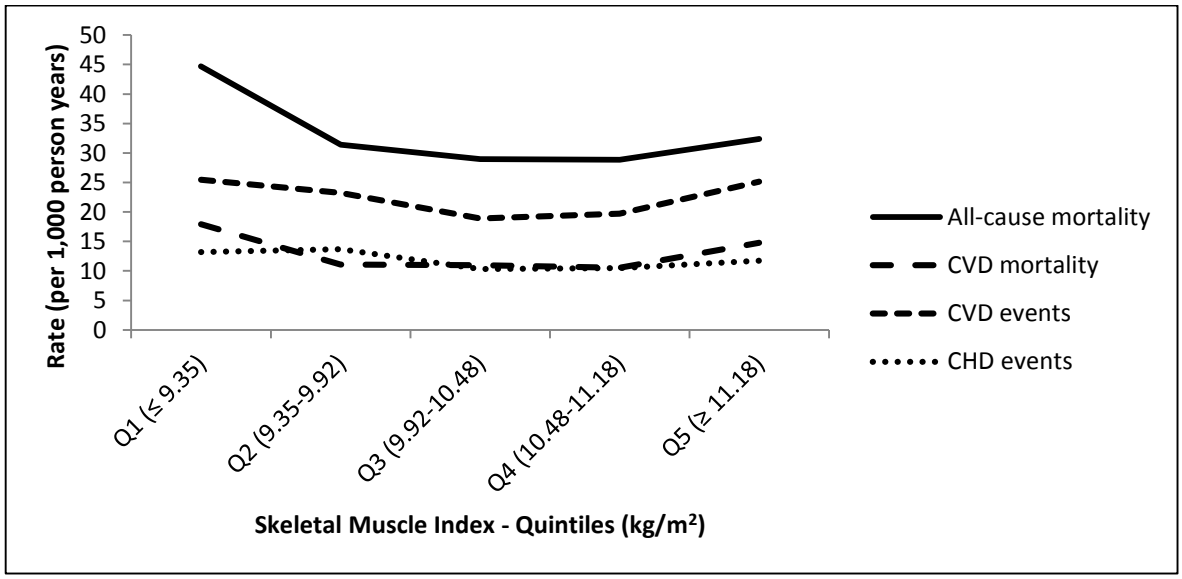
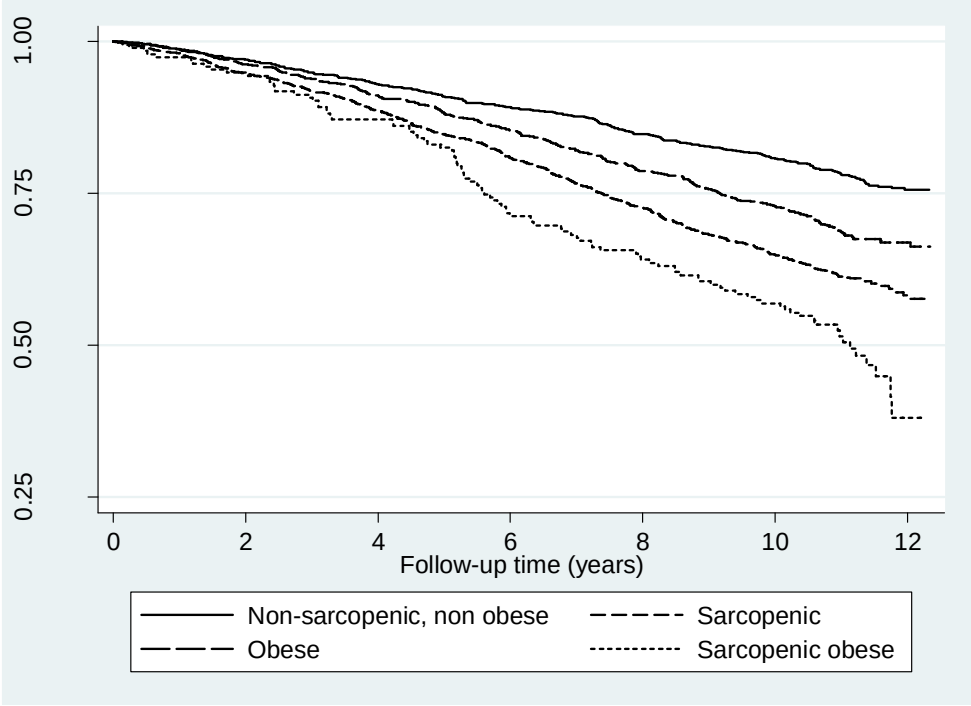
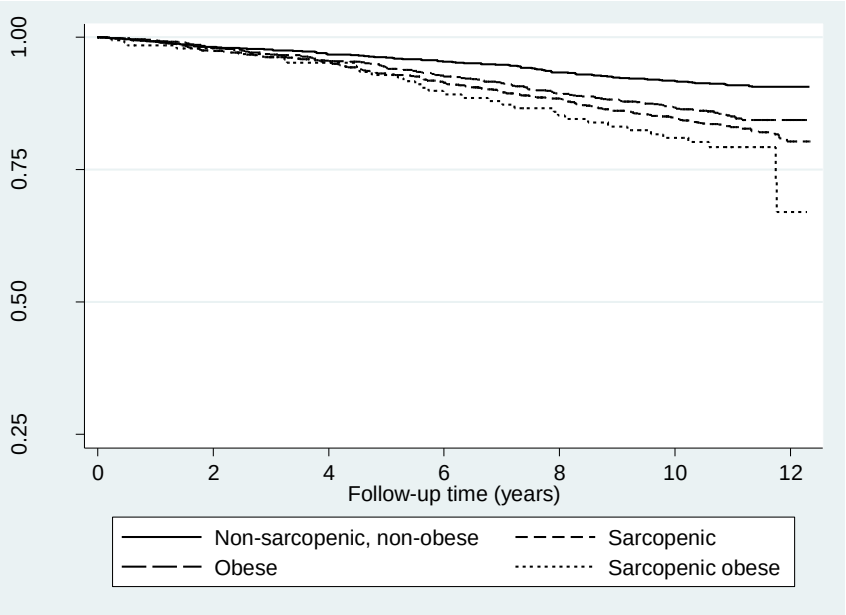


Figure 5.10 Kaplan-Meier survival curves comparing all-cause mortality by sarcopenic obesity groups (defined by mid-arm muscle circumference and waist circumference) in men aged 60-79 years in 1998-2000



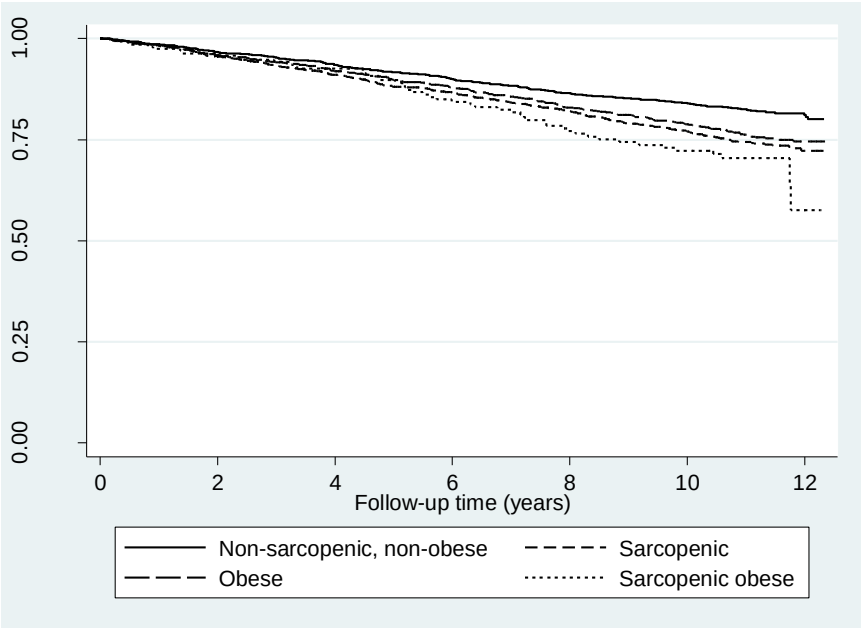
Sarcopenic obesity defined as: MAMC = below the second quintile; WC >102cm.

Figure 5.11 Kaplan-Meier survival curves comparing CVD mortality by sarcopenic obesity groups (defined by mid-arm muscle circumference and waist circumference) in men aged 60-79 years in 1998-2000



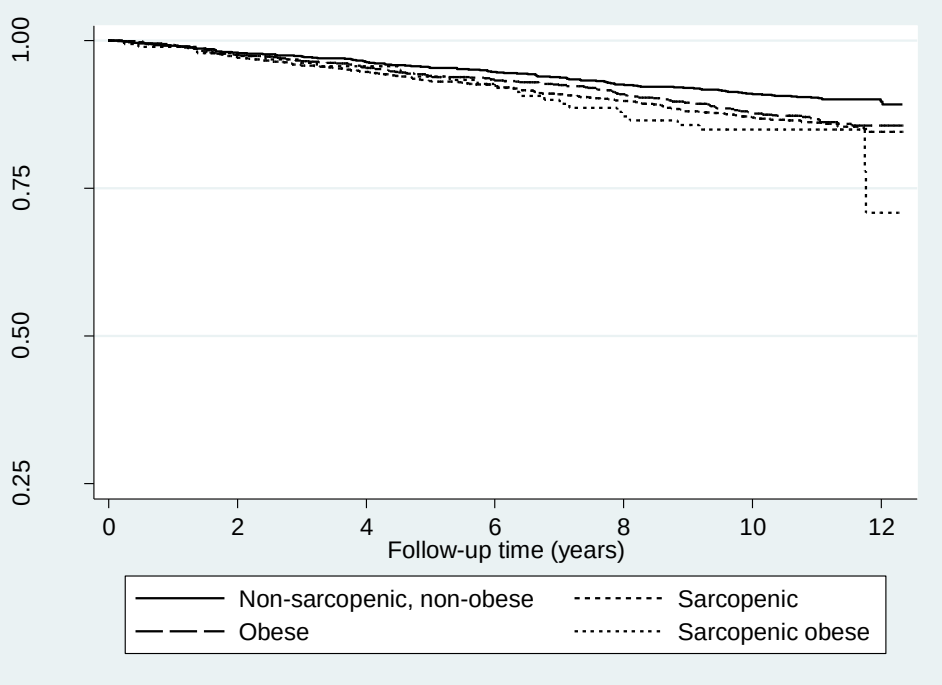
Sarcopenic obesity defined as: MAMC = below the second quintile; WC >102cm.

Figure 5.12 Kaplan-Meier survival curves comparing CVD events by sarcopenic obesity groups (defined by mid-arm muscle circumference and waist circumference) in men aged 60-79 years in 1998-2000



Sarcopenic obesity defined as: MAMC = below the second quintile; WC >102cm.

Figure 5.13 Kaplan-Meier survival curves comparing CHD events by sarcopenic obesity groups (defined by mid-arm muscle circumference and waist circumference) in men aged 60-79 years in 1998-2000



Sarcopenic obesity defined as: MAMC = below the second quintile; WC >102cm.

CHAPTER 6 Associations between diet quality scores, cardiovascular risk factors and risk of cardiovascular disease and mortality in older British men

6.1. Summary

Diet is a well-established risk factor for cardiovascular disease (CVD) and in recent times the focus of dietary research has been on overall diet quality rather than on individual foods or nutrients. However, few studies have investigated the relationship between *a priori* defined dietary patterns (using pre-defined diet indexes or scores) and the risks of CVD and mortality in older adults. This chapter examines the prospective associations between *a priori* diet quality scores and the risk of CVD and all-cause mortality in older British men. At the 20 year re-examination in 1998-2000, 4252 men from the British Regional Heart Study (BRHS) attended a physical examination, provided a fasting blood sample and completed both a general lifestyle questionnaire and a food frequency questionnaire (FFQ), and were followed up until 2010 for cardiovascular events and mortality. Baseline FFQ data were used to generate two dietary scores – the Healthy Diet Indicator (HDI), based on World Health Organization (WHO) dietary guidelines, and the Elderly Dietary Index (EDI), based on a Mediterranean-style dietary intake, with higher scores of both indicating healthier diets. A total of 3328 men, aged 60-79 years, free from CVD at baseline, were included in the analysis. Cox proportional hazards regression analyses were used to assess prospective associations between quartiles of adherence to the HDI or the EDI and the risk of all-cause mortality, CVD mortality, CVD events and coronary heart disease (CHD) events. During the follow-up period, there were 933 deaths, 327 CVD deaths, 582 incident CVD events and 307 incident CHD events. Men in the highest compared to the lowest quartile of EDI adherence had significantly lower risks of all-cause mortality (hazard ratio [HR]: 0.75, 95% CI: 0.60-0.94, p-trend: 0.03), CVD mortality (HR: 0.63, 95% CI: 0.42-0.94, p-trend: 0.03) and CHD events (HR: 0.66, 95% CI: 0.45-0.97, p-trend: 0.05), and a lower risk, but non-significant, for CVD events (HR: 0.79, 95% CI: 0.60-1.05, p-trend: 0.16) after adjustment for socio-demographic, behavioural and cardiovascular risk factors. However, HDI was not significantly associated with any of the outcomes. Thus the EDI rather than the HDI was associated with CVD and mortality risk in older men. Encouraging older adults to adhere to a dietary pattern close to that defined in the

EDI criteria may reduce the risk of all-cause mortality, especially from CVD, and hence have public health benefits.

6.2. Introduction

Diet quality is a major modifiable risk factor well established in the prevention of CVD and mortality and diet may be particularly important in the elderly, who are a group at high risk of CVD [8;23;202], as discussed in Chapter 2, section 2.5. Historically, research into the relationships between diet and CVD or mortality has focused on single nutrients or foods, but more recently the focus has shifted towards markers of overall diet quality and dietary patterns, in order to reflect the multidimensional nature of diets consumed in the population[28;29]. Chapter 2 introduced the two main approaches to assess dietary patterns: (1) *a priori* approaches, which are hypothesis oriented or theoretically defined, since they use available scientific evidence to generate predefined dietary scores or indices based on dietary recommendations or guidelines; and (2) *a posteriori* approaches, which are data-driven or exploratory, since dietary patterns are derived from the available data based on methods such as principal component analysis, or cluster analysis[29;30]. However, few studies have examined the relationship between both *a priori* or *a posteriori* defined dietary patterns and the risk of CVD and mortality in older adults in particular. This chapter will focus on *a priori* diet quality scores in relation to CVD and mortality, and the associations with *a posteriori* dietary patterns will be addressed later in the thesis (see Chapter 8).

To date, many different *a priori* dietary scores have been developed to assess diet quality, based on adherence to dietary patterns or dietary recommendations[195;204]. Although several studies have examined the associations between *a priori* diet quality scores and CVD risk in middle age, few studies have investigated the relationship specifically in older adults[31-33;335]. The Healthy Diet Indicator (HDI) is based on adherence to WHO nutrient intake dietary guidelines, and which has been shown to be inversely associated with all-cause mortality risk in older European men[234]. One of the most commonly used predefined dietary patterns is the Mediterranean Diet Score (MDS), which is characterised by a high consumption of fruit, vegetables, legumes, cereal and fish, and a low-to-moderate consumption of meat, dairy products and

alcohol, mostly as wine[226]. MDS adherence has been consistently associated with a lower risk of CVD and mortality in European cohorts[31;32;226;336]. However, the MDS is based on a dichotomous scoring system, defining each food intake as high/low using the median intake of foods as a cut-point. Such an approach may be too crude to apply to a UK population, which has previously shown to have low adherence to a Mediterranean style diet[223]. The Elderly Dietary Index (EDI) was developed as a slightly modified version of the MDS based on the consumption frequency of specific foods, but it was developed specifically to address adherence to nutritional recommendations for older adults in the Mediterranean Islands Study[233]. Unlike the MDS, the EDI uses a four-point scoring system for each food component and it therefore takes account of the U-shaped relationship between certain foods and the risk of health outcomes e.g. meat. Therefore, the EDI may be better suited to an older UK population in which intake of Mediterranean style dietary components is low.

The majority of studies examining the associations between *a priori* diet quality scores and health outcomes in the older adults have focused on all-cause mortality and a recent review suggested that scores which reflect adherence to dietary recommendations based on single nutrients, such as the HDI, were not as strongly associated with mortality as alternative scores based on whole foods or patterns, such as the MDS [234;335;336]. Fewer studies in older age have provided evidence on associations between *a priori* diet quality scores with the risk of cardiovascular outcomes[33]. The EDI is associated with CVD risk factors in the Mediterranean population in which it was developed but it has not been applied to other populations or compared to more widely used dietary indices such as the HDI, which uses a fundamentally different approach to the assessment of diet quality. The HDI is based on adherence to international dietary recommendations (nutrient intake guidelines developed by the WHO)[234] so it has been more widely used (not only in Mediterranean populations) and would therefore make a useful complement to the EDI.

The aim of this chapter is therefore to examine existing dietary patterns that have been shown to have a protective effect on CVD and mortality and to investigate which marker of diet quality would be most applicable to an older UK population. Two *a*

priori dietary scores (the HDI and the EDI), were applied to older British men aged 60-79 years and cross-sectional associations between these dietary patterns and cardiovascular risk factors, and prospective associations with the risk of incident CHD events, incident CVD events, CVD mortality and all-cause mortality were examined.

6.3. Objectives

To examine the associations of *a priori* defined dietary scores and cardiovascular risk factors, and the risk of CVD and mortality in older age (60-79 years). The specific aims of this chapter are:

i) To describe the dietary intake of a cohort of older men.
ii) To apply *a priori* dietary scores to the BRHS cohort.
iii) To examine the relationship of *a priori* dietary scores and cardiovascular risk factors.
iv) To examine the association between *a priori* dietary scores and risk of CHD events, CVD events, CVD mortality and all-cause mortality.
v) To examine the association between individual components of *a priori* dietary scores and risk of CHD events, CVD events, CVD mortality and all-cause mortality.

6.4. Methods

6.4.1. Subjects and methods of data collection

Data analysed in this chapter are based on the 20 year re-examination of BRHS participants in 1998-2000, aged 60-79 years. In all, 4252 men (77% of survivors) attended a physical examination, provided a fasting blood sample, and completed both a general questionnaire, answering questions on their lifestyle and medical history, and a food frequency questionnaire (FFQ)[264]. Participants were then followed up prospectively from re-examination (1998-2000) through to June 2010 for cardiovascular mortality and morbidity; follow-up was successfully achieved for 98% of the cohort[35]. Information on deaths was collected through the National Health Service Central Register (death certificates were coded using International Classification of Diseases, ninth revision [ICD-9]). On-going reports from general practitioners and biennial

reviews of the patients' medical records provided evidence regarding non-fatal cardiovascular events[264]. The four main outcomes examined in this chapter were: CHD events (diagnosis of non-fatal myocardial infarction [MI] or fatal CHD [ICD-9 codes 410-414]); CVD events (diagnosis of non-fatal MI, non-fatal stroke or fatal CVD [ICD-9 codes 390-459]); CVD mortality (ICD-9 codes 390-459) and all-cause mortality. Two additional outcomes were also considered in further exploratory analysis: stroke events (defined as non-fatal or fatal stroke; ICD-9 codes 430-438) and non-CVD mortality (all deaths excluding ICD-9 codes 390-459). Participants were censored at date of death or at the end of the study period (June 2010) if still alive. Of the 4252 men attending the physical examination, 723 participants free from prevalent MI, stroke and heart failure at baseline were excluded, leaving 3529 participants for analysis. Men with prevalent CVD were excluded, since dietary changes may have occurred in these individuals following diagnosis and also no measure of the severity of CVD was available for these participants.

6.4.2. **Dietary assessment**

Dietary intake was measured at aged 60-79 years in 1998-2000 via a self-completed postal FFQ, with participants reporting their usual frequency of consumption of 86 food and drink items, as described in detail in Chapter 3, section 3.3.2 (see Appendix VI for a copy of the FFQ used). Total macronutrient and micronutrient intakes were derived using a validated computer program to calculate the total nutrient composition of foods consumed[301]. The multivariate nutrient density model was used to adjust macronutrients for energy intake[280]; carbohydrates, fats and protein were expressed as percentages of energy (% kcal). Participants were asked how often they consumed fresh fruit and vegetables (rarely/never, monthly, or 1, 2, 3, 4, 5, 6, or 7 days per week), with daily consumption classified as 7 days per week. Plasma vitamin C and E levels were also available from blood samples collected at the re-examination (1998-2000)[301].

6.4.3. **Defining dietary patterns *a priori***

Diet quality was assessed using two predefined *a priori* dietary scores – the Healthy Diet Indicator (HDI) and the Elderly Dietary Index (EDI). In additional analyses, the Mediterranean Diet Score (MDS) was also used for comparative purposes.

6.4.3.1 The Healthy Diet Indicator

The HDI was constructed using the WHO dietary guidelines for the intake of nutrients and food components, as originally used by Huijbregts et al[8;234] (see table 2.3 for details of original components and scoring). The slightly modified HDI used here consisted of eight components (saturated fatty acids [SFA]; polyunsaturated fatty acids [PUFA]; protein; carbohydrates; sugar; fibre; cholesterol; fruit and vegetables), each scoring one if the dietary guideline was met or zero otherwise, resulting in a total score ranging from 0 to 8 (see Table 6.1 for full details). Dietary data for pulses, nuts and seeds were not available so this component could not be included in the HDI. The cut-off points for PUFA and fibre intake were modified for use in a British population as performed previously[232;337]. The weight of fruit and vegetables consumed was not available, so this component was modified from the recommendation of ≥ 400g/day to the daily consumption of both fruit and vegetables (defined as a consumption frequency of 7 days per week for both fruits and vegetables). A higher HDI score indicated greater compliance with WHO dietary recommendations and hence a healthier diet.

6.4.3.2 The Elderly Dietary Index

The EDI was developed by Kourlaba et al, specifically to address adherence to nutritional recommendations for older adults, based on the consumption frequency of specific foods in the Modified MyPyramid for Older Adults[233]. The EDI consisted of nine components (meat; fish and seafood; legumes; fruit; vegetables; cereals; bread; olive oil; dairy), each assigned a four-point scoring system based on the frequency of consumption, resulting in a total score range from 9 to 36 (see Table 6.2 for full details). Score 4 was assigned for the highest consumption of fruits, vegetables, cereals and olive oil. However, for meat, fish/seafood, and legumes, score 4 was achieved for moderate consumption (1-2 days/week). For bread intake, score 4 was assigned when someone consumed only whole grain bread and for dairy, score 4 was assigned for low fat milk and cheese intake only. The frequency of olive oil consumption was not available so the scoring of this component was modified from the original score used (1 = <1 day/week; 2 = 1-2 days/week; 3 = 3-6 days/week; 4 = daily) to the quantity of weekly consumption (1 = never/rarely consumed; 2-4 = tertiles 1-3 of intake for those who did consume olive

oil). The EDI was limited to food items to make it more comparable to the HDI and therefore the alcohol component was not included. However, alcohol (frequency of wine consumption collected as glasses/week in the FFQ) was included as an additional component of the EDI for sensitivity analysis only. A higher EDI score indicated greater adherence to the dietary pattern and hence a healthier diet.

6.4.3.3 The Mediterranean Diet Score

For comparative purposes with the HDI and the EDI, the modified Mediterranean Diet Score (MDS), as initially developed by Trichopoulou et al[226;336], was also applied to this cohort. The MDS consisted of eight components with a total score range from 0 to 8 (see Table 6.3 for details). Participants whose consumption of each of six beneficial dietary components (vegetables; legumes; fruits; cereals; fish and the ratio of the intakes of the sum of monounsaturated and polyunsaturated to saturated fatty acids) was below the median scored zero for each item, or a value of one otherwise. Participants whose consumption of detrimental components (meat; dairy) was below the median consumption scored one or a value of zero otherwise.

6.4.4. **Cardiovascular risk factors**

Established and emerging cardiovascular risk factors were measured at the 20 year re-examination in 1998-2000. Self-reported measures of smoking, physical activity and alcohol intake were collected via questionnaire as described in Chapter 3, section 3.3.3 Participants were classified into four cigarette smoking groups (never smoked; long-term ex-smokers, >15 years; recent ex-smokers, ≤ 15 years; current smokers)[90]. Current physical activity was classified into six groups based on frequency and intensity of exercise (inactive; occasional; light; moderate; moderately vigorous and vigorous)[283]. Alcohol intake was classified into five groups based on the number and frequency of alcoholic drinks consumed per week (none; occasional; light; moderate; heavy)[282]. Adult occupational social class was based on the longest held occupation recorded at study entry, in 1978-80, using the Registrar General's occupational classification[285], as described in Chapter 3 (section 3.3.4). Participants were classified as manual, non-manual or armed forces. Region of residence was categorised according to whether the town of each participant at the examination in 1998-2000 was in southern England

region or the rest of Britain. At the physical examination in 1998-2000, systolic blood pressure (SBP) was measured and the collection of a fasting blood sample allowed the measurement of plasma concentrations of metabolic risk factors (glucose, triglyceride and high density lipoprotein [HDL]) and inflammatory/hemostatic markers (C-reactive protein [CRP], tissue plasminogen activator [t-PA], D-dimer, von Willebrand Factor [vWF], fibrinogen, interleukin 6 (IL-6) and homocysteine) as described in Chapter 3 (section 3.3.5 and 3.3.6). In addition, at the 20 year examination, participants were classified as having prevalent diabetes if they had a self-reported previous diagnosis. Assessment of body composition also occurred at the 20 year re-examination and measures used within this chapter include body mass index (BMI), waist circumference (WC) and mid-arm muscle circumference (MAMC), as described in Chapter 3 (section 3.3.1). Participants were classified into four BMI categories using WHO cut-points (underweight, <18.5 kg/m^2; normal weight, 18.5-24.99 kg/m^2; overweight, 25-29.99 kg/m^2; obese, ≥ 30 kg/m^2)[105].

6.4.5. **Statistical methods**

Of the 3529 men free from prevalent CVD, 3328 had adequate data to generate either the HDI or the EDI score (n = 3133 and n = 3269 respectively). Sensitivity analyses were carried out, restricting the sample to those where both HDI and EDI measures were available (n = 3074). However, the results were largely unchanged, so the number of individuals with data on HDI or EDI respectively were kept in the analysis for each index in order to maximise the sample size and hence the power. Participants were categorised into quartiles of the HDI and the EDI, using cut off points that produced the nearest categorisation into equal sized groups that these integer data would allow. Baseline cardiovascular risk factors of participants were presented by quartiles of HDI and EDI scores with continuous variables reported as means and standard deviations, and categorical variables as percentages. The distributions of CRP, D-dimer, IL-6 and homocysteine were highly skewed, so log transformation and the interquartile range was presented.

Cox proportional hazards models were used to estimate HRs and 95% CIs for the associations between individual components of the HDI/EDI scores with the risk of

each outcome. To assess the effect of each indivivual HDI/EDI component independently of the other compoenents, modified versions of the HDI/EDI score, not containing the individual component of interest, was generated. For example, when examining the association between meat intake (an individual component of the EDI) and outcomes, a modified version of the EDI score was created which did not contain meat as a component part. Models were then adjusting for age (model 1) and energy intake, smoking status, alcohol intake, physical activity, social class, BMI and the modified version of the HDI/EDI score, not containing the individual component of interest (model 2).

Cox proportional hazards models were also used to assess associations between quartiles of the total HDI/EDI scores with the risk of each outcome. Tests for trend of outcome risk across quartiles of HDI/EDI were performed. Similarly, comparative analyses were carried out to assess associations between quartiles of the total MDS score with the risk of outcomes. All Cox models were tested for the proportional-hazards assumption, on the basis of Schoenfeld residuals, which was not found to be violated. Models were adjusted by adding potential confounders, related to both diet quality and cardiovascular risk, in a sequential manner, including age (model 1), energy intake, smoking status, alcohol intake, physical activity, social class and BMI (model 2), HDL, SBP and diabetes (model 3) and finally CRP and vWF (model 4). Age, energy intake, HDL, SBP, CRP and vWF were fitted as continuous variables. Smoking status, alcohol intake, physical activity, social class, BMI and diabetes were fitted as categorical variables.

6.5. Results

6.5.1. Dietary characteristics of the study population

The proportion of men adhering to dietary guidelines according to the HDI is presented in Table 6.1, the proportion of men achieving the highest score for each of the EDI components is presented in Table 6.2 and the mean dietary intake of the cohort is presented in Table 6.4. The mean total energy intake was 2140 kcal/day, with 52.4% of energy coming from carbohydrates, 15.6% from protein and 30.3% from fat (of which

12.4% was from saturated fat and 4.5% from polyunsaturated fat). The HDI and EDI scores were both normally distributed. The mean HDI score was 2.9, ranging from 0 to 7, and the mean EDI score was 24.2, ranging from 12 to 35. HDI and EDI scores were significantly, but modestly correlated (r: 0.25, 95% CI: 0.22-0.29, p <0.001). Most men met the HDI dietary guideline for carbohydrate intake (64.6% had between 50 and 70% energy from carbohydrates). However, only 41.4% of men had sufficient protein intake to meet the recommended protein intake (10-15% of total energy). Intake of saturated and polyunsaturated fat was higher than recommended for most men; only 25.2% met the dietary guideline of less than 10% energy intake from saturated fat and only 14.6% met the dietary guideline of between 6 and 10% energy intake for polyunsaturated fat. The mean cholesterol intake was 278 mg/d, with 64.4% of the cohort meeting the dietary recommendation of less than 300 mg/d. The dietary recommendation for fibre was met by 61.3% of the men, with a mean daily intake of 26g. Over a third of participants consumed fruit (42.3%) or vegetables (33.4%) daily but less than one in five consumed both fruit and vegetables daily (18.1%). In terms of the individual EDI components, more than half of all men achieved the highest score for intake of fish/seafood (56.0% had a consumption of 1-2 days/week), legumes (50.6% had a consumption of 1-2 days/week) and cereals (65.8% had daily consumption). Components of the EDI in which very few men achieved the highest score included meat (only 4.9% consumed meat on 1-2 days/week) and olive oil (only 9.2% were in the highest tertile of intake).

6.5.2. *A priori* diet quality scores, cardiovascular risk factors and dietary factors

6.5.2.1 Healthy Diet Indicator, cardiovascular risk factors and dietary factors

Cardiovascular risk factors and dietary factors are presented by quartiles of HDI in Table 6.5. Men with a higher adherence to the HDI were significantly less likely to be current smokers, heavy drinkers and of manual social class, and significantly more likely to live in the southern England region. HDI scores showed a significant inverse trend with the proportion of obese men and with mean WC, but no significant trend was observed with MAMC. As expected, several dietary variables showed significant trends with HDI. Men with the highest adherence to HDI dietary recommendations had lower levels of total energy intake and a lower percentage energy from total fat, saturated fat and protein, and a higher percentage energy from carbohydrates, higher intake of fibre,

vitamin C, vitamin E, higher plasma vitamin E and a higher proportion of these men consumed fruit and vegetables daily. Men with higher HDI scores showed significantly lower HDL and glucose levels, but SBP, triglycerides and prevalent diabetes were not associated. HDI scores also showed significant inverse trends with a number of inflammatory and haemostatic markers, including CRP, t-PA, IL-6 and homocysteine, but no relationship was seen with D-dimer, vWF or fibrinogen.

6.5.2.2 Elderly Dietary Index, cardiovascular risk factors and dietary factors

Cardiovascular risk factors and dietary factors are presented by quartiles of EDI in Table 6.6. Very similar relationships were observed as with the HDI, with participants in the highest EDI quartile having the least adverse cardiovascular risk profile. However, in contrast to HDI, EDI showed a significant positive, rather than an inverse, trend with percentage energy from protein. Compared to the HDI, the EDI also showed significant inverse trends with age and triglycerides, and significant positive trends with MAMC, iron intake, plasma vitamin C, the prevalence of diabetes, and levels of glucose, D-dimer, VWF and fibrinogen.

6.5.3. ***A priori* diet quality scores and risk of CVD/mortality**

During a mean follow-up period of 11.3 years, there were 933 deaths from all causes, 327 CVD deaths, 582 CVD events and 307 CHD events.

Associations between *a priori* diet quality scores (HDI and EDI scores) and risk of cardiovascular outcomes and all-cause mortality were all adjusted for total energy intake[280]. However, since total energy intake showed strong inverse associations with both the HDI and the EDI dietary scores (Table 6.5 and Table 6.6), the associations between total energy intake and the risks of outcomes were investigated, to ensure adjusting for energy intake would not represent an over-adjustment[338]. However, total energy intake was not significantly associated with all-cause mortality, CVD mortality or CHD events in age-adjusted analysis (p-trend all less than 0.05). Energy intake showed a slight positive association with CVD events (p-trend: 0.03), but this became non-significant after adjustment for cardiovascular risk factors including, smoking

status, alcohol intake, physical activity, social class, BMI, HDL, SBP and prevalent diabetes.

6.5.3.1 Healthy Diet Indicator and risk of CVD/mortality

Hazard ratios for CHD events, CVD events, CVD mortality and all-cause mortality by quartiles of total HDI score are presented in Table 6.7. Quartiles of HDI were not significantly associated with all-cause mortality, CVD mortality, CVD events or CHD events after adjustment for age (model 1). This lack of association was unchanged after further adjustment for energy intake, socio-demographic, behavioural and cardiovascular risk factors.

6.5.3.2 Healthy Diet Indicator components and risk of CVD/mortality

The associations between individual HDI components and the risk of CHD events, CVD events, CVD mortality and all-cause mortality were also examined (Table 6.8). Few individual components were significantly related to outcomes. Meeting the dietary guideline for protein intake was associated with an increase in risk of all-cause mortality and CHD events in the age-adjusted model. However, these associations became non-significant after further adjustment for socio-demographic and behavioural risk factors, and a modified version of the HDI score not containing the individual component of interest. Dietary cholesterol was the only component associated with outcomes after adjustment, with participants meeting the dietary recommendation for cholesterol intake having a 33% lower risk of CVD mortality (HR: 0.67, 95% CI; 0.50-0.90.)

6.5.3.3 Elderly Dietary Index and risk of CVD/mortality

Hazard ratios for the risks of CHD events, CVD events, CVD mortality and all-cause mortality are presented by quartiles of total EDI in Table 6.9. The risk of all-cause mortality showed a significant inverse trend with EDI quartiles, which remained but was attenuated slightly after adjustment for energy intake, smoking status, alcohol intake, physical activity, social class, BMI, HDL, SBP, diabetes, CRP and vWF (model 4); the risk of all-cause mortality was significantly lower in participants in the highest compared to the lowest EDI quartile (HR: 0.75, 95% CI: 0.60-0.94, p-trend; 0.03).

Similarly, the risks of CVD mortality and CHD events were also inversely associated with EDI quartiles and although the association was attenuated slightly by adjustment for socio-demographic, behavioural and cardiovascular risk factors, participants in the highest quartile of EDI still had a significantly lower risk of CVD mortality (HR: 0.63, 95% CI: 0.42-0.94, p-trend: 0.03) and CHD events (HR: 0.66, 95% CI: 0.45-0.97, p-trend: 0.05). To explore whether the inverse associations observed between EDI quartiles and risk of all-cause mortality, CVD mortality and CHD events were potentially mediated by the effects of muscle mass, analyses were further adjusted for MAMC. However, results were virtually unchanged after this additional adjustment.

Although the risk of CVD events was lower in participants in the highest EDI quartile, this difference was not however significant after adjustment for confounders (HR: 0.79, 95% CI: 0.60-1.05, p-trend: 0.16) [model 4]. Further exploration of the data showed that there was no appreciable association between quartiles of EDI and stroke events (stroke events, n = 221; age-adjusted p-trend: 0.41). Additional analysis of cause-specific mortality showed that the risk of non-CVD mortality was not significantly associated with EDI quartiles after adjusting for confounders (p-trend: 0.24).

A sensitivity analysis was also carried out, including alcohol as an additional component of the EDI, and this yielded broadly similar results to those presented above. Risks of outcomes tended to show an inverse trend with EDI quartiles, with men in the highest compared to the lowest EDI quartile having lower risks of all-cause mortality (HR: 0.71, 95% CI: 0.55-0.91, p-trend : 0.02) and CVD mortality (HR: 0.58, 95% CI: 0.37-0.91, p-trend: 0.03), after adjustment for socio-demographic, behavioural and cardiovascular risk factors. However, this trend was weaker and was of borderline significance for CVD events (HR: 0.70, 95% CI: 0.51-0.96, p-trend: 0.06) and CHD events (HR: 0.66, 95% CI: 0.43-1.02, p-trend: 0.08).

6.5.3.4 Elderly Dietary Index and risk of CVD/mortality, in men with prevalent CVD

The results presented above on the associations between EDI quartiles and outcomes are based on participants free from prevalent MI, stroke and heart failure at baseline. In

sensitivity analysis, analyses were also carried out in participants with and without prevalent CVD at baseline (n = 4252) and in those with prevalent CVD at baseline only (n = 723). However, no significant associations were observed between EDI quartiles and all-cause mortality, CVD mortality, CVD events or CHD events in either of these groups. This justifies excluding individuals with prevalent CVD from the current analysis, as including them would have contaminated results.

6.5.3.5 Elderly Dietary Index components and risk of CVD/mortality

The associations between individual EDI components and the risk of CHD events, CVD events, CVD mortality and all-cause mortality were also examined (Table 6.10). As with the individual HDI components, few EDI components were significantly related to outcomes. Participants in the highest EDI quartile for fish/seafood intake had a lower risk of CVD mortality and CHD events, and those in the highest EDI quartile for fruit and vegetables had a lower risk of all-cause mortality in the age-adjusted models (model 1). However, these associations became non-significant after further adjustment for socio-demographic and behavioural risk factors, and a modified version of the EDI score not containing the individual component of interest (model 2). Olive oil intake was the only individual component associated with outcomes after adjustment (model 2); participants in the highest quartile of intake had a lower risk of all-cause mortality (HR: 0.68, 95% CI: 0.51-0.91), CVD mortality (HR: 0.43, 95% CI: 0.24-0.80), CVD events (HR: 0.58, 95% CI: 0.40-0.86) and CHD events (HR: 0.55, 95% CI: 0.32-0.95).

6.5.3.6 Mediterranean Diet Score and risk of CVD/mortality

Comparative analyses using the MDS yielded weaker associations compared to the EDI (results not presented). A strong significant inverse trend was observed between MDS quartiles and the risk of all-cause mortality in age adjusted analysis (highest vs. lowest quartile; HR: 0.68, 95% CI: 0.57-0.82, p-trend <0.001). However, this trend showed only borderline significance after adjustment for energy intake, smoking status, alcohol intake, physical activity, social class, BMI, HDL, SBP, diabetes, CRP and vWF (highest vs. lowest quartile; HR: 0.87, 95% CI: 0.70-1.07, p-trend: 0.05). However no significant trend was observed between MDS quartiles and the risk of CVD mortality (p-trend: 0.40), CVD events (p-trend: 0.97) or CHD events (p-trend: 0.57) in adjusted analysis.

6.6. Discussion

6.6.1. Summary of main findings

This chapter applied two *a priori* diet quality scores to an older British population, the HDI (based on WHO dietary recommendations) and the EDI (based on the consumption frequency of specific foods/food groups) and examined their associations with cardiovascular risk factors, and the risk of cardiovascular events and mortality. Higher adherence to either the HDI or the EDI dietary scores was associated with the least adverse cardiovascular risk profile. Men with higher adherence to the EDI had a significantly lower risk of all-cause mortality, CVD mortality and CHD events, which was independent of socio-demographic, behavioural and cardiovascular risk factors. However, the HDI score was not significantly associated with any of the outcome measures, suggesting that the EDI is more strongly associated with CHD events, CVD mortality and all-cause mortality in an older population. The results from this chapter add to the limited literature on the relationships between *a priori* diet quality scores and cardiovascular mortality and morbidity in older adults.

6.6.2. Comparison with previous studies

6.6.2.1 Diet of the cohort

The key features of dietary intake of BRHS participants observed in this chapter, obtained from a FFQ in 1998-2000, were broadly comparable with those from the National Diet and Nutrition Survey (NDNS), a nationally representative sample of adults aged 19 to 64 years in Great Britain, carried out between 2000 and 2001[339]. Men aged 50 to 64 years olds in the NDNS, the oldest age group, had a slightly higher mean total energy intake (2271 kcal compared to 2139 kcal in the BRHS), a lower mean percentage of energy from carbohydrates (47.4 % compared to 52.4%), a higher mean percentage of energy from protein (17.0 % compared to 15.6%) and a higher mean percentage energy from total fat (35.6 % compared to 30.3%). In terms of meeting the WHO dietary guidelines included in the HDI[8;234], only three components (total carbohydrates, dietary fibre and cholesterol) were met by the majority (>50%) of the men. The mean percent of energy from carbohydrate was within the 50-70% WHO

recommendation, however, the mean percent of energy from protein and saturated fat were above the WHO recommendations of 10-15% and 0-10% respectively.

6.6.2.2 Healthy Diet Indicator, CVD and mortality risk

Cross-sectional analyses showed that diet quality, assessed by the HDI, was inversely associated with adverse cardiovascular risk factors, which was consistent with previous studies[340;341]. Men with a higher adherence to the HDI were less likely to be current smokers, heavy drinkers, from manual social class, had a lower proportion of obesity, lower WC, lower level of HDL, glucose and several plasma/inflammatory markers. These findings are consistent with a review in older adults which showed that diets characterised by more favorable dietary scores or indices (including one study using the HDI[342]), are generally inversely related to BMI and WC[343]. HDI, was not however associated with MAMC, despite evidence that low muscle mass is related to several dietary components including low intake of protein, total energy, vitamin D, antioxidants and omega-3 polyunsaturated fatty acids[132;133].

However, despite cross-sectional association between the HDI and cardiovascular risk factors, the HDI was not significantly associated in prospective analyses with the risk of all-cause mortality, CVD mortality, CVD events or CHD events in the present study. The HDI was initially developed by Huijbregts et al who, in contrast to findings in this chapter, found a significant inverse association between HDI and all-cause mortality risk and an even stronger association with CVD mortality risk, over 20 years of follow-up in elderly men from Finland, Italy and the Netherlands[234]. Results in this chapter also contrast with those from a review in older adults, aged 60 years or older, which assessed the association between adherence to the HDI and risk of mortality in 11 prospective cohort studies[236]. The meta-analysis showed that closer adherence to the WHO guidelines of the HDI was associated with greater longevity in elderly men and women in Europe and the United States. However, findings in this chapter are consistent with those of two studies not included in this meta-analysis. An elderly British cohort of men and women, aged 65 years and older, showed no significant association between a slightly modified version of the HDI and all-cause mortality during a follow-up period

of 14 years[232]. Similarly, an elderly male Swedish cohort, with a mean age of 71 years, also found no consistent associations between HDI and all-cause or CVD mortality over 10 years of follow-up[237]. These differences in findings could perhaps be explained by different populations being studied or due to the sample size differences between studies.

6.6.2.3 Elderly Dietary Index, CVD and mortality risk

As with the HDI, cross-sectional analyses showed that diet quality, assessed by the EDI, was inversely associated with adverse cardiovascular risk factors. These results are consistent with the original study by Kourlaba et al, who developed the EDI, and showed cross-sectional associations between higher adherence to the EDI and a lower risk of CVD risk factors including obesity and hypertension in the Mediterranean Islands Study[233]. A significant positive association was also observed in this cohort between the EDI and the MAMC. Interestingly, in this cohort, measures of muscle mass showed weak associations with individual nutrients (see Chapter 4) but stronger associations were observed here between muscle mass and diet quality.

One important finding in this chapter was the observation that only one individual component of the EDI (olive oil intake) was inversely associated with CVD outcomes and mortality. This is consistent with the results of a meta-analysis showing that higher intake of olive oil is associated with a lower risk of all-cause mortality, CVD mortality and CVD events in pooled analysis of 32 cohort studies[344]. There was a significant trend between increasing EDI score and decreasing risk of CHD events, CVD mortality and all-cause mortality, and broadly similar results were found in sensitivity analysis when including alcohol as an additional component of the EDI. The fact that the majority of individual components of the EDI were not associated with outcomes (except olive oil), but the total score was significantly associated with CHD events, CVD mortality and all-cause mortality supports the notion that research on individual food items is not useful and justifies the use of diet scores in nutritional research, as suggested previously[28;29;195].

To my knowledge, this is the first study to apply the EDI to another population, and to examine the incidence of cardiovascular events and mortality by EDI score. The results observed in this cohort are consistent with those of Kourlaba et al[233], while also extending them in suggesting that the EDI is valid for use in an older British population and that higher adherence to the EDI showed significant lower risks of all-cause mortality, CVD mortality and CHD events. These results are consistent with a substantial body of literature showing strong associations between a Mediterranean style diet and lower risk of CVD and all-cause mortality, in both middle aged and older populations[31-33;336;345]. The associations observed here between the EDI and CHD events, CVD mortality and all-cause mortality were attenuated slightly, although they remained statistically significant, after adjustment for BMI, HDL, SBP and diabetes, The relationship could therefore to some extent be associated with higher BMI in those with lower EDI scores which in turn may lead to physiological risk factors for CVD e.g. higher lipid levels and blood pressure. Further adjustment for CRP and vWF attenuated the association slightly further suggesting that the association between diet quality and CVD could to a small extent also be explained by chronic inflammation and endothelial dysfunction, with a diet low in antioxidants possibly leading to higher inflammation, as has been suggested previously[346-348]. Muscle mass however, did not appear to be a mediator of this relationship, as results were essentially unchanged after adjustment for MAMC.

Despite the observed association with CVD mortality and CHD events, EDI was not associated with CVD events. This could be explained by the fact that the EDI was not associated with stroke events, and fatal CVD was dominated by fatal CHD (n = 189) with far fewer stroke deaths (n = 64) in this cohort. Results observed in this chapter are in keeping with literature suggesting adherence to a Mediterranean style diet is more strongly associated with fatal CVD than total CVD[349].

In comparison with the EDI, the MDS showed a weaker association with all-cause mortality and no significant associations with CVD mortality, CVD events or CHD mortality. EDI components are very similar to those of the MDS but the EDI was developed specifically to address adherence to nutritional recommendations for older

adults. The MDS uses dichotomous median cut-off values, and hence does not take into account the full range of consumed foods, which may not be appropriate for a population with low adherence to dietary guidelines[204;223]. In comparison, the EDI uses a four-point scoring range which captures a wider range of food intakes and also takes into account U-shaped relationships that exist between some foods, such as meat, and disease risk[204;233;336]. Results in this chapter suggest that the EDI may be more suited to an older UK population than the MDS, as it seemed to be a less crude Mediterranean diet quality measure for use in a population with low Mediterranean style dietary adherence[223]. The median scoring system used for the MDS makes generalisability to other populations difficult, in contrast with the EDI.

6.6.2.4 Elderly Dietary Index versus the Healthy Diet Indicator

Results from this chapter suggest that diet quality scores based on specific food or food groups, such as the EDI, may be a better predictor of CHD events, CVD mortality and all-cause mortality compared to scores based on recommended nutrient intakes, such as the HDI, in an older population. This is consistent with the findings of a recent review which found that *a priori* defined scores based on nutrient dietary recommendations, such as the HDI, were not as strongly associated with mortality as scores based on whole foods or dietary patterns, such as the EDI or MDS[335]. This may be explained by the fact that the intake of specific food/food groups are simpler to measure and less prone to measurement error compared to the process of generating total dietary macronutrient and micronutrient intakes for the HDI, which assumes standard portion sizes of foods consumed and relies on having a food composition database that is complete and up to date[104]. Furthermore, a critical review of predefined diet quality scores previously questioned the use of diet quality indexes based on dietary guidelines, such as the HDI, and suggested that diet score ranges are preferable to simple cut-offs, since they are more subtle; the EDI may be more nuanced than the HDI as it uses a four-point scoring system as opposed to a dichotomous scoring system, and can also take into account U-shaped associations between foods and health outcomes[204]. The EDI therefore seems to have practical advantages over the HDI, as it is a more easily applicable tool for assessing diet quality among the elderly[233] and more strongly predictive of the risk of CHD events, CVD mortality and all-cause mortality.

6.6.3. **Strengths and limitations**

The major strengths of the results presented in this chapter are that data are from a moderately large and representative prospective population-based study, with negligible loss to follow-up and objective ascertainment of CVD and mortality outcomes[35;264]. However, since the study comprised predominately of white European older male participants, the generalisability of the findings to non-white ethnic groups and women is uncertain. Moreover, results may not be applicable to men with prevalent MI, stroke or heart failure since such participants were excluded from analyses.

Assessment of dietary intake by self-reported measures can be prone to measurement error through misreporting, which can affect the estimation of energy intake and micronutrient intake[321;322]. The FFQ method in particular, as used in this study, is more prone to measurement error than other dietary measures such as 24-hour dietary recall, dietary diaries or weighed food records that have been collected on several separate occasions[198;200]. Also, in older populations non-response to FFQ questions may have increased the chance of underreporting[190;312]. Misreporting of energy intake may therefore affect dietary pattern analysis, especially since underreporting can be more prevalent for some specific food groups[350;351]. However, the FFQ used in this study has previously been validated against weighed food intakes in British populations[273;274]. In addition, to reduce the risk of bias in dietary assessment, established minimum and maximum cut-offs for total energy intake were applied to the data (<500 or > 8000 kcal[279]) to exclude under and over-reporters. All statistical models were also adjusted for total energy intake to reduce the risk of bias[280], and since total energy intake was not associated with the risk of mortality or cardiovascular outcomes this was not considered an over-adjustment[338]. It is possible that some residual confounding remains in the assessment of dietary patterns, but underreporting of food intake is only likely to have biased the relative risk estimates towards the null.

Another consideration is that the FFQ measured dietary intake at one time point only, so no information was available on whether participants maintained dietary practices throughout the study period or if diet quality changed over time. *A priori* methods of defining dietary patterns also have some limitations. They may be culturally or

regionally specific so may not be universally applicable[30;204]. Results from this chapter show that the HDI did not seem to be associated with the risk of CVD or mortality in an older UK population, but the EDI did show associations. Another limitation of *a priori* diet quality scores is that adding together equally weighed dietary components implies that each component is equally important to the risk of an outcome, which may not be the case[30]. For example, when individual components of the EDI were analysed, olive oil was the only specific component significantly associated with the risk of all-cause mortality, CVD mortality, CVD events and CHD events.

A number of the cardiovascular risk factors examined in this chapter are self-reported in nature, including smoking status, alcohol intake, and physical activity. Therefore, misclassification is possible which could have led to over or under-estimates of hazard ratios. In particular, self-reported measures of physical activity can be a particular problem in older age groups due to the light intensities of activity and vast variability in duration of activity in these age groups which make accurate recall especially difficult[315-317] (as discussed in Chapter 4, Section 4.6.3). However, a validation study in older men within the BRHS has shown self-reported physical activity questions used within this cohort are associated with a graded increase in objectively measured physical activity[318]. This reduces the risk of measurement error, and any possible misclassification of physical activity is likely to have been non-differential between participants with low and high dietary scores and is only likely to have attenuated relative risk estimates between *a priori* dietary scores and outcomes[320].

It is also possible a healthy-adherer/healthy-user effect may also have existed in participants with higher dietary scores, meaning these participants may have been on average more health-conscious and more likely to have exhibited a series of healthier behaviours, including regular visits to their general practitioner, having more preventive tests, higher adherence to medicine etc[352;353]. Such potential confounding variables were unmeasured in this study and hence may have caused a slight over-estimation of the magnitude of effect of diet quality scores on CVD and mortality risk.

6.6.4. **Conclusions**

High adherence to *a priori* diet quality scores, such as the HDI and the EDI, are associated with the least adverse cardiovascular risk factors in older British men. In this cohort, higher adherence to the EDI dietary score was associated with a lower risk of all-cause mortality, CVD mortality and CHD events which were independent of socio-demographic, behavioural and cardiovascular risk factors, including inflammation. Among older men, the EDI is a better measure of a healthy diet than the HDI and may be a more useful tool for diet quality assessment as it was more strongly associated with CHD events, CVD mortality and all-cause mortality risk compared to the HDI, which was not significantly associated with these outcomes. Encouraging older adults to adhere to the dietary patterns inherent in the EDI criteria may lower the risk of all-cause mortality, CVD mortality and CHD events and hence have public health benefits. The influence of social circumstances across the life course on EDI will be explored in Chapter 7.

Table 6.1 Healthy Diet Indicator scoring criteria and baseline scores of men aged 60-79 years in 1998-2000

Component	Criteria for score (0)	Criteria for score (1)	Proportion scoring 1* (%)
Saturated fatty acids (% energy)	>10	0-10	25.2
Polyunsaturated fatty acids (% energy)	<6 and >10	6-10	14.6
Protein (% energy)	<10 and >15	10-15	41.4
Total carbohydrates (% energy)	<50 and >70	50-70	64.6
Sugar (% energy)	>10	0-10	1.2
Dietary Fibre (g/day)	<18 and >32	18-32	61.3
Cholesterol (mg/d)	>300	0-300	64.4
Fruits and Vegetables†	Less frequent than daily consumption of both	Daily consumption of both	18.1

*Proportion adhering to dietary guideline.
†The weight of fruit and vegetables consumed was not available so this component was modified from the original scoring used (1 = ≥ 400g/day; 0 = <400g/day) to the consumption of both fruit and vegetables daily.

Table 6.2 Elderly Dietary Index scoring criteria and baseline scores of men aged 60-79 years in 1998-2000

Component	Criteria for score (1)	Criteria for score (2)	Criteria for score (3)	Criteria for score (4)	Proportion scoring 4 (%)
Meat	≥ 3 days/week	Never/rarely	<1 day/week	1-2 days/week	4.9
Fish/Seafood	Never/rarely	<1 day/week	≥ 3 days/week	1-2 days/week	56.0
Legumes	Never/rarely	<1 day/week	≥ 3 days/week	1-2 days/week	50.6
Fruit	<1 day/week	1-2 days/week	3-6 days/week	Daily	39.7
Vegetables	<1 day/week	1-2 days/week	3-6 days/week	Daily	28.5
Cereals	<1 day/week	1-2 days/week	3-6 days/week	Daily	65.8
Bread	None	White	White and whole grain	Whole grain	28.6
Olive oil*	Never/Rarely	Tertile 1 of intake	Tertile 2 of intake	Tertile 3 of intake	9.2
Dairy	Full-fat milk and full-fat cheese	Semi-skimmed milk and full-fat cheese/full-fat milk and low-fat cheese	Skimmed milk and full-fat cheese	Skimmed/Semi-skimmed milk and low-fat cheese	13.0
Alcohol†	>4 glasses wine/day	3-4 glasses wine/day	No consumption	>0-2 glasses wine/day	41.7

*The frequency of olive oil consumption was not available so this component was modified from the original score used (1 = <1 day/week; 2 = 1-2 days/week; 3 = 3-6 days/week; 4 = daily) to the quantity of weekly consumption.
† Alcohol included as an additional component of the EDI in sensitivity analysis only. 1 glass = 175 ml.

Table 6.3 Mediterranean Diet Score scoring criteria

Component	Score = 0	Score = 1
Vegetables	<median intake	≥ median intake
Legumes	<median intake	≥ median intake
Fruit	<median intake	≥ median intake
Cereal	<median intake	≥ median intake
Fish/Seafood	<median intake	≥ median intake
Monounsaturated & polyunsaturated/saturated fat ratio	<median intake	≥ median intake
Meat*	≥median intake	< median intake
Dairy	≥median intake	< median intake

*Does not contain poultry or fish.

Table 6.4 Dietary intake of men aged 60-79 years in 1998-2000

Dietary variables	n	Mean (SD)*	Range
Energy intake (kcal/d)	3292	2139.2 (531.6)	683.5-5379.1
Carbohydrates (% kcal)	3292	52.4 (6.9)	21.1-75.8
Protein (% kcal)	3292	15.6 (2.3)	7.9-25.9
Fat (% kcal)	3292	30.3 (6.2)	9.5-60.2
Saturated fat (% kcal)	3262	12.4 (3.6)	2.4-34.0
Polyunsaturated fat (% kcal)	3262	4.5 (1.5)	1.2-17.9
Cholesterol (mg/day)	3164	278.1 (113.7)	31.6-972.0
Fibre (g/day)	3328	26.2 (8.7)	0.6-77.0
Vitamin C (mg/day)	3328	83.3 (37.1)	4.3-297.3
Vitamin E (mg/day)	3150	8.5 (4.8	0.9-58.3
Iron (mg/day)	3172	14.2 (5.2)	1.6-44.7
Daily fruit intake (%)	3323	42.3	-
Daily vegetable intake (%)	3325	33.4	-
Plasma vitamin C (µmol/L)	3115	30.7 (26.9)	0-447.9
Plasma vitamin E (µmol/L)	2976	33.8 (12.1)	0.6-118.7
Healthy Diet Indicator score	3133	2.9 (1.3)	0-7
Elderly Dietary Index score	3269	24.2 (3.2)	12-35

*Values presented as mean (SD) unless otherwise stated.

Table 6.5 Cardiovascular risk factors and dietary factors by quartiles of Healthy Diet Indicator in men aged 60-79 years in 1998-2000

	HDI Quartiles				P (trend)
	Q1 (0-2 points)	Q2 (3 points)	Q3 (4 points)	Q4 (5-7 points)	
n	1164	928	728	313	
Median HDI score	2	3	4	5	
Socio-demographic/Behavioural variables					
Age (years)	68.3 (5.5)	68.2 (5.5)	68.4 (5.3)	67.5 (5.0)	0.16
Current smokers (%)	16.2	12.1	8.7	7.1	<0.001
Heavy drinkers (%)	3.9	2.2	2.1	2.3	0.02
Physically inactive (%)	10.4	8.7	9.5	7.7	0.20
Manual social class (%)	50.5	49.7	44.6	48.6	0.04
Living in southern England region (%)	31.9	33.8	38.1	36.1	0.01
Body composition					
Obesity (BMI $\geq$ 30 kg/m^2) (%)	18.4	15.4	13.6	13.8	0.004
WC (cm)	97.9 (10.5)	96.6 (10.7)	96.1 (9.6)	95.7 (9.9)	<0.001
MAMC (cm)	26.6 (2.4)	26.6 (2.3)	26.4 (2.2)	26.5 (2.2)	0.18
Dietary variables					
Energy intake (kcal)	2242.3 (601.4)	2136.4 (529.6)	2047.0 (431.9)	1998.5 (395.4)	<0.001
Carbohydrates (% kcal)	47.9 (6.2)	53.6 (5.9)	56.0 (5.6)	57.0 (5.0)	<0.001
Protein (% kcal)	15.9 (2.2)	15.6 (2.3)	15.5 (2.3)	14.7 (2.0)	<0.001
Fat (% kcal)	33.8 (5.6)	29.6 (5.4)	27.3 (5.3)	26.2 (5.1)	<0.001
Saturated fat (% kcal)	14.5 (3.6)	12.1 (3.0)	10.6 (2.7)	9.5 (2.2)	<0.001
Fibre (g/day)	25.0 (9.8)	26.9 (8.9)	27.3 (7.3)	26.7 (4.9)	<0.001
Vitamin C (mg/day)	78.5 (35.2)	83.9 (38.4)	87.7 (36.0)	93.2 (37.8)	<0.001
Vitamin E (mg/day)	8.0 (4.8)	8.1 (4.4)	8.8 (4.8)	10.5 (5.6)	<0.001
Iron (mg/day)	14.3 (5.6)	14.3 (5.1)	14.5 (5.2)	13.2 (3.4)	0.07
Daily fruit intake (%)	30.7	42.2	53.4	63.5	<0.001
Daily vegetable intake (%)	26.2	31.7	39.9	54.3	<0.001
Plasma vitamin C (µmol/L)	29.8 (24.4)	30.5 (26.9)	32.8 (32.9)	31.1 (19.8)	0.08
Plasma vitamin E (µmol/L)	33.1 (11.6)	33.6 (12.1)	34.2 (12.3)	35.8 (12.3)	0.001

Table 6.5 *Continued*. Cardiovascular risk factors and dietary factors by quartiles of Healthy Diet Indicator in men aged 60-79 years in 1998-2000

	HDI Quartiles				P (trend)
	Q1 (0-2 points)	Q2 (3 points)	Q3 (4 points)	Q4 (5-7 points)	
Metabolic variables					
SBP (mmHg)	150.3 (23.6)	149.8 (24.5)	149.4 (23.7)	150.0 (23.3)	0.56
Triglycerides (mmol/L)	1.8 (1.1)	1.9 (1.1)	1.8 (1.0)	1.7 (0.9)	0.70
HDL (mmol/L)	1.4 (0.3)	1.3 (0.3)	1.3 (0.3)	1.3 (0.3)	0.006
Glucose (mmol/L)	6.1 (2.0)	5.9 (1.5)	6.0 (1.9)	5.8 (1.0)	0.02
Diabetes (%)	6.5	6.5	5.9	5.0	0.33
Inflammatory/hemostatic markers					
CRP (mg/L)*	1.7 (0.9-3.4)	1.6 (0.7-3.2)	1.6 (0.7-3.2)	1.4 (0.6-2.8)	0.01
t-PA (ng/mL)	11.0 (4.2)	10.8 (4.5)	10.2 (3.8)	10.7 (4.4)	0.001
D-dimer (ng/mL)*	78.1 (46.0-117.0)	77.1 (47.0-114.0)	80.1 (50.0-119.0)	77.9 (45.0-112.0)	0.71
vWF (IU/dL)	136.9 (45.2)	135.2 (44.9)	137.5 (45.3)	134.8 (43.8)	0.76
Fibrinogen (g/L)	3.2 (0.7)	3.2 (0.7)	3.3 (0.7)	3.2 (0.7)	0.81
IL-6 (pg/mL)*	2.4 (1.5-3.3)	2.3 (1.5-3.4)	2.2 (1.5-3.1)	2.2 (1.5-3.0)	0.001
Homocysteine (µmol/L)*	12.7 (10.3-14.8)	12.3 (10.0-14.3)	12.3 (10.0-14.4)	12.2 (10.1-13.9)	0.004

Values presented as mean (SD) unless otherwise stated.
BMI, body mass index; CRP, C-reactive protein; HDI, Healthy Diet Indicator; HDL, high density lipoprotein; IL-6, interleukin 6; MAMC, mid-arm muscle circumference; SBP, systolic blood pressure; t-PA, tissue plasminogen activator; vWF, von Willebrand factor; WC, waist circumference.
*Log transformed - geometric mean and interquartile range presented.

Table 6.6 Cardiovascular risk factors and dietary factors by quartiles of Elderly Dietary Index in men aged 60-79 years in 1998-2000

	EDI Quartiles				P (trend)
	Q1 (12-22 points)	Q2 (23-24 points)	Q3 (25-26 points)	Q4 (27-35 points)	
n	897	840	744	788	
Median EDI score	21	24	26	28	
Socio-demographic/Behavioural variables					
Age (years)	68.5 (5.4)	68.3 (5.5)	68.3 (5.6)	67.9 (5.2)	0.02
Current smokers (%)	25.7	11.6	7.3	4.5	<0.001
Heavy drinkers (%)	4.1	3.0	2.9	1.4	0.002
Physically inactive (%)	13.4	8.6	8.4	7.5	<0.001
Manual social class (%)	64.7	53.3	40.5	35.9	<0.001
Living in southern England region (%)	30.9	33.1	37.4	37.1	0.002
Body composition					
Obesity (BMI ≥ 30 kg/m^2) (%)	17.4	17.6	16.5	12.7	0.009
WC (cm)	97.3 (10.9)	97.2 (10.7)	97.0 (9.7)	95.9 (9.7)	0.006
MAMC (cm)	26.3 (2.5)	26.6 (2.3)	26.7 (2.2)	26.7 (2.1)	<0.001
Dietary variables					
Energy intake (kcal)	2162.1 (574.8)	2192.4 (539.5)	2160.7 (542.0)	2054.9 (442.3)	<0.001
Carbohydrates (% kcal)	50.3 (7.3)	52.1 (6.7)	52.8 (6.4)	54.5 (6.5)	<0.001
Protein (% kcal)	14.8 (2.3)	15.5 (2.2)	15.9 (2.3)	16.2 (2.1)	<0.001
Fat (% kcal)	32.9 (6.2)	31.0 (5.6)	29.6 (5.7)	27.5 (5.9)	<0.001
Saturated fat (% kcal)	14.0 (3.7)	12.8 (3.3)	11.9 (3.3)	10.7 (3.3)	<0.001
Fibre (g/day)	20.4 (6.8)	25.9 (8.0)	28.3 (7.8)	31.2 (8.1)	<0.001
Vitamin C (mg/day)	63.3 (30.4)	81.4 (35.0)	92.1 (34.1)	100.5 (37.1)	<0.001
Vitamin E (mg/day)	7.8 (5.3)	8.5 (5.0)	8.8 (4.5)	8.9 (4.4)	<0.001
Iron (mg/day)	11.8 (3.7)	14.1 (5.1)	15.4 (5.4)	15.9 (5.4)	<0.001
Daily fruit intake (%)	12.8	34.5	54	73.6	<0.001
Daily vegetable intake (%)	13.4	25.4	40.8	57.8	<0.001
Plasma vitamin C (µmol/L)	26.6 (30.9)	30.4 (29.2)	32.1 (21.1)	34.8 (24.3)	<0.001
Plasma vitamin E (µmol/L)	33.0 (12.6)	33.2 (11.5)	33.9 (11.6)	35.4 (12.4)	<0.001

Table 6.6 *Continued*. Cardiovascular risk factors and dietary factors by quartiles of Elderly Dietary Index in men aged 60-79 years in 1998-2000

	EDI Quartiles				P (trend)
	Q1 (12-22 points)	Q2 (23-24 points)	Q3 (25-26 points)	Q4 (27-35 points)	
Metabolic variables					
SBP (mmHg)	149.9 (24.3)	150.4 (23.9)	150.5 (23.4)	149.3 (23.8)	0.64
Triglycerides (mmol/L)	1.9 (1.2)	1.9 (1.1)	1.8 (0.9)	1.8 (1.0)	0.03
HDL (mmol/L)	1.3 (0.4)	1.3 (0.3)	1.4 (0.3)	1.3 (0.3)	0.34
Glucose (mmol/L)	5.9 (1.5)	5.9 (1.7)	6.0 (1.8)	6.1 (1.9)	0.03
Diabetes (%)	3.9	4.8	7.7	8.6	<0.001
Inflammatory/hemostatic markers					
CRP (mg/L)*	2.0 (0.9-4.2)	1.7 (0.8-3.4)	1.5 (0.7-3.0)	1.3 (0.6-2.4)	<0.001
t-PA (ng/mL)	11.5 (4.6)	10.7 (4.2)	10.7 (4.2)	10.2 (3.9)	<0.001
D-dimer (ng/mL)*	84.4 (50.0-128.0)	77.0 (46.0-111.0)	78.6 (46.0-118.5)	74.3 (45.0-107.5)	0.003
vWF (IU/dL)	140.0 (45.6)	138.1 (44.3)	135.2 (45.2	131.8 (45.1)	<0.001
Fibrinogen (g/L)	3.3 (0.7)	3.2 (0.7)	3.2 (0.8)	3.1 (0.7)	<0.001
IL-6 (pg/mL)*	2.7 (1.7-3.7)	2.4 (1.5-3.4)	2.2 (1.4-3.2)	2.0 (1.4-2.8)	<0.001
Homocysteine (µmol/L)*	13.7 (10.8-16.2)	12.6 (10.2-14.7)	12.0 (9.8-13.9)	11.4 (9.7-13.1)	<0.001

Values presented as mean (SD) unless otherwise stated.
BMI, body mass index; CRP, C-reactive protein; EDI, Elderly Dietary Index; HDL, high density lipoprotein; IL-6, interleukin 6; MAMC, mid-arm muscle circumference; SBP, systolic blood pressure; t-PA, tissue plasminogen activator; vWF, von Willebrand factor; WC, waist circumference.
*Log transformed - geometric mean and interquartile range presented.

Table 6.7 Hazard ratios (95% CI) for CHD events, CVD events, CVD mortality and all-cause mortality by quartiles of total Healthy Diet Indicator score in men aged 60-79 years in 1998-2000

	HDI Quartiles	Cases (n)	Rate (per 1,000 person years)	Model 1	Model 2	Model 3	Model 4
All-cause mortality	Q1	327	28.47	1.00	1.00	1.00	1.00
	Q2	249	26.97	0.94 (0.80-1.11)	1.00 (0.84-1.19)	1.06 (0.89-1.28)	1.06 (0.89-1.28)
	Q3	209	29.17	1.03 (0.86-1.22)	1.11 (0.92-1.33)	1.18 (0.97-1.44)	1.17 (0.96-1.42)
	Q4	72	22.73	0.91 (0.70-1.17)	0.94 (0.71-1.23)	1.01 (0.75-1.34)	0.96 (0.72-1.29)
	p-trend			0.77	0.72	0.31	0.46
CVD mortality	Q1	118	10.27	1.00	1.00	1.00	1.00
	Q2	83	8.99	0.87 (0.66-1.16)	0.91 (0.68-1.23)	1.02 (0.75-1.39)	1.03 (0.75-1.41)
	Q3	69	9.63	0.95 (0.70-1.27)	1.03 (0.75-1.41)	1.11 (0.79-1.55)	1.12 (0.80-1.58)
	Q4	23	7.26	0.85 (0.54-1.33)	0.84 (0.51-1.38)	0.94 (0.56-1.59)	0.84 (0.49-1.43)
	p-trend			0.49	0.74	0.83	0.98
CVD events	Q1	197	17.82	1.00	1.00	1.00	1.00
	Q2	155	17.48	0.98 (0.79-1.20)	1.00 (0.80-1.25)	1.07 (0.85-1.34)	1.07 (0.85-1.35)
	Q3	142	20.98	1.18 (0.95-1.47)	1.27 (1.01-1.60)*	1.28 (1.01-1.64)*	1.27 (0.99-1.62)
	Q4	44	14.49	0.90 (0.65-1.25)	0.88 (0.62-1.27)	0.92 (0.64-1.34)	0.89 (0.61-1.31)
	p-trend			0.62	0.43	0.35	0.45
CHD events	Q1	101	8.96	1.00	1.00	1.00	1.00
	Q2	75	8.27	0.92 (0.68-1.24)	0.92 (0.67-1.25)	0.97 (0.70-1.35)	0.99 (0.71-1.37)
	Q3	78	11.18	1.25 (0.93-1.67)	1.31 (0.96-1.79)	1.33 (0.95-1.85)	1.35 (0.97-1.89)
	Q4	32	10.32	1.26 (0.85-1.88)	1.21 (0.78-1.87)	1.31 (0.83-2.07)	1.28 (0.81-2.04)
	p-trend			0.10	0.10	0.08	0.08

CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HDI, Healthy Diet Indicator.
Model 1: Age adjusted. Model 2: Adjusted for model 1 + energy intake, smoking, alcohol, physical activity, social class and BMI. Model 3. Adjusted for model 2 + HDL, SBP and diabetes. Model 4. Adjusted for model 3 + CRP and vWF.
*P <0.05

Table 6.8 Hazard ratios (95% CI) for CHD events, CVD events, CVD mortality and all-cause mortality by Healthy Diet Indicator components in men aged 60-79 years in 1998-2000

HDI components	All-cause mortality		CVD mortality		CVD events		CHD events	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Did not meet guideline (score=0)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Met guideline (score=1)								
SFA	1.05 (0.90-1.23)	1.14 (0.96-1.36)	1.10 (0.83-1.44)	1.28 (0.94-1.72)	1.06 (0.87-1.30)	1.15 (0.92-1.43)	1.09 (0.84-1.43)	1.14 (0.85-1.53)
PUFA	1.14 (0.95-1.37)	1.15 (0.95-1.39)	1.29 (0.95-1.73)	1.30 (0.95-1.78)	1.13 (0.90-1.43)	1.09 (0.86-1.39)	1.28 (0.95-1.74)	1.27 (0.93-1.75)
Protein	1.19 (1.04-1.36)*	1.11 (0.95-1.29)	1.18 (0.93-1.48)	1.06 (0.82-1.37)	1.17 (0.99-1.39)	1.07 (0.89-1.30)	1.28 (1.01-1.61)*	1.15 (0.89-1.48)
Carbohydrates	0.94 (0.82-1.08)	0.93 (0.79-1.09)	0.98 (0.77-1.25)	0.90 (0.69-1.19)	1.12 (0.93-1.34)	1.01 (0.83-1.24)	1.23 (0.96-1.58)	1.05 (0.79-1.38)
Sugar	1.25 (0.69-2.27)	1.10 (0.58-2.06)	0.73 (0.18-2.92)	0.79 (0.20-3.22)	0.51 (0.16-1.59)	0.56 (0.18-1.77)	0.64 (0.16-2.58)	0.73 (0.18-2.95)
Fibre	1.00 (0.87-1.14)	1.04 (0.90-1.20)	0.92 (0.73-1.16)	1.02 (0.80-1.31)	0.95 (0.80-1.13)	1.06 (0.88-1.27)	1.20 (0.94-1.53)	1.32 (1.02-1.70)
Cholesterol	0.91 (0.79-1.04)	0.88 (0.74-1.04)	0.73 (0.58-0.92)*	0.67 (0.50-0.90)*	0.90 (0.76-1.08)	0.90 (0.72-1.12)	0.87 (0.68-1.10)	0.78 (0.58-1.05)
Fruits & Vegetables	0.80 (0.67-0.97)*	0.92 (0.75-1.11)	0.83 (0.61-1.14)	0.92 (0.66-1.28)	0.91 (0.73-1.13)	1.01 (0.80-1.28)	0.90 (0.66-1.22)	1.01 (0.74-1.39)

CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HDI, Healthy Diet Indicator; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids.
Model 1: Age adjusted. Model 2: Adjusted for model 1 + energy intake, smoking, alcohol, physical activity, social class, BMI and a modified version of the HDI score, not containing the individual component of interest. HDI components - score 1 vs. score 0.
*P <0.05

Table 6.9 Hazard ratios (95% CI) for CHD events, CVD events, CVD mortality and all-cause mortality by quartiles of total Elderly Dietary Index score in men aged 60-79 years in 1998-2000

	EDI Quartiles	Cases (n)	Rate (per 1,000 person years)	Model 1	Model 2	Model 3	Model 4
All-cause mortality	Q1	314	37.28	1.00	1.00	1.00	1.00
	Q2	233	28.06	0.75 (0.63-0.89)*	0.88 (0.73-1.06)	0.85 (0.70-1.03)	0.85 (0.70-1.03)
	Q3	200	26.86	0.72 (0.60-0.86)*	0.89 (0.74-1.09)	0.88 (0.72-1.08)	0.89 (0.72-1.10)
	Q4	160	19.69	0.55 (0.46-0.67)*	0.74 (0.60-0.91)*	0.73 (0.59-0.92)*	0.75 (0.60-0.94)*
	p-trend			<0.001	0.01	0.01	0.03
CVD mortality	Q1	115	13.65	1.00	1.00	1.00	1.00
	Q2	85	10.24	0.75 (0.57-1.00)*	0.87 (0.64-1.18)	0.80 (0.58-1.12)	0.79 (0.57-1.10)
	Q3	69	9.27	0.68 (0.50-0.91)*	0.79 (0.57-1.10)	0.78 (0.55-1.11)	0.79 (0.55-1.13)
	Q4	48	5.91	0.47 (0.33-0.66)*	0.60 (0.41-0.88)*	0.60 (0.41-0.90)*	0.63 (0.42-0.94)*
	p-trend			<0.001	0.008	0.02	0.03
CVD events	Q1	181	22.42	1.00	1.00	1.00	1.00
	Q2	145	18.17	0.81 (0.65-1.01)	0.88 (0.70-1.12)	0.85 (0.66-1.08)	0.84 (0.66-1.08)
	Q3	126	17.7	0.80 (0.64-1.00)	0.91 (0.71-1.16)	0.89 (0.69-1.16)	0.91 (0.70-1.18)
	Q4	118	15.22	0.71 (0.56-0.90)*	0.82 (0.63-1.07)	0.79 (0.60-1.04)	0.79 (0.60-1.05)
	p-trend			0.01	0.17	0.14	0.16
CHD events	Q1	104	12.67	1.00	1.00	1.00	1.00
	Q2	77	9.47	0.75 (0.56-1.01)	0.81 (0.59-1.11)	0.75 (0.54-1.05)	0.75 (0.54-1.06)
	Q3	66	9.03	0.72 (0.53-0.98)*	0.80 (0.57-1.12)	0.79 (0.55-1.12)	0.80 (0.56-1.14)
	Q4	54	6.74	0.56 (0.40-0.78)*	0.64 (0.44-0.92)*	0.64 (0.44-0.94)*	0.66 (0.45-0.97)*
	p-trend			0.001	0.02	0.03	0.05

CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; EDI, Elderly Dietary Index.
Model 1: Age adjusted. Model 2: Adjusted for model 1 + energy intake, smoking, alcohol, physical activity, social class and BMI. Model 3. Adjusted for model 2 + HDL, SBP and diabetes. Model 4. Adjusted for model 3 + CRP and vWF.
*P <0.05.

Table 6.10 Hazard ratios (95% CI) for CHD events, CVD events, CVD mortality and all-cause mortality by Elderly Dietary Index components in men aged 60-79 years in 1998-2000

EDI components	All-cause mortality		CVD mortality		CVD events		CHD events	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Lowest compliance with guideline (score=1)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Highest compliance with guideline (score=4)								
Meat	0.90 (0.65-1.23)	1.11 (0.79-1.55)	0.64 (0.34-1.21)	0.92 (0.49-1.75)	0.63 (0.40-1.01)	0.75 (0.46-1.22)	0.59 (0.30-1.14)	0.73 (0.38-1.44)
Fish/Seafood	0.76 (0.53-1.09)	0.91 (0.62-1.34)	0.53 (0.31-0.91)*	0.66 (0.36-1.21)	0.75 (0.48-1.16)	0.85 (0.52-1.37)	0.54 (0.32-0.94)*	0.67 (0.37-1.21)
Legumes	0.85 (0.69-1.03)	0.91 (0.74-1.13)	0.81 (0.58-1.13)	0.83 (0.58-1.19)	0.92 (0.71-1.21)	0.94 (0.71-1.24)	0.83 (0.59-1.18)	0.89 (0.61-1.30)
Fruit	0.61 (0.48-0.76)*	0.86 (0.66-1.11)	0.67 (0.45-1.02)	0.95 (0.59-1.53)	0.75 (0.55-1.01)	0.90 (0.64-1.28)	0.68 (0.45-1.03)	0.86 (0.54-1.35)
Vegetables	0.67 (0.47-0.96)*	1.05 (0.70-1.58)	0.63 (0.36-1.12)	0.88 (0.47-1.65)	0.84 (0.52-1.35)	1.17 (0.69-2.01)	0.89 (0.46-1.72)	1.29 (0.65-2.56)
Cereals	0.86 (0.67-1.10)	1.15 (0.87-1.52)	1.10 (0.70-1.72)	1.37 (0.83-2.25)	1.08 (0.77-1.51)	1.13 (0.79-1.62)	0.99 (0.64-1.53)	1.19 (0.73-1.93)
Bread	0.67 (0.27-1.62)	0.77 (0.32-1.90)	0.55 (0.14-2.24)	0.57 (0.14-2.40)	0.57 (0.21-1.54)	0.60 (0.22-1.65)	0.62 (0.15-2.52)	0.76 (0.18-3.15)
Olive oil	0.59 (0.45-0.77)*	0.68 (0.51-0.91)*	0.42 (0.24-0.72)*	0.43 (0.24-0.80)*	0.54 (0.37-0.77)*	0.58 (0.40-0.86)*	0.47 (0.28-0.79)*	0.55 (0.32-0.95)*
Dairy	1.07 (0.86-1.32)	1.14 (0.90-1.44)	1.00 (0.70-1.45)	1.09 (0.73-1.62)	1.04 (0.78-1.37)	1.12 (0.83-1.52)	0.95 (0.65-1.39)	0.90 (0.59-1.36)

CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; EDI, Elderly Dietary Index.
Model 1: Age adjusted. Model 2: Adjusted for model 1 + energy intake, smoking, alcohol, physical activity, social class, BMI and a modified version of the EDI score, not containing the individual component of interest. EDI components - score 4 vs. score 1.
*P <0.05

CHAPTER 7 Dietary quality scores in older British men: the influence of childhood and adult socioeconomic circumstances

7.1. Summary

High diet quality is associated with a reduced risk of cardiovascular disease (CVD) and mortality in older age and strong socioeconomic gradients in diet quality exist. However, the influence of material conditions particularly in childhood, and the use of a range of distinct socioeconomic measures on diet quality have been little studied in older adults. In this chapter, the roles of childhood and adult socioeconomic factors, social interaction and family circumstances, as determinants of diet quality are examined in participants from the British Regional Heart Study (BRHS). At the 20 year re-examination in 1998-2000, 4252 men, aged 60-79 years, attended a physical examination, provided a fasting blood sample and completed both a general lifestyle questionnaire and a food frequency questionnaire (FFQ). The FFQ provided data on daily fruit and vegetable intake and the Elderly Dietary Index (EDI), with higher scores indicating higher diet quality. Socioeconomic measures in childhood and adulthood included own occupation, father's occupation, education and household amenities, which were combined to create composite socioeconomic scores. Measures of social interaction included social contact, and measures of family circumstances included living arrangements and marital status. Both childhood and adult socioeconomic measures were independently associated with diet quality. Men of manual childhood social class were less likely to consume fruit and vegetables daily (odds ratio [OR]: 0.80, 95% CI: 0.66-0.97) compared to non-manual childhood social class, as were men of manual adult social class (OR: 0.65, 95% CI: 0.54-0.79) compared to non-manual adult social class. Similarly, men of manual childhood social class were less likely to be in the top quartile of the EDI (OR: 0.73, 95% CI: 0.61-0.88), as were men of manual adult social class (OR: 0.66, 95% CI: 0.55-0.79). Diet quality showed an inverse trend with a composite score combining different adverse adult socioeconomic indictors (manual social class; education ≤ 14 years; no car; not a house owner; state pension only; no central heating). An inverse trend was also shown between diet quality and a composite score combining adverse childhood socioeconomic indictors (manual childhood social class; no bathroom; no hot water supply; no family car ownership), but this association was attenuated after adjustment for adult social class. A combined childhood and adulthood adverse socioeconomic score was associated with lower diet

quality in later adult life. Diet quality was higher in men not living alone and in married men, but was not associated with social contact. Therefore, diet quality in older men is influenced by both childhood and adulthood socioeconomic factors, in addition to marital status and habitation.

7.2. Introduction

Diet is an important modifiable risk factor for cardiovascular disease and mortality[8;23;202] and, as observed in Chapter 6, associations between *a priori* dietary scores and the risk of cardiovascular disease and mortality are present in older men. Chapter 6 demonstrated that older British men with higher scores of the Elderly Dietary Index (EDI), a Mediterranean style dietary score developed specifically to address adherence to nutritional recommendations for older adults[233;354] was strongly associated with a lower risk of CHD events, CVD mortality and all-cause mortality. In addition, older British men with higher EDI scores had the least adverse cardiovascular risk profiles, including having the lowest proportion of men from manual social class. Strong socioeconomic gradients in the overall quality of diet are well established and previous studies have consistently shown that individuals from higher adult socioeconomic position are more likely to have a Mediterranean style dietary pattern, characterised by high consumption of fresh fruit and vegetables, whole grains, lean meats, fish and low-fat dairy products[222;355-357]. A meta-analysis of data from seven European countries, including 18-85 year olds, has also shown strong associations between higher socioeconomic position, defined by occupation or education, and a greater daily consumption of fruit and vegetables[358]. It has also been suggested that childhood socioeconomic factors may have an additional impact on adult dietary quality, independent of adult socioeconomic factors[359;360]. Moreover, as well as socioeconomic factors, social circumstances such as frequency of contact, living arrangement and marital status, which have been shown to be associated with an increased risk of CVD and mortality[361], are also increasingly being identified as important determinants of diet particularly in older populations[362;363]. Socioeconomic gradients in the quality of diet appear to persist in older populations[364-368]. However, the influence of differing material socioeconomic conditions, especially in childhood, and the use of a range of distinct socioeconomic measures on quality of diet have been little studied in older adults.

This chapter will therefore focus on socioeconomic circumstances across the life course as determinants of diet quality in older men. Specifically, the Chapter aims to assess the relationship between a range of childhood and adult socioeconomic measures (including occupation/father's occupation, education and household amenities), family circumstances (living arrangements and marital status) and social interactions with diet quality in older British men. The EDI will be used as an *a priori* marker of a Mediterranean style diet and hence of diet quality[233], as Chapter 6 showed it was strongly associated with a lower risk of CHD events, CVD mortality and all-cause mortality in this cohort. In addition, frequency of fruit and vegetable consumption will also be used as a marker of diet quality, as this has been consistently shown to be strongly related to a lower risk of CVD mortality[369] and fruit and vegetable intake is simpler to measure than the EDI and hence less prone to measurement error.

7.3. Objectives

To examine the influences of social circumstances on an *a priori* defined dietary score and fruit and vegetable intake in older age (60-79 years). The specific aims of this chapter are:

i) To examine the relationship of an *a priori* defined dietary score and fruit and vegetable intake with childhood socioeconomic factors.
ii) To examine the relationship of an *a priori* defined dietary score and fruit and vegetable intake with adult socioeconomic factors.
iii) To examine the relationship of an *a priori* defined dietary score and fruit and vegetable intake with combined childhood and adult socioeconomic factors.
iv) To examine the relationship of an *a priori* defined dietary score and fruit and vegetable intake with social interaction and family circumstances.

7.4. Methods

7.4.1. Subjects and methods of data collection

Analyses described in this chapter were carried out on cross-sectional data from the 20 year re-examination of participants in the BRHS in 1998-2000, when aged 60-79 years.

4252 men (77% of survivors) attended a physical examination, provided a fasting blood sample, and completed both a general questionnaire, answering questions on their lifestyle and medical history, and an FFQ[264]. In addition data on childhood and adult social circumstances were collected via postal questionnaire in 1978-80, 1992 and 1996.

7.4.2. **Dietary assessment and defining diet scores**

Dietary intake was measured in 1998-2000 via a self-completed postal FFQ, with participants reporting their usual frequency of consumption of 86 food and drink items, as described in detail in Chapter 3, section 3.3.2. Diet quality was examined using an *a priori* dietary score, the EDI, a Mediterranean style dietary score developed specifically to address adherence to nutritional recommendations for older adults[233;354]. The EDI was chosen as results in Chapter 6 demonstrated it was the *a priori* dietary score most strongly associated with CHD events, CVD mortality and all-cause mortality, compared to the HDI and the MDS. The EDI consisted of nine components (meat; fish and seafood; vegetables; cereals; fruit; legumes; olive oil; dairy; bread), each assigned a four-point scoring system based on the frequency of consumption, resulting in a total score range from 9 to 36. Score 4 was assigned for the highest consumption of fruits, vegetables, cereals and olive oil. However, for meat, fish/seafood, and legumes, score 4 with achieved for moderate consumption (1-2 days/week). For bread intake, score 4 was assigned when someone consumed only whole grain bread and for dairy, score 4 was assigned for low fat milk and cheese intake only. Higher scores of the EDI indicated greater adherence to the EDI dietary pattern and hence a higher diet quality. Full detail of the scoring criteria used for the EDI can be found in Chapter 6 (Section 6.4.3 and Table 6.2).

As an additional marker of diet quality, frequency of fruit and vegetable consumption was used in addition to the EDI. This has been consistently shown to be strongly related to a lower risk of CVD mortality[369]. Fruit and vegetable intake is also simpler to measure than the EDI and hence less prone to measurement error. In the FFQ, participants were asked how frequently they consumed fresh fruit and vegetables (1, 2, 3, 4, 5, 6, or 7 days per week; monthly; rarely/never. Daily consumption was classified as intake of both fruit and vegetable on 7 days per week.

7.4.3. **Measurement of socioeconomic position**

The measurement of all adult and childhood socioeconomic variables has been described in detail in Chapter 3 (Section 3.3.4). Adult occupation was recorded at study entry (aged 40-59 years), by a nurse-administered questionnaire in 1978-2000, and social class was based on the longest held occupation recorded using the Registrar General's occupational classification[285]. The six occupational social class categories were: I (professional occupations e.g. barristers, physicians, engineers), II (intermediate 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). Participants were classified as having either a manual (social classes III manual, IV, V) or non-manual (social classes I, II, III non-manual) occupational social class and men who were in the Armed Forces were excluded (n = 112). Additional socioeconomic measures available from the 1996 postal questionnaire were education (age at leaving full-time education) and pension (financial support the participant has or will have on retirement - state only or state plus private pension). The 20 years re-examination questionnaire in 1998-2000 also provided data on car and house ownership, and whether participants had central heating at home. Adverse socioeconomic measures were combined to create a composite score in order to investigate the cumulative impact of low socioeconomic position, and to take a range of socioeconomic measures into account that may have a greater impact than occupation alone. One point was assigned for each of the following: manual adult social class; education ≤ 14 years; no car; not a house owner; state pension only; no central heating; to generate a total score between 0 and 6[370].

Childhood socioeconomic variables were collected via postal questionnaire in 1992. Childhood occupational social class was based on father's longest held occupation and participants were classified as manual or non-manual using the Office of Population Censuses and Surveys Classification of Occupations social class coding manual[371]. Men whose father's longest held occupation was in the Armed Forces were excluded from analysis (n = 81). Data were also available on childhood household amenities.

Participants were asked if their home had a bathroom, hot water supply or family car ownership, up to 10 years old. A cumulative adverse childhood socioeconomic score was created, as an overall marker of early life socioeconomic position. One point was assigned for each of the following: manual childhood social class; no bathroom; no hot water supply; no family car ownership, to generate a total score from 0 to 4[370].

To assess the combined effects of childhood and adult social occupational social class on diet quality, participants were categorised into four combined childhood and adult social class groups: childhood and adult non-manual; childhood non-manual and manual adult; manual childhood and adult non-manual; childhood and manual adult social class. Additionally, a combined adverse childhood and adulthood socioeconomic measures score was created by summing the adverse adult and childhood scores, to generate a total from 0 to 10.

7.4.4. **Social interaction and family circumstances variables**

The measurement of variables on social interactions and family circumstances has been described in detail in Chapter 3 (Section 3.3.4). In the 1998-2000 questionnaire, men were asked how often they saw or spoke to their children, siblings, friends and neighbours (every week; every month; every few months; every year; rarely/never; does not apply), whether they were living alone (living alone; living with a partner/spouse; living with other family members; living with other people), and what their marital status is (single; married; widowed; divorced/separated; other). A small number of men whose marital status was "other" were excluded from the analysis (n = 8).

7.4.5. **Cardiovascular risk factors**

Established and emerging cardiovascular risk factors were measured at the 20 year re-examination in 1998-2000 as described in Chapter 3, section 3.3. Information on cigarette smoking, alcohol intake and physical activity were self-reported via questionnaire. Men were classified into four smoking groups (never smoked; long-term ex-smokers, >15 years; recent ex-smokers, ≤ 15 years; current smokers)[282]. Alcohol intake was classified into five groups based on the number and frequency of alcoholic

beverages consumed per week (none; occasional; light; moderate; heavy)[91]. Current physical activity was classified into six groups based on the frequency and intensity of exercise(inactive; occasional; light; moderate; moderately vigorous and vigorous)[283]. Height and weight were measured at physical examination in 1998-2000. Body mass index (BMI) was calculated and participants were classified into four BMI categories: (underweight, <18.5; normal weight, 18.5-24.99; overweight, 25-29.99; obese, ≥ 30 kg/m^2)[105].

7.4.6. **Statistical methods**

Of the 4252 men attending the twenty year re-examination, data were available on fruit and vegetable intake for 4067 participants and 3924 of these men had adequate data to apply the EDI score. Participants were categorised into quartiles of the EDI using cut off points, which produced the nearest categorisation into equal sized groups that these integer data would allow. Descriptive characteristics of participants were presented by daily fruit and vegetable intake and by EDI quartiles. P values for difference between groups for daily fruit and vegetable intake were obtained using chi squared tests and p values for trend across EDI quartiles were obtained using regression analyses. Chi squared analysis was also used to assess the relationship between childhood and adult socioeconomic measures. Multivariable logistic regression assessed associations between childhood and adult socioeconomic measures, social interactions and family circumstances, with daily fruit and vegetable intake and EDI quartiles. Odds ratios for EDI were presented for being in the highest quartile compared to the reference group of the lower three quartiles combined. Logistic regression models were adjusted for age, energy intake (kcal/day), smoking status, alcohol intake, physical activity and BMI. In addition, childhood socioeconomic measures, social interactions and family circumstances were adjusted for adult occupational social class and conversely, adult socioeconomic measures were adjusted for childhood occupational social class. Age and energy intake were fitted continuously and smoking status, alcohol intake, physical activity, BMI, adult and childhood social class were fitted as categorical variables in the adjustments. A test for interaction between childhood and adult social class was also performed.

7.5. Results

In this cohort of older men, less than one in five (17.9%) participants consumed fresh fruit and vegetables daily. The EDI score was normally distributed with a mean of 24.2 (SD 3.3), ranging from 12 to 35. Table 7.1 presents the characteristics of the men by EDI quartiles and by daily fruit and vegetable intake. As described previously in Chapter 6, the EDI score was inversely associated with adverse cardiovascular risk factors. Men in the highest EDI quartile were younger on average and significantly less likely to be current smokers, heavy drinkers, physically inactive, of manual adult social class and of manual childhood social class, and had a slightly lower mean age and total energy intake. Men who consumed fruit and vegetables daily had a significantly lower energy intake and were significantly less likely to be current smokers, physically inactive, manual adult social class and manual childhood social class. Table 7.2 presents childhood socioeconomic measures in relation to adult socioeconomic measures, all of which were significantly associated with each other.

7.5.1. Diet quality and childhood socioeconomic factors

Table 7.3 presents odds ratios for being in the top EDI quartile and consuming fruit and vegetables daily according to childhood socioeconomic measures. Childhood occupational social class was the childhood socioeconomic measure most strongly associated with diet quality; men of manual childhood social class were significantly less likely to be in the top EDI quartile (OR: 0.73, 95% CI: 0.61-0.88) and to consume fresh fruit and vegetables daily (OR: 0.80, 95% CI: 0.66-0.97), which was independent of age, energy intake, smoking, physical activity, alcohol, BMI and adult social class. In sensitivity analysis, further adjusting for all other adult socioeconomic measures, the associations were weakened slightly between childhood social class and EDI (OR: 0.81, 95% CI: 0.67-0.98) and daily fruit and vegetable consumption (OR: 0.82, 95% CI: 0.66-1.02). Men without a family car in childhood were less likely to be in the highest quartile of EDI, with borderline statistical significance after adjustment for behavioural factors and adult social class. Family car ownership was not however significantly associated with fruit and vegetable intake. The presence of a bathroom or a hot water supply in the childhood home showed no significant associations with either EDI or daily fruit and vegetable consumption after adjustment. A significant trend was seen between the cumulative adverse childhood socioeconomic score and EDI, but no

significant trend was seen with daily fruit and vegetable consumption after adjustment for behavioural factors and adult social class.

7.5.2. **Diet quality and adult socioeconomic factors**

The odds ratios for being in the top EDI quartile and for consuming fruit and vegetable daily according to adult socioeconomic measures are presented in Table 7.4. Adult occupational social class was strongly associated with diet quality; men of manual social class were significantly less likely to be in the top EDI quartile (OR: 0.66, 95% CI: 0.55-0.79) and to consume fresh fruit and vegetables daily (OR: 0.65, 95% CI: 0.54-0.79), independent of age, energy intake, smoking, physical activity, alcohol, BMI and childhood social class. These results suggest that occupational adult social class had a greater magnitude of effect on EDI and fruit and vegetable intake than occupational childhood social class. Additional sensitivity analysis, further adjusting for all other adult socioeconomic measures, showed that the associations between adult social class and EDI (OR: 0.86, 95% CI: 0.70-1.06) and daily fruit and vegetable consumption (OR: 0.74, 95% CI: 0.59-0.93) were attenuated. When examining occupational social class as a continuous variable, for every unit decrease in social class the odds of being in the top EDI quartile (OR: 0.82, 95% CI: 0.77-0.88) and of consuming fruit and vegetables daily (OR: 0.81, 95% CI: 0.75-0.88) both decreased. Men with a state pension only or $\leq$ 14 years of education were significantly less likely to be in the highest quartile of EDI and to consume fruit and vegetables daily. When examining education as a continuous variable, for every additional year of education, the odds of being in the top EDI quartile (OR: 1.03, 95% CI: 1.01-1.05) and of consuming fruit and vegetables daily (OR: 1.02, 95% CI: 1.01-1.04) both increased. In addition, men who did not own a car, did not own a house or did not have central heating were significantly less likely to be in the highest EDI quartile, but no associations were seen with daily fruit and vegetable consumption. A significant inverse trend was observed between the cumulative adverse adult socioeconomic score and both EDI and daily consumption of fruit and vegetables.

7.5.3. **Diet quality and combined childhood and adult socioeconomic factors**

Examining the combined effects of occupational social class in childhood and adulthood showed that diet quality was highest in men with both childhood and adult non-manual

social class and lowest in those with both childhood and manual adult social class (Table 7.5). Whether in childhood or adulthood, exposure to manual social class was associated with a poorer diet quality. A test for interaction between childhood and adult occupational social class showed evidence that the effect of childhood social class (manual/non-manual) was strengthened in those whose adult social class had also been manual (interaction test $p = 0.02$ for EDI quartiles). However, no such interaction was seen for daily fruit and vegetable intake ($p = 0.44$). A significant inverse trend was also seen between the combined childhood and adulthood adverse socioeconomic score with both EDI and daily consumption of fruit and vegetables. Additional sensitivity analyses, examining fruit intake and vegetable intake individually, showed significant inverse trends with the combined childhood and adulthood adverse socioeconomic score, with a stronger association for vegetables than for fruit.

7.5.4. **Diet quality and social interaction and family circumstances variables**

Table 7.6 presents the odds ratios for of being in the top EDI quartile and for consuming fruit and vegetable daily according to social interactions and family circumstances. Men who were widowed or divorced/separated were significantly less likely to eat fruit and vegetables daily, compared to married men. Men living alone were significantly less likely to be in the highest quartile of EDI (OR: 0.71, 95% CI: 0.53-0.95) and to eat fruit and vegetables daily (OR: 0.61, 95% CI: 0.44-0.85) compared to those living with other people. However, social contact with children, siblings, friends or neighbours did not show any associations with EDI or daily fruit and vegetable consumption. Further sensitivity analysis, stratifying men in to those who were married and unmarried showed that social contact was still not significantly associated with diet quality in either subgroup.

7.6. Discussion

7.6.1. **Summary of main findings**

This chapter examined associations between a range of childhood and adult socioeconomic factors, social interaction and family circumstances with diet quality, assessed by daily fruit and vegetable consumption and the EDI, in older British men aged 60-79 years. Both childhood and adult socioeconomic factors were independently

associated with diet quality, with adult factors appearing to be more influential than childhood factors. Diet quality was also influenced by marital status and living arrangements, but did not show an association with social contact. Results from this chapter add to the limited literature on the role of social and material conditions particularly in childhood and the use of multiple disaggregated socioeconomic measures on diet quality in the older age. The results show that childhood social class persists as a strong influence on diet quality in older ages.

7.6.2. **Comparison with previous studies**

Several adult socioeconomic measures showed strong associations with diet quality in older men, which were independent of age, energy intake, smoking, physical activity, alcohol and BMI and childhood social class. The strength of associations with EDI were strongest jointly for pension status and home ownership (which are two strong markers of material wealth), followed by education, car ownership, social class, and then central heating. In contrast, associations with daily fruit and vegetable intake were strongest for social class, followed by receipt of a pension, and then educational status. These observed socioeconomic gradients in diet quality are consistent with previous literature showing a healthier diet (characterised by a high intake of fruit, vegetables and other Mediterranean style food groups) in higher socioeconomic groups, measured by either occupation, education, income, house ownership or car access in both middle aged[222;356-358;372] and older adult populations[208;373-376]. In a previous study using the EDI it was shown that being in the highest EDI tertile was associated with better financial status and a higher educational level[233]. Results in this chapter extend the previous findings by Kourlaba et al[233] by including socioeconomic measures particularly relevant to older adults (pension status and central heating) and used a combination of different adverse adult socioeconomic factors, which showed a strong inverse trend with both the EDI score and daily fruit and vegetable intake.

Childhood occupational social class was also strongly associated with diet quality, with men of manual childhood social class less likely to be in the top quartile of EDI and to consume fruit and vegetables daily, independent of behavioural factors and adult social class. In relation to childhood household amenities, there was a borderline significant

association between family car ownership and EDI, which may be due to car ownership being a strong marker of SEP or material wealth, particularly for the generation of this cohort. However, the presence of a bathroom and hot water supply in the house in childhood were not associated with diet quality in later life. These findings are consistent with previous studies showing that childhood social class is associated with dietary intake in middle-aged populations[359;360;377]. However, a previous study in early old age (61-80 years) showed that childhood social circumstances (social class and per capita household food expenditure) were not strongly related to adult diet quality, measured by the Healthy Diet Score[373]. To my knowledge, the results presented in this chapter are the first to confirm that the influences of childhood social class on diet quality in middle aged populations can persist at older ages.

Analyses combining childhood and adult socioeconomic factors were consistent with the possibility of cumulative effects of adverse childhood and adult socioeconomic factors on diet quality in older age. Results also suggested there was a possibly interaction between childhood and adult social class, showing that the effect of childhood social class was strengthened in those whose adult social class had also been manual. This lends support to previous research in an adult British population suggesting that although adult dietary patterns are determined by childhood influences, diet can be modified by change in socioeconomic position in adulthood[359]. Previous studies have suggested that adult socioeconomic measures are more important than childhood socioeconomic measures (based on father's occupation or mother's education) in influencing adult diet quality[360;373;378]. Results in this chapter support this notion, but in an older adult population, as the magnitude of effect on diet quality observed for adult occupational social class was greater than that for occupational childhood social class. Examining the combined effects of occupational social class in both childhood and adulthood showed that diet quality was highest in men with both childhood and adult non-manual social class and lowest in those with both manual childhood and adult social class.

A higher diet quality in older men was associated with not living alone and with being married. This finding is consistent with those of previous studies which have showed

that these measures of family circumstances are important determinants of diet in older adults[362;363;374;379;380]. Previous exploratory research has suggested that barriers to healthy eating in older men living alone include poor cooking skills and low motivation to change eating habits[381]. The literature has also shown that diet quality in older adults is affected by frequency of social contact[362;363] but no such association was found here. This could be explained by the fact that men in this cohort were not socially isolated; the majority of participants had contact with their children, siblings, friends or neighbours once a week or more. More refined categories of social contact were not available in the study questionnaire but could potentially have helped to identify associations with diet quality.

7.6.3. **Strengths and limitations**

The major strength of the results presented in this chapter is that it is a moderately large population-based cohort, assessing a range of socioeconomic measures across the life course and including the assessment of several potentially important confounding factors, which have been taken into account in analyses. However, misclassification of childhood socioeconomic status is possible with participants, from lower socioeconomic positions in particular, being more likely to over-estimate the social class of their father[382]. This recall bias could have resulted in a weakened association between childhood socioeconomic measures and diet quality. The socioeconomic variables used were dichotomous in nature, which represents a coarse gradation, but even when socioeconomic variables were examined continuously (e.g. occupational adult social class and education) the results in relation to diet quality were very similar. Information on pension status was collected in 1996, so it is possible that if the men had not yet retired at this time point, pension status may have changed by the re-examination in 1998-2000. However, this is unlikely as the vast majority of men (74%) had already retired by 1996.

Dietary intakes were assessed using an 86-item FFQ. Assessment of dietary intake by self-reported measures can be prone to measurement error through misreporting, which can affect the estimation of energy intake and micronutrient intake[321;322]. The FFQ

method in particular can be more prone to measurement error than other measures such as weighted food records or 24-hour dietary recall[198;200]. In elderly populations non-response to questions may have increased the chance of dietary underreporting[190;312]. The collection of dietary data may also have been subject to social desirability bias[200] and it is possible low socioeconomic groups could have been more affected by this, with previous studies showing that lower socioeconomic status and lower education are predictors of underreporting[321]. However, the FFQ used here has been validated previously against weighed food intakes in the British population[273;274] and the dietary intake of participants was broadly comparable with those from the National Diet and Nutrition Survey[339] (as discussed in section 6.6.2.1). In addition, to reduce the risk of bias in dietary assessment, established minimum and maximum cut-offs for total energy intake were applied to the data (<500 or > 8000 kcal[279]) to exclude under and over-reporters, and all analyses were adjusted for total energy intake[280]. It is possible that some residual confounding remains in the assessment of dietary intake, but underreporting of food intake is only likely to have biased the relative risk estimates towards the null, leading to an underestimation of the associations between socioeconomic circumstances and diet quality.

Observed associations between socioeconomic indicators and diet quality, were generally stronger based on the EDI score instead of daily fruit and vegetable intake. This may indicate that a high EDI score is a better marker of an overall healthy diet in this older population, than using the simpler measure of daily fruit and vegetable consumption.

Results in this chapter are based on older men of predominantly of white European ethnic origin and may therefore be limited to this population. Although gender differences exist in dietary intake[383;384], the social gradients in diet quality observed in this study are also likely to exist in older women. Some residual confounding is possible due to the self-reported nature of variables such as smoking status, alcohol intake and physical activity. Self-reported measures of physical activity can be a particular problem in older age groups due to the light intensities of activity and vast variability in duration

of activity in these age groups which make accurate recall especially difficult[315-317] (as discussed in Chapter 4, Section 4.6.3). However, a validation study in older men within the BRHS has shown self-reported physical activity questions used within this cohort are associated with a graded increase in objectively measured physical activity[318]. This reduces the risk of measurement error and any possible misclassification of physical activity is only likely to have attenuated relative risk estimates between dietary scores and socioeconomic factors[320]. Lastly, it is possible additional confounders such as health status and dentition could also influence diet quality – these unmeasured confounders may have underestimated or exaggerated the measures of association observed.

7.6.4. **Conclusions**

The diet quality of older men is independently influenced by socioeconomic factors both in childhood and adulthood, with adult socioeconomic position being more influential than early life socioeconomic position in determining dietary patterns. In addition, diet quality seems to be influenced by marital status and adult living arrangements. Public health interventions aimed at improving diet quality of older people with low diet quality need to consider both early and later life socioeconomic factors and circumstances.

Table 7.1 Characteristics of men aged 60-79 years in 1998-2000 by diet quality (Elderly Dietary Index and daily fruit and vegetable intake)

	EDI Quarters*				p	Daily Fruit and Vegetable Intake†		p
	1st (12-22 points)	2nd (23-24 points)	3rd (25-26 points)	4th (27-35 points)		No	Yes	
n	1074	982	901	967		3338	729	
Age (years), mean (SD)	68.8 (5.5)	68.6 (5.5)	68.6 (5.6)	68.1 (5.3)	0.007	68.6 (5.5)	68.8 (5.4)	0.54
Energy intake (kcal/d), mean (SD)	2142.5 (574.7)	2181.6 (535.3	2139.1 (530.2)	2032 (443.2)	<0.001	2120.4 (537.3)	2100.6 (486.1)	0.001
Current smokers, n (%)	265 (24.7)	114 (11.7)	67 (7.4)	45 (4.7)	<0.001	473 (14.2)	36 (5.0)	<0.001
Heavy drinkers, n (%)	43 (4.2)	30 (3.1)	22 (2.5)	12 (1.3)	<0.001	97 (3.0)	16 (2.2)	0.26
Physically inactive, n (%)	158 (15.4)	99 (10.4)	95 (10.8)	80 (8.6)	<0.001	385 (12.0)	66 (9.3)	0.04
Obese, BMI >30kg/$m^{2,}$ [n] (%)	190 (17.8)	180 (18.4)	162 (18.1)	145 (15.1)	0.110	575 (17.3)	125 (17.2)	0.95
Manual adult social class, n (%)	687 (66.0)	518 (54.1)	374 (42.6)	357 (38.2)	<0.001	1757 (54.1)	279 (39.7)	<0.001
Manual childhood social class, n (%)	745 (78.2)	637 (72.7)	565 (68.1)	545 (60.9)	<0.001	2171 (72.2)	422 (63.3)	<0.001

BMI, body mass index; EDI, Elderly Dietary Index.
*Data for EDI available for 3924 participants. P for trend across EDI quarters.
†Data for fruit and vegetable intake available for 4067 participants. P for difference between groups

Table 7.2 Childhood socioeconomic measures according to adult socioeconomic measures in men aged 60-79 years in 1998-2000

Childhood socioeconomic measures		Adult socioeconomic measures					
		Non-manual adult social class (%)	Education >14 years (%)	Car ownership (%)	House ownership (%)	State and private pension (%)	Central heating (%)
Childhood social class	Manual	39.0	56.7	81.6	86.2	79.2	92.4
	Non-Manual	73.2	82.0	91.2	94.1	90.3	95.4
p value*		<0.001	<0.001	<0.001	<0.001	<0.001	0.005
Bathroom	Yes	58.3	73.8	87.7	90.3	85.4	94.3
	No	38.2	53.6	80.1	85.6	78.8	92.1
p value*		<0.001	<0.001	<0.001	<0.001	<0.001	0.006
Hot water supply	Yes	59.0	74.7	87.6	90.4	85.6	94.5
	No	37.0	52.0	80.1	85.4	78.4	91.9
p value*		<0.001	<0.001	<0.001	<0.001	<0.001	0.001
Family car ownership	Yes	71.7	84.8	92.5	92.7	86.7	95.9
	No	43.7	59.8	82.3	87.0	81.2	92.7
p value*		<0.001	<0.001	<0.001	<0.001	0.001	0.004

*p value for difference between groups.

Table 7.3 Odds ratios (95% CI) for the top quartile of the Elderly Dietary Index and daily fruit and vegetable intake by childhood socioeconomic measures in men aged 60-79 years in 1998-2000

		EDI Quartiles *						Daily Fruit and Vegetable Intake†					
		n	% Q4	Unadjusted		Adjusted		n	%	Unadjusted		Adjusted	
				OR (95% CI)	p	OR (95% CI)	p			OR (95% CI)	p	OR (95% CI)	p
Childhood social class*	Non-Manual	1062	33.0	1.00		1.00		1081	22.7	1.00		1.00	
	Manual	2492	21.9	0.57 (0.49-0.67)	<0.001	0.73 (0.61-0.88)	0.001	1593	16.3	0.66 (0.56-0.79)	<0.001	0.80 (0.66-0.97)	0.03
Childhood household amenities													
Bathroom	Yes	1906	27.2	1.00		1.00		1960	19.1	1.00		1.00	
	No	1820	22.9	0.79 (0.68-0.92)	0.002	0.95 (0.81-1.12)	0.57	1895	17.0	0.87 (0.74-1.02)	0.09	0.95 (0.80-1.14)	0.61
Hot water supply	Yes	1955	27.7	1.00		1.00		2013	20.0	1.00		1.00	
	No	1768	22.3	0.75 (0.64-0.87)	<0.001	0.94 (0.80-1.12)	0.51	1838	16.0	0.76 (0.64-0.90)	0.001	0.85 (0.71-1.02)	0.08
Family car ownership	Yes	617	31.9	1.00		1.00		630	19.8	1.00		1.00	
	No	3110	23.8	0.66 (0.55-0.80)	<0.001	0.81 (0.66-1.00)	0.05	3227	17.7	0.87 (0.70-1.08)	0.20	1.01 (0.80-1.27)	0.95
Adverse childhood amenities score‡	0	356	33.7	1.00		1.00		361	19.1	1.00		1.00	
	1	570	32.8	0.96 (0.73-1.27)	<0.001	1.11 (0.82-1.51)	0.03	578	24.7	1.39 (1.01-1.92)	<0.001	1.42 (1.01-1.99)	0.12
	2	845	22.6	0.57 (0.44-0.75)		0.78 (0.57-1.05)		885	16.4	0.83 (0.60-1.14)		1.01 (0.72-1.42)	
	3	479	25.7	0.68 (0.50-0.92)		0.93 (0.67-1.29)		491	21.4	1.15 (0.82-1.62)		1.33 (0.92-1.91)	
	4	1281	21.1	0.53 (0.410.68)		0.78 (0.58-1.05)		1333	15.0	0.75 (0.55-1.01)		0.93 (0.66-1.29)	

EDI, Elderly Dietary Index. Analyses adjusted for age, energy intake, smoking, physical activity, alcohol, BMI, and adult social class.

*Data for EDI available for 3924 participants. Odds ratio for quartile 4 vs. quartiles 1-3.

†Data for fruit and vegetable intake available for 4067 participants.

‡Score includes: manual childhood social class; no bathroom; no hot water supply; no family car ownership.

Table 7.4 Odds ratios (95% CI) for the top quartile of Elderly Dietary Index and daily fruit and vegetable intake by adult socioeconomic measures in men aged 60-79 years in 1998-2000

		EDI Quartiles*						Daily Fruit and Vegetable Intake†					
				Unadjusted		Adjusted				Unadjusted		Adjusted	
		n	% Q4	OR (95% CI)	p	OR (95% CI)	p	n	%	OR (95% CI)	p	OR (95% CI)	p
Adult social class	Non-Manual	1875	30.8	1.00		1.00		1916	22.1	1.00		1.00	
	Manual	1936	18.4	0.51 (0.44-0.59)	<0.001	0.66 (0.55-0.79)	<0.001	2036	13.7	0.56 (0.47-0.66)	<0.001	0.65 (0.54-0.79)	<0.001
Education	>14 years	2280	28.8	1.00		1.00		2336	20.0	1.00		1.00	
(age leaving full-time)	≤ 14 years	1209	18.4	0.56 (0.47-0.66)	<0.001	0.61 (0.49-0.76)	<0.001	1264	15.3	0.72 (0.60-0.87)	0.001	0.76 (0.60-0.96)	0.02
Car ownership	Yes	3271	26.6	1.00		1.00		3368	18.8	1.00		1.00	
	No	591	13.7	0.44 (0.34-0.56)	<0.001	0.64 (0.48-0.85)	0.002	635	13.2	0.66 (0.51-0.84)	0.001	0.80 (0.60-1.07)	0.13
House ownership	Yes	3360	26.7	1.00		1.00		3464	18.9	1.00		1.00	
	No	457	11.4	0.35 (0.26-0.48)	<0.001	0.53 (0.37-0.75)	<0.001	494	12.2	0.60 (0.45-0.79)	<0.001	0.77 (0.55-1.08)	0.14
Pension	State + private	2971	27.7	1.00		1.00		3053	19.7	1.00		1.00	
	State only	612	13.1	0.39 (0.31-0.50)	<0.001	0.53 (0.40-0.71)	<0.001	656	10.8	0.50 (0.38-0.64)	<0.001	0.66 (0.49-0.88)	0.005
Central heating	Yes	3517	25.6	1.00		1.00		3632	18.5	1.00		1.00	
	No	253	14.6	0.50 (0.35-0.71)	<0.001	0.67 (0.46-0.99)	0.04	266	13.5	0.69 (0.48-0.99)	0.05	0.85 (0.57-1.25)	0.40

Table 7.4 *Continued*. Odds ratios (95% CI) for the top quartile of Elderly Dietary Index and daily fruit and vegetable intake by adult socioeconomic measures in men aged 60-79 years in 1998-2000

		EDI Quartiles*						Daily Fruit and Vegetable Intake†					
				Unadjusted		Adjusted				Unadjusted		Adjusted	
		n	% Q4	OR (95% CI)	p	OR (95% CI)	p	n	%	OR (95% CI)	p	OR (95% CI)	p
Adverse SE score‡	0	1123	35.4	1.00		1.00		1137	24.4	1.00		1.00	
	1	834	25.9	0.64 (0.52-0.78)		0.74 (0.59-0.92)		857	18.2	0.69 (0.55-0.86)		0.74 (0.58-0.94)	
	2	593	19.7	0.45 (0.35-0.57)	<0.001	0.56 (0.42-0.74)	<0.001	616	14.9	0.55 (0.42-0.71)	<0.001	0.65 (0.48-0.88)	<0.001
	≥ 3	547	12.8	0.27 (0.20-0.35)		0.43 (0.31-0.59)		580	11.2	0.39 (0.29-0.52)		0.50 (0.35-0.71)	

EDI, Elderly Dietary Index; SE, socioeconomic. Analyses adjusted for age, energy intake, smoking, physical activity, alcohol, BMI and childhood social class.
*Data for EDI available for 3924 participants. Odds ratio for quartile 4 vs. quartiles 1-3.
†Data for fruit and vegetable intake available for 4067 participants.
‡Score includes: manual social class; education ≤ 14 years; no car; not a house owner; state pension only; no central heating.

Table 7.5 Odds ratios (95% CI) for the top quartile of Elderly Dietary Index and daily fruit and vegetable intake by combined childhood and adult socioeconomic measures in men aged 60-79 years in 1998-2000

		EDI Quartiles*						Daily Fruit and Vegetable Intake†					
				Unadjusted		Adjusted				Unadjusted		Adjusted	
		n	% Q4	OR (95% CI)	p	OR (95% CI)	p	n	%	OR (95% CI)	p	OR (95% CI)	p
Childhood/adult social class	Non-manual/ Non-manual	764	34.2	1.00		1.00		775	23.7	1.00		1.00	
	Manual/ Non-manual	978	28.7	0.78 (0.63-0.95)	<0.001	0.84 (0.68-1.05)	<0.001	1002	20.8	0.84 (0.67-1.05)	<0.001	0.84 (0.67-1.06)	<0.001
	Non-manual/ Manual	271	28.0	0.75 (0.55-1.02)		0.92 (0.66-1.27)		279	17.9	0.70 (0.50-0.99)		0.74 (0.51-1.07)	
	Manual/ Manual	1454	17.1	0.40 (0.33-0.49)		0.49 (0.39-0.61)		1529	13.1	0.48 (0.39-0.60)		0.53 (0.42-0.67)	
Combined childhood & adult adverse SE score‡	0-2	788	35.4	1.00		1.00		801	23.5	1.00		1.00	
	3-4	1024	27.5	0.69 (0.57-0.85)	<0.001	0.74 (0.60-0.92)	<0.001	1045	20.7	0.85 (0.68-1.06)	<0.001	0.83 (0.66-1.05)	<0.001
	5	851	20.9	0.48 (0.39-0.60)		0.57 (0.45-0.73)		884	14.3	0.54 (0.42-0.70)		0.57 (0.44-0.75)	
	≥ 6	338	12.1	0.25 (0.18-0.36)		0.37 (0.25-0.54)		358	11.2	0.41 (0.28-0.59)		0.46 (0.31-0.68)	

EDI, Elderly Dietary Index; SE, socioeconomic. Analyses adjusted for age, energy intake, smoking, physical activity, alcohol and BMI.
*Data for EDI available for 3924 participants. Odds ratio for quartile 4 vs. quartiles 1-3.
†Data for fruit and vegetable intake available for 4067 participants.
‡Score includes: childhood socioeconomic measures (manual childhood social class; no bathroom; no hot water supply; no family car ownership) and adult socioeconomic measures (manual social class; education ≤ 14 years; no car; not a house owner; state pension only; no central heating)

Table 7.6 Odds ratios (95% CI) for the top quartile of Elderly Dietary Index and daily fruit and vegetable intake by social interaction and family circumstances in men aged 60-79 years in 1998-2000

		EDI Quartiles*						Daily Fruit and Vegetable Intake†					
				Unadjusted		Adjusted				Unadjusted		Adjusted	
		n	% Q4	OR (95% CI)	p	OR (95% CI)	p	n	%	OR (95% CI)	p	OR (95% CI)	p
Marital status	Married	3224	26.3	1.00		1.00		3332	19.2	1.00		1.00	
	Single	131	16.0	0.53 (0.33-0.86)	0.01	0.69 (0.42-1.16)	0.16	142	13.4	0.65 (0.40-1.07)	0.09	0.66 (0.38-1.15)	0.14
	Widowed	280	16.8	0.57 (0.41-0.78)	0.001	0.70 (0.49-1.00)	0.05	292	9.6	0.45 (0.30-0.67)	<0.001	0.53 (0.35-0.80)	0.003
	Divorced/Separated	157	16.6	0.56 (0.36-0.85)	0.007	0.65 (0.41-1.04)	0.07	166	10.2	0.48 (0.29-0.80)	0.005	0.42 (0.23-0.76)	0.004
Living alone	No	3386	25.9	1.00	<0.001	1.00	0.02	3497	18.8	1.00	<0.001	1.00	0.003
	Yes	423	17.0	0.59 (0.45-0.76)		0.71 (0.53-0.95)		450	12.0	0.59 (0.44-0.79)		0.61 (0.44-0.85)	

Table 7.6 *Continued.* Odds ratios (95% CI) for the top quartile of Elderly Dietary Index and daily fruit and vegetable intake by social interaction and family circumstances in men aged 60-79 years in 1998-2000

		EDI Quartiles*						Daily Fruit and Vegetable Intake†					
		n	% Q4	Unadjusted OR (95% CI)	p	Adjusted OR (95% CI)	p	n	%	Unadjusted OR (95% CI)	p	Adjusted OR (95% CI)	p
Social contact - Children	Every week	3082	24.5	1.00		1.00		3184	17.5	1.00		1.00	
	Every month	217	30.9	1.37 (1.02-1.85)	0.78	1.17 (0.84-1.63)	0.54	224	22.3	1.35 (0.97-1.88)	0.62	1.19 (0.83-1.70)	0.80
	Every few months to every year	95	29.5	1.29 (0.82-2.01)		1.49 (0.91-2.45)		100	13.0	0.70 (0.39-1.27)		0.71 (0.38-1.33)	
	Rarely/Never/Does not apply	210	22.4	0.89 (0.63-1.24)		0.96 (0.66-1.39)		215	19.1	1.11 (0.78-1.58)		1.10 (0.75-1.62)	
Social contact - Siblings	Every week	990	23.5	1.00		1.00		1036	17.7	1.00		1.00	
	Every month	680	24.3	1.04 (0.83-1.31)	0.16	0.89 (0.70-1.14)	0.31	699	18.3	1.04 (0.81-1.34)	0.90	0.98 (0.75-1.27)	0.80
	Every few months to every year	787	26.4	1.17 (0.94-1.45)		1.07 (0.85-1.36)		810	17.4	0.98 (0.77-1.25)		0.92 (0.71-1.20)	
	Rarely/Never/Does not apply	687	25.9	1.14 (0.91-1.42)		1.09 (0.85-1.40)		709	18.2	1.04 (0.81-1.32)		0.99 (0.76-1.30)	
Social contact - Friends	Every week	3247	25.0	1.00		1.00		3357	17.9	1.00		1.00	
	Every month	246	28.9	1.22 (0.91-1.62)	0.70	1.12 (0.82-1.52)	0.34	253	18.2	1.02 (0.73-1.42)	0.36	0.97 (0.68-1.38)	0.33
	Every few months to every year	79	30.4	1.31 (0.81-2.13)		1.43 (0.85-2.41)		84	19.1	1.08 (0.62-1.87)		1.20 (0.68-2.11)	
	Rarely/Never/Does not apply	55	18.2	0.67 (0.33-1.33)		0.92 (0.43-1.96)		60	23.3	1.39 (0.76-2.55)		1.46 (0.73-2.92)	
Social contact - Neighbours	Every week	3306	24.9	1.00		1.00		3425	18.1	1.00		1.00	
	Every month	211	25.1	1.01 (0.73-1.40)	0.58	0.87 (0.62-1.23)	0.60	217	13.8	0.72 (0.49-1.08)	0.70	0.62 (0.41-0.95)	0.35
	Every few months to every year	57	36.8	1.76 (1.02-3.03)		1.76 (0.97-3.20)		59	23.7	1.40 (0.77-2.58)		1.25 (0.64-2.42)	
	Rarely/Never/Does not apply	91	23.1	0.91 (0.55-1.48)		1.01 (0.59-1.73)		95	16.8	0.91 (0.53-1.58)		0.87 (0.47-1.60)	

EDI, Elderly Dietary Index. Analyses adjusted for age, energy intake, smoking, physical activity, alcohol, BMI, and adult social class.
*Data for EDI available for 3924 participants. Odds ratio for quartile 4 vs. quartiles 1-3.
†Data for fruit and vegetable intake available for 4067 participants.

CHAPTER 8 Associations between a principal component analysis of dietary patterns, cardiovascular risk factors and risk of cardiovascular disease and mortality in older British men

8.1. Summary

Diet is a major modifiable risk factor for morbidity and mortality, but few studies have examined the relationship between *a posteriori* defined dietary patterns (a data-driven, exploratory approach to define dietary patterns based on the available data) and the risk of cardiovascular disease (CVD) and mortality in older adults. This chapter examines prospective associations between *a posteriori* dietary patterns (defined using principal component analysis) and the risk of CVD and all-cause mortality in older British men. At the 20 year re-examination in 1998-2000, 4252 men from the British Regional Heart Study (BRHS), aged 60-79 years, attended a physical examination, provided a fasting blood sample and completed both a general lifestyle questionnaire and a food frequency questionnaire (FFQ), and were followed up until 2010 for CVD and mortality. 3226 men, free from CVD at baseline and with available dietary data, were included in the analysis. Principal component analysis of 34 food groups, derived from the FFQ items, was used to identify dietary patterns. Cox proportional hazards regression was used to assess associations between quartiles of adherence to dietary patterns and risk of coronary heart disease (CHD) events, CVD events, CVD mortality and all-cause mortality. Principal component analysis identified three interpretable dietary patterns, which together explained 20.8% of the total variance in diet: 'high fat/low fibre' (high consumption of red meat, meat products, white bread, fried potato), 'prudent' (high consumption of poultry, fish, fruit, vegetables, pasta, rice, wholemeal bread) and 'high sugar' (high consumption of biscuits, puddings, chocolate, sweets) explaining 7.9%, 7.1% and 5.8% of the variance respectively. There were 899 deaths, 316 CVD deaths, 569 CVD events and 301 CHD events during a mean follow-up period of 11.3 years. The 'high fat/low fibre' dietary pattern was associated with an increased risk of all-cause mortality only, even after adjustment for cardiovascular risk factors (highest vs. lowest quartile; hazard ratio [HR]: 1.44, 95% CI: 1.13-1.84). Adherence to a 'high sugar' diet was associated with a borderline significant trend for an increased risk of CVD events and CHD events in fully adjusted models. The 'prudent' diet did not show a significant relationship with any cardiovascular outcomes or mortality. Adopting a

diet which avoids 'high fat/low fibre' and 'high sugar' components may reduce the risk of cardiovascular events and all-cause mortality in older adults.

8.2. Introduction

Diet is an important and well-established major modifiable risk factor for cardiovascular mortality and morbidity[6;8;23;202], as discussed in Chapter 2, section 2.5. Chapter 2 also introduced the two main approaches which have been used to assess dietary patterns: (1) *A priori* approaches, which are hypothesis oriented or theoretically defined, since they use available scientific evidence to generate predefined dietary scores or indexes based on dietary recommendations or guidelines; and (2) *A posteriori* approaches, which are data-driven or exploratory, since dietary patterns are derived from the available data based on methods such as principal component analysis, or cluster analysis[29;30]. Although the relationship between both *a priori* or *a posteriori* defined dietary patterns and the risk of CVD and mortality has been examined in middle-aged populations, few studies have been in older adults in particular[208;257]. The associations between *a priori* defined patterns and cardiovascular risk factors and the risk of CVD and mortality, and socioeconomic circumstances, in older aged men have already been examined in Chapter 6 and Chapter 7 respectively. However, using *a posteriori* methods to define dietary patterns in relation to disease outcomes has the advantage of not making any prior assumptions or hypotheses but uses the existing data to characterise total diet, so that patterns describe the eating behaviour of a population and can allow for biological interactions among nutrients[30]. Principal component analysis is one common method of deriving *a posteriori* dietary patterns and is a data-reduction technique, which identifies foods that are frequently consumed together and aggregates food items or groups on the basis of the degree of correlation with one another[29;30]. Principal component analysis is useful for describing the intercorrelation of foods consumed[299]. It has been suggested that principal component analysis may generate more meaningful and interpretable dietary patterns than cluster analysis (an alternative *a posteriori* method which separates individuals into mutually exclusive groups based on differences in dietary intake) as it has higher statistical power, and is less influenced by extreme values[195;207].

Defining dietary patterns *a posteriori* has typically identified two major types of dietary patterns – healthy ('prudent') and unhealthy ('Western') diets[207;385;386]. Healthy/prudent dietary patterns have tended to show inverse associations with CVD and mortality risk, whereas unhealthy/Western patterns have either shown positive associations or no significant association at all[385;386]. In the elderly specifically, few studies have used *a posteriori* methods to define dietary patterns in relation to CVD, in particular, and mortality risk[208], with a particular paucity of studies in older British populations[257].

The aim of this chapter is therefore to identify *a posteriori* dietary patterns, defined using principal component analysis, of older British men aged 60-79 years, and to examine the cross-sectional associations between these dietary patterns and cardiovascular risk factors, and the prospective associations with the risk of CHD events, CVD events, CVD mortality and all-cause mortality.

8.3. Objectives

To examine the associations of *a posteriori* dietary patterns with cardiovascular risk factors and the risk of CVD and mortality in older age (60-79 years). The specific aims of this chapter are:

i) To identify typical patterns of diet using *a posteriori* derived dietary patterns (identified using principal component analysis) in older men.
ii) To examine the relationship of *a posteriori* dietary patterns with established and emerging cardiovascular risk factors.
iii) To examine the association between *a posteriori* derived dietary patterns and risk of CHD events, CVD events, CVD mortality and all-cause mortality.

8.4. Methods

8.4.1. Subjects and methods of data collection

Data used in this chapter are based on the 20 year re-examination of British Regional Heart Study participants in 1998-2000, aged 60-79 years. 4252 men (77% of survivors) completed a questionnaire answering questions on their lifestyle and medical history,

completed a FFQ, attended a physical examination and provided a fasting blood sample[264]. Participants were prospectively followed for cardiovascular mortality and morbidity from re-examination (1998-2000) through to June 2010. Follow-up was achieved for 98% of the cohort[35]. Information on deaths was collected through the National Health Service Central Register (death certificates coded using International Classification of Diseases, ninth revision [ICD-9]). Evidence regarding non-fatal events was obtained by on-going reports from general practitioners and by biennial reviews of the patients' medical records[264]. The four outcomes examined in this chapter were: CHD events (diagnosis of non-fatal myocardial infarction [MI] or fatal CHD [ICD-9 codes 410-414]); CVD events (diagnosis of non-fatal MI, non-fatal stroke or fatal CVD [ICD-9 codes 390-459]); CVD mortality (ICD-9 codes 390-459) and all-cause mortality. Two additional outcomes were also considered in further exploratory analysis: non-CVD mortality (all deaths excluding ICD-9 codes 390-459) and cancer mortality (ICD-9 codes 140-209). Participants were censored at date of death or at the end of the study period (June 2010) if still alive. Of the 4252 men attending the physical examination, 723 men with prevalent heart failure, MI or stroke at baseline were excluded, leaving 3529 participants for inclusion in this study.

8.4.2. **Dietary assessment**

A self-administered postal FFQ, completed in 1998/2000, provided dietary intake data on the usual frequency of consumption of 86 food and drink items, as described in detail in Chapter 3, section 3.3.2 (see Appendix VI for a copy of the FFQ used). Nutrient intakes were derived using a validated computer program to calculate the total macronutrient and micronutrient composition of foods consumed[301]. The multivariate nutrient density model was used to adjust macronutrients for energy intake; carbohydrates, protein, total fat and saturated fat were expressed as percentages of energy (% kcal). Participants were also asked to indicate how often they consumed fresh fruit and vegetables (rarely/never, monthly, or 1, 2, 3, 4, 5, 6, or 7 days per week), with daily consumption classified as 7 days per week. Plasma vitamin C and E levels were also available from blood samples at the re-examination (1998-2000)[301]. The Healthy Diet Indictor (HDI) and the Elderly Dietary Index (EDI) dietary scores were generated as described previously in Chapter 6, section 6.4.3.

The 86 food items in the FFQ were aggregated into 34 mutually exclusive food groups, on the basis of the similarity of food types and nutrient composition; these were comparable to food groups used previously for a national representative dietary survey of British adults[387]. Individual food items were summed to generate a total score for each of the 34 food groups. The food groups were generated if at least one of the food items within the group was not missing. A list of these 34 food groups generated from the FFQ, together with their units of measurement and range, is shown in Table 8.1. Of the 3529 participants who attended the twenty year re-examination and were free from prevalent heart failure, MI or stroke, 303 participants with missing data on any of the 34 food groups were excluded, leaving 3226 men for inclusion in the final analysis.

8.4.3. **Cardiovascular risk factors**

Established and emerging cardiovascular risk factors were measured at the re-examination in 1998-2000. Socio-demographic and behavioural risk factors were assessed by self-report in the questionnaire and included smoking, physical activity and alcohol intake, as described in Chapter 3, section 3.3.3. Participants were classified into four cigarette smoking groups (never smoked; long-term ex-smokers, >15 years; recent ex-smokers, ≤ 15 years; current smokers)[90]. Current physical activity was classified into six groups based on intensity and frequency of exercise (inactive; occasional; light; moderate; moderately vigorous and vigorous)[283]. Alcohol intake was classified into five groups based on the number and frequency of alcoholic drinks consumed per week (none; occasional; light; moderate; heavy)[282]. Social class was measured using the baseline questionnaire in 1978-80, as described in Chapter 3, section 3.3.4. Social class was based on the longest held occupation coded using the Registrar General's occupational classification[285] and participants were classified as manual, non-manual or armed forces. Region of residence was categorised according to whether the town of each participant at the examination in 1998-2000 was in the southern England region or the rest of Britain. Systolic blood pressure (SBP) was assessed by physical examination, and plasma concentrations of metabolic risk factors (glucose, triglyceride and high density lipoprotein [HDL]) and inflammatory/hemostatic markers (C-reactive protein [CRP], tissue plasminogen activator [t-PA], D-dimer, von Willebrand Factor [vWF],

fibrinogen, interleukin 6 [IL-6] and homocysteine) were measured from fasting blood samples collected at re-examination in 1998-2000 as described in Chapter 3 (section 3.3.5 and 3.3.6). In addition, at the 20th year examination, participants were classified as having prevalent diabetes if they had a previous diagnosis, according to self-report. Assessment of body composition also occurred at the 20th year re-examination and measures used within this chapter include body mass index (BMI), waist circumference (WC) and mid-arm muscle circumference (MAMC), the measurements of which were described in Chapter 3 (section 3.3.1). Participants were classified into four BMI categories using WHO cut-points (underweight, <18.5 kg/m^2; normal weight, 18.5-24.99 kg/m^2; overweight, 25-29.99 kg/m^2; obese, ≥ 30 kg/m^2)[105].

8.4.4. **Statistical methods**

Principal component analysis was conducted using orthogonal varimax rotation on the 34 food groups generated from the FFQ, in order to identify dietary patterns. Principal component analysis was performed in Stata 13.1 (Stata Corp., College Station, Texas), using a correlation matrix which transformed the input variables (food groups) to z scores[388], to account for the different scales of measurement of the food groups used. Three principal components were retained based on having an eigenvalue greater than one, the scree plot of eigenvalues and the interpretability of the rotated factors[389]. Food groups with factor loading of more than 0.20 or less than -0.20 were considered to be important contributors to the component/dietary pattern. The factors scores for each dietary pattern were calculated for each participant by summing the intakes of the food groups weighted by their factor loadings. The higher the score the closer the diet to the dietary pattern, and the lower the score the further the diet from the dietary pattern. Participants were then classified into quartiles of adherence to each of the three dietary patterns.

Baseline cardiovascular risk factors of participants were presented by quartiles of the distribution of the three dietary patterns with continuous variables reported as means and standard deviations, and categorical variables as percentages. The distributions of CRP, D-dimer, IL-6 and homocysteine were highly skewed and were log transformed. Cox proportional hazards regression models were fitted to assess the association

between quartiles of adherence to dietary patterns and the risk of all-cause mortality, CVD mortality, CVD events and CHD events. All Cox models were tested for the proportional-hazards assumption, on the basis of Schoenfeld residuals, which was not found to be violated. Multivariable models were adjusted for potential confounders in a sequential manner, including age (model 1), energy intake, smoking status, alcohol intake, physical activity, social class and BMI (model 2), HDL, SBP and diabetes (model 3) and CRP and vWF (model 4). Age, energy intake, HDL, SBP, CRP and vWF were fitted as continuous variables. Smoking status, alcohol intake, physical activity, social class, BMI and diabetes were fitted as categorical variables.

8.5. Results

8.5.1. *A posteriori* dietary patterns, derived by principal component analysis

Analyses were based on 3226 men, aged 60-79 years, who attended the 20 year re-examination, were free from prevalent heart failure, MI and stroke at baseline, and provided information on the 34 food groups. Table 8.2 shows the food group factor loadings for the three major dietary patterns identified by principal component analysis. From the 34 factors extracted, 12 had an eigenvalue greater than one, of which three factors were selected with meaningful interpretability. These three interpretable *a posteriori* dietary patterns identified by principal component analysis explained 20.8% of the total variance in diet. The dietary pattern defined by the first principal component was labeled ‘high fat/low fibre’ and explained 7.9% of the total variance. This dietary pattern was characterised by a high consumption of red meat, meat products, fried potato, white bread, eggs and beer (positive scoring coefficients) and a low intake of wholemeal bread (negative scoring coefficients). The strongest component of this pattern was meat products with a factor loading of 0.42. The second principal component reflected a ‘prudent’ diet, explaining 7.1% of the variance, and was characterised by a high consumption of poultry, fish, vegetables, legumes, fruit, pasta and rice, wholemeal bread, eggs, sauces, soups and olive oil (positive scoring coefficients). The strongest component of this pattern was fish with a factor loading of 0.38. The third principal component reflected a ‘high sugar’ diet, and explained 5.8% of the total variance. This dietary pattern was characterised by a high consumption of breakfast cereal, full-fat cheese, biscuits, puddings, chocolate, sweets and sweet spreads

(positive scoring coefficients) and a low consumption of beer (negative scoring coefficients). The strongest component of this pattern was biscuits and puddings with a factor loading of 0.46.

8.5.2. *A posteriori* dietary patterns and cardiovascular risk factors

8.5.2.1 'High fat/low fibre' dietary pattern and cardiovascular risk factors

Cardiovascular risk factor and dietary factors for each quartile of the 'high fat/low fibre' dietary pattern are presented in Table 8.3. In unadjusted analyses, adherence to the 'high fat/low fibre' dietary pattern showed a strong positive association with current smoking, heavy drinking, physical inactivity and manual social class and a strong inverse association with living in Southern England. Two measures of obesity (BMI and WC) were positively associated with this dietary pattern but muscle mass (MAMC) was not. As expected, many dietary variables were strongly associated with this dietary pattern, with strong positive associations seen with energy intake, percent of energy from fat and saturated fat, and inverse associations with percent of energy from carbohydrates, percent of energy from protein, fibre, vitamin C, iron, daily fruit and vegetable intake and plasma vitamin C and E. The 'high fat/low fibre' dietary pattern was also inversely associated with the HDI and the EDI (two *a priori* defined dietary scores introduced in Chapter 6). Among metabolic variables, triglyceride level was positively associated with this dietary pattern and HDL was inversely associated. The prevalence of diabetes was also inversely associated with the 'high fat/low fibre' dietary pattern, which was an unexpected finding and may be an example of dietary change, secondary to the development of illness. All inflammatory/hemostatic markers (CRP, t-PA, D-dimer, vWF, fibrinogen, IL-6 and homocysteine) were positively associated with adherence to this diet pattern.

8.5.2.2 'Prudent' dietary pattern and cardiovascular risk factors

Table 8.4 presents cardiovascular risk factors and dietary factors by quartiles of the 'prudent' dietary pattern. Unadjusted analysis showed that adherence to the 'prudent' pattern was strongly inversely associated with current smoking, physical inactivity and manual social class. However, heavy drinking and living in Southern England were not significantly associated with the 'prudent' dietary pattern. Measures of obesity (BMI

and WC) were not associated with this dietary pattern but MAMC showed a very modest positive association. Associations between dietary variables and the 'prudent' dietary pattern were generally in the opposite direction to the 'high fat/low fibre' dietary pattern. Participants with higher adherence to the 'prudent' dietary pattern had a significantly higher percent of energy from protein, higher intakes of fibre, iron, vitamin C and E, higher plasma vitamin C and E levels, a higher proportion of daily fruit and vegetable intake, and a higher EDI score and significant lower intakes of percent of energy from fat and saturated fat. However, as for the 'high fat/low fibre' dietary pattern, the 'prudent' dietary pattern was positively associated with total energy intake and inversely associated with the HDI score. Triglyceride level and all inflammatory/hemostatic markers were inversely associated, and HDL and diabetes were positively associated with the 'prudent' dietary pattern.

8.5.2.3 'High sugar' dietary pattern and cardiovascular risk factors

Cardiovascular risk factors and dietary factors are presented by quartiles of the 'high sugar' dietary pattern in Table 8.5. Contrary to expectations, in unadjusted analyses manual social class, several behavioural variables (current smoking, heavy drinking and physical inactivity) and body composition variables (BMI and WC) were inversely associated with adherence to a 'high sugar' dietary pattern. The proportion of participants living in the southern region of England was positively associated with the 'high sugar' diet, but no association was found with MAMC. Participants consuming a 'high sugar' diet had a significantly higher intake of total energy, higher percent of energy from carbohydrates, fat and saturated fat, higher intakes of fibre, vitamin C and E, iron, higher plasma vitamin C, a higher proportion of people consuming fruit and vegetables daily and a higher EDI score, but a significantly lower percent of energy from protein. Prevalent diabetes, some metabolic variables (triglycerides, HDL and glucose) and some inflammatory/hemostatic markers (CRP, t-PA and IL-6) were inversely associated with a 'high sugar' diet, but D-dimer was positively associated with this dietary pattern.

To test whether the observed inverse associations between a 'high sugar diet and behavioural, body composition and cardiovascular risk factors could be explained by an

inverse association between a 'high sugar' diet and manual social class, analyses were stratified into manual and non-manual occupational social class but the inverse associations were still apparent within both groups. Men in the highest quartile of the 'high sugar' diet also had the lowest proportion of obese individuals and it is therefore possible that obese men had made changes to their diet to reduce sugar intake. However, when analyses were stratified into obese and non-obese participants, inverse associations between a 'high sugar' diet and adverse behavioural risk and cardiovascular risk factors remained in both groups.

8.5.3. *A posteriori* dietary patterns and risk of CVD/mortality

There were a total of 899 deaths, 316 CVD deaths, 569 CVD events and 301 CHD events during a mean period of 11.3 years of follow-up.

8.5.3.1 'High fat/low fibre' dietary pattern and CVD/mortality

Adjusted hazard ratios (HRs) for CHD events, CVD events, CVD mortality and all-cause mortality by quartiles of adherence to a 'high fat/low fibre' dietary pattern are presented in Table 8.6. A 'high fat/low fibre' dietary pattern was associated with a graded increase in all-cause mortality risk. Although attenuated slightly, this association remained after adjustment for socio-demographic, behavioural and cardiovascular risk factors, with a 44% increase in risk in the highest compared to the lowest quartile of adherence to the 'high fat/low fibre' pattern (HR: 1.44, 95% CI: 1.13-1.84, p-trend: 0.007). In age-adjusted analysis, participants in the highest quartile of the 'high fat/low fibre' dietary pattern had an increased risk of CVD mortality with a significant trend (p –trend: 0.002) and incident CVD events with a borderline significant trend (p-trend: 0.06). However, these trends disappeared after adjustment for energy intake, smoking, alcohol, physical activity, social class and BMI. No significant trends were seen between the 'high fat/low fibre' dietary pattern and risk of incident CHD events.

To investigate the factors underlying the significant association between adherence to the 'high fat/low fibre' and an increased risk of all-cause mortality, the risks of cause-specific mortality were also examined in further exploratory analysis. Non-CVD

mortality was strongly associated with the 'high fat/low fibre' diet (highest vs. lowest quartile; HR: 1.47, 95% CI: 1.09-1.99, p-trend: 0.008) and in particular cancer mortality was strongly associated with this diet pattern in the fully adjusted model (highest vs. lowest quartile; HR: 1.62, 95% CI: 1.09-2.40, p-trend: 0.01).

8.5.3.2 'Prudent' dietary pattern and CVD/mortality

Table 8.7 presents the adjusted HRs for the four outcomes by quartiles of adherence to a 'prudent' dietary pattern. Adherence to the 'prudent' dietary pattern was associated with a significant graded decrease in risk of all-cause mortality across quartiles (p-trend: 0.001). However, after adjustment for socio-demographic, behavioural and cardiovascular risk factors (model 4) HRs was attenuated slightly but men in the second quartile of the 'prudent' diet still had a significantly decreased risk of all-cause mortality (second vs. first quartile; HR: 0.77, 95% CI: 0.63-0.95), although the trend across quartiles was not significant (p-trend: 0.28). Similar associations were observed with CVD mortality; in the fully adjusted model, men in second quartile of adherence to a 'prudent' diet had a lower risk but the trend across quartiles was not significant (second vs. first quartile; HR: 0.68, 95% CI: 0.47-0.98, p-trend: 0.74). No significant associations were seen between quartiles of a 'prudent' diet and the risk of either incident CVD events or incident CHD events.

8.5.3.3 'High sugar' dietary pattern and CVD/mortality

Adjusted HRs for the four outcomes examined by quartiles of adherence to a 'high sugar' dietary pattern are presented in Table 8.8. This dietary pattern was not significantly associated with all-cause-mortality after adjustment for cardiovascular risk factors (highest vs. lowest quartile; HR: 1.00, 95% CI: 0.77-1.29, p-trend: 0.71) [model 4]. The risk of CVD mortality was increased in the top quartile of adherence to the 'high sugar' pattern but the trend was not significant (highest vs. lowest quartile; HR: 1.32, 95% CI: 0.84-2.05, p-trend: 0.33) in the model adjusted for cardiovascular risk factors (model 4). A borderline significant trend was observed between adherence to a 'high sugar' diet and an increased risk of both incident CVD events (highest vs. lowest quartile; HR: 1.47, 95% CI: 1.06-2.04, p-trend: 0.06) and incident CHD events (highest vs. lowest quartile; HR: 1.57, 95% CI: 1.00-2.46, p-trend: 0.06) in fully adjusted models.

8.6. Discussion

8.6.1. Summary of main findings

In this chapter, principal component analysis has been used to apply *a posteriori* defined dietary patterns to a cohort of older men. This data-driven method identified three interpretable dietary patterns: 'high fat/low fibre', 'prudent' and 'high sugar' which reflect typical eating habits of older men in the BRHS. Adherence to a 'high fat/low fibre' pattern (a high intake of red meat, meat products, white bread, fried potato and eggs), characteristic of a traditional British diet, was associated with higher levels of adverse cardiovascular risk factors and an increased risk of all-cause mortality, with a 44% higher risk in those in the highest compared to the lowest quartile of adherence. However, adherence to a 'prudent' diet (characterised by a high consumption of poultry, fish, fruit, vegetables, pasta, rice, and wholemeal bread) more closely resembled a Mediterranean-style diet and was associated with lower levels of cardiovascular risk factors in crude analysis, but did not show a significant trend with cardiovascular outcomes or mortality in adjusted analysis. The third dietary pattern identified was a 'high sugar' pattern (characterised by a high consumption of biscuits, puddings, chocolate, sweets), which showed an inverse association with a number of cardiovascular risk factors. However, adherence to a 'high sugar' diet was associated with a borderline significant trend for an increased risk of CVD events and CHD events in fully adjusted models.

8.6.2. Comparison with previous studies

In this cohort of older British men, principal component analysis identified three dietary patterns: a 'high fat/low fibre' pattern which was characteristic of a typical British diet and could also have been referred to as a traditional or Western style diet; a 'prudent' pattern which more closely resembled a Mediterranean-style diet or healthy diet; and a 'high sugar' pattern with a high consumption of sweet item and confectionary. These emerging dietary patterns are consistent with those reported in previous studies using principal component analysis, which have typically identified two major types of dietary patterns, an unhealthy/Western diet and a healthy/prudent diet[207;385;386]. One study in older British adults, aged 59 to 73 years, identified very similar dietary patterns

(prudent and traditional) to those identified in this chapter[374]. In this previous study, by Robinson et al[374], the prudent diet (high in consumption of fruit, vegetables, oily fish and wholemeal cereals) is comparable to the 'prudent' diet observed in this cohort and adherence was also associated with non-manual social class and being a non-smoker. The traditional diet (high in consumption of vegetables, processed and red meat, fish and puddings) had similarities with the 'high fat/low fibre' diet in this cohort and was also associated with higher alcohol consumption. The three dietary patterns identified in this chapter together explained ~21% of the total variance in the dietary data. Although this proportion of variance seems low, this is actually greater than the variance explained by a comparable study in older British adults, aged 65 years and over, which identified four interpretable principal components from the National Diet and Nutrition Survey data, explaining 9.8% of the total variance[257].

Results in this chapter showed a significant graded association between adherence to a 'high fat/low fibre' dietary pattern and an increased risk of all-cause mortality. This association was attenuated slightly after adjustment for BMI, HDL, SBP and diabetes suggesting physiological cardiovascular risk factors may in part be mediating the association between a 'high fat/low fibre' diet and an increased risk of all-cause mortality. Further adjustment for CRP and vWF attenuated the association slightly further suggesting a possible mechanism of inflammation, caused by a diet low in antioxidant components such as fruit and vegetables, potentially leading to an increased mortality risk. In particular, adherence to the 'high fat/low fibre' diet was associated with an increased risk of cancer mortality. These results for the so called 'high fat/low fibre' diet are consistent with studies showing that fibre intake and all-cause mortality are inversely associated[390]. These results are also support those from previous studies which have found that the consumption of red meat and processed meat (two components of the 'high fat/low fibre' dietary patterns with high factor loadings) is associated with an increased risk of all-cause and cancer mortality[219;391]. Adherence to a 'prudent' diet was associated with a non-significantly reduced risk of all-cause mortality; there was also no significant trend between a 'high sugar' diet and the risk of all-cause mortality. None of the three dietary patterns described here were associated with CVD mortality. A comparable study of an older British population, aged 65 years and older, from the National Diet and Nutrition Survey, identified four interpretable diet

patterns using principal component analysis: 'Mediterranean–style', 'health aware', 'traditional' and 'sweet and fat'[257]. Only the Mediterranean–style dietary pattern was associated with a reduced risk of all-cause mortality, with an 18% reduction in risk in those in the highest compared to the lowest tertile[257]. However, in men only, the traditional diet was also a risk factor for mortality, similar to the 'high fat/low fibre' results observed in this cohort.

A recent meta-analysis of 13 prospective studies involving 338,787 participants examined the association between dietary patterns defined by principal component analysis and risk of all-cause and CVD mortality[385]. Summary relative risk estimates (SRREs) showed a significant inverse association between a prudent/healthy dietary pattern and all-cause mortality (highest vs. lowest category of dietary pattern score; SRRE: 0.76, 95% CI: 0.68-0.86) and CVD mortality (SRRE: 0.81, 95% CI: 0.75-0.87) but non-significant associations between the Western/unhealthy dietary pattern and all-cause mortality (SRRE: 1.07, 95% CI: 0.96-1.20) and CVD mortality (SRRE: 0.99, 95% CI: 0.91-1.08). The risk estimates observed in the present study for the association between a prudent diet and a lower risk of all-cause mortality and CVD mortality were in the same direction as those in the meta-analysis but statistically non-significant. Also, a significant association was observed in the present study between an unhealthy diet (the 'high fat/low fibre' diet) and a higher risk of all-cause mortality which was not seen in the meta-analysis. These discrepancies may have been due to the much bigger sample size in the meta-analysis giving greater power to detect smaller effects or due to the differences in confounder adjustments; few studies included in this meta-analysis had such a comprehensive adjustment for established and emerging cardiovascular risk factors as were included in this chapter.

In this chapter, there was no significant association between a 'high fat/low fibre' diet or a 'prudent' diet and the risk of CVD events or CHD events, but adherence to a 'high sugar' diet was associated with a borderline significant trend for an increased risk of CVD events and CHD events in fully adjusted models. These results are in keeping with the American Heart Association recommendation of reducing dietary intake of added sugars in order to lower the risk of cardiovascular disease[392] and the recent suggestion

that sugar may be a more important risk factor than fat for cardiovascular disease[393;394]. A meta-analysis of 12 prospective studies involving 409,780 participants examined the association between principal component analysis defined dietary patterns and CHD risk. Summary relative risks showed an inverse association between the prudent/healthy diet and CHD risk, but no association with the Western/unhealthy diet[386]. The observed association between a healthy diet and CHD events in this meta-analysis but not in the current study may again possibly be explained by the much larger sample size in the meta-analysis giving greater power to detect smaller effects. This meta-analysis did not identify any studies from the UK specifically and did not mention high sugar/sweet dietary patterns, as observed in this cohort. Results from this chapter may therefore be the first study of principal component analysis defined dietary patterns and CHD risk in the UK, and this study has shown that a high sugar dietary pattern may increase CHD and CVD risk in older British men.

8.6.3. **Strengths and limitations**

A major strength of the results presented in this chapter is that data are from a moderately large prospective population-based study, with negligible loss to follow-up and the ascertainment of CVD and mortality outcomes was objective[35;264]. However, since the study comprised predominately of white European older male participants, the applicability of the findings to women and non-white ethnic groups is uncertain. Moreover, results may not be applicable to men with prevalent MI, stroke or heart failure since such participants were excluded from analyses.

The FFQ measured dietary intake at baseline only, so whether dietary patterns of participants changed throughout follow-up was unknown. Also, as discussed in Chapter 6, dietary intake was assessed using a FFQ, which can be prone to measurement error through misreporting and can affect the estimation of energy intake and micronutrient intake[321;322]. Misreporting of energy intake may therefore affect dietary pattern analysis, especially since underreporting can be more prevalent for some unhealthy food groups[350;351]. Also, in older populations non-response to FFQ questions could have increased the chance of dietary underreporting[104;323]. However, the FFQ used in this study has previously been validated against weighed food intakes in British populations[273;274], and the dietary intake of BRHS participants was broadly comparable

with those from the National Diet and Nutrition Survey[339], as discussed in section 6.6.2.1. In addition, to reduce the risk of bias in dietary assessment, established minimum and maximum cut-offs for total energy intake were applied to the data (<500 or > 8000 kcal[279]) to exclude under and over-reporters. It is possible that some residual confounding remains in the assessment of dietary patterns, but underreporting of food intake is only likely to have biased the relative risk estimates towards the null.

All analyses were adjusted for total energy intake to reduce the risk of bias[280]. Total energy intake showed strong positive associations with all three dietary patterns. However, analyses in Chapter 6 already showed that energy intake was not significantly associated with all-cause mortality, CVD mortality, CVD events of CHD events after adjustment for cardiovascular risk factors (see section 6.5.3), and therefore the adjustment for energy intake in this chapter did not represent an over-adjustment[338]. A previous study also suggested that it is not necessary to adjust individual food items for energy intake before entry into a principal component analysis but that energy adjustment should be made when analysing the effects of the dietary patterns on the outcome of interest[395], which supports the method of adjustment used here.

A posteriori methods of defining dietary patterns have the advantage over using *a priori* methods, of making no prior assumptions about dietary patterns, instead using an empirical, data-driven approach to derive typical patterns of dietary intake[30]. The 'high fat/low fibre' dietary pattern was inversely associated with the EDI dietary score and the 'prudent' dietary pattern and was positively associated with the EDI. Since strong inverse associations between the EDI and risk of CVD mortality and all-cause mortality were observed (Chapter 6), the observed associations between dietary patterns and the EDI support the validity of these principal component analysis-derived dietary patterns as measures of unhealthy/healthy diets. However, principal component analysis has some limitations. Firstly, data on the reproducibility and validity of this method in nutritional epidemiology is limited[396-398]. Secondly, subjectivity was introduced at various points in the analysis, such as the grouping of dietary variables and the choice of how many components to retain, which may have influenced the observed associations with disease risk[30;389;399]. However, as outlined in methods section above,

the food groups used were comparable to those used previously for a national representative dietary survey of British adults[387] (section 8.4.2) and criteria for deciding how many components to retain was decided in advance of the analysis (section 8.4.4), both of which helped to reduce this bias.

The 'high sugar' dietary pattern was inversely associated with several cardiovascular risk factors in crude cross-sectional analysis, including current smoking, heavy drinking, physical inactivity, BMI and WC, and these associations could not be explained by stratifying for social class or obesity status. These results for a 'high sugar' diet were contrary to expectations since a significant relationship between added sugar consumption and increased risk of CVD mortality was previously observed in American adults[400] and an association between a high sugar intake and a higher risk of CHD events and CVD events was observed prospectively in this cohort. However, several items with a high factor loading in the 'high sugar' dietary pattern contained a mixture of types of food, which could not be separated due to the nature of the FFQ questions, and may possibly explain the unexpected directions of association. For example, the 'breakfast cereal' food group included both high sugar and high fibre cereal types (e.g. porridge, muesli) and the 'biscuits and puddings' food group included both high sugar items and healthier items (e.g. tinned fruit, yoghurt).

The self-reported nature of some of the cardiovascular risk factors, including smoking status, alcohol intake, and physical activity, may possibly have caused misclassification which could have led to over or under-estimates of hazard ratios. In particular, self-reported measures of physical activity can be a problem in older age groups due to the light intensities of activity and very variable duration of activity in these age groups which make accurate recall especially difficult[315-317] (as discussed in Chapter 4, Section 4.6.3). However, a validation study in older men within the BRHS has shown self-reported physical activity questions used within this cohort are associated with a graded increase in objectively measured physical activity[318]. This reduces the risk of measurement error and any possible misclassification of physical activity is likely to have been non-differential across participants of varying diet quality and is only likely

to have attenuated relative risk estimates between *a posteriori* dietary scores and outcomes[320].

Lastly, there may have been a healthy-adherer/healthy-user effect in people who adhered to a healthier diet. In particular, people with a high intake of fruit, vegetables, wholegrain bread, olive oil etc., may have been on average more health-conscious and more likely to have exhibited a series of healthier behaviours, including regular visits to their general practitioner, having more preventive tests, higher adherence to medicine etc[352;353]. Such confounding variables were unmeasured in this study and hence may have caused a slight over-estimation of the magnitude of effect of dietary patterns on CVD and mortality risk.

8.6.4. **Conclusion**

A posteriori, data-driven, methods can be used to identify typical dietary patterns of a population. In this cohort of older men, principal component analysis identified three interpretable dietary patterns: 'high fat/low fibre', 'prudent' and 'high sugar'. Dietary patterns persist as an important risk factor for CVD and all-cause mortality in the elderly, with high adherence to a 'high fat/low fibre' dietary pattern being associated with an increased risk of all-cause mortality, and adherence to a 'high sugar' diet being associated with an modest increase in risk of CVD events and CHD events, which could not be explained by adjustment for cardiovascular risk factors. The 'prudent' diet was not significantly associated with cardiovascular outcomes or mortality. Adopting a diet which avoids 'high fat/low fibre' and 'high sugar' components may be beneficial to reduce the risk of cardiovascular events and all-cause mortality in older adults.

Table 8.1 List of 34 food groups derived from items in the food frequency questionnaire, used in men aged 60-79 years in 1998-2000

Food group	Food items	Units	Range
Red meat	Beef (including minced beef, beef burgers); lamb; pork, bacon, ham, salami	days/week	0-7
Poultry	Chicken, turkey, other poultry	days/week	0-7
Meat products	Tinned meat (all types, corned beef, etc.); pork sausages; beef sausages; meat pies, pasties; liver, kidney, heart	days/week	0-7
Fish	White fish (cod, haddock, hake, plaice, fish fingers, etc.); kippers, herrings, pilchards, tuna, sardines, salmon, mackerel (including tinned); shellfish	days/week	0-7
Potatoes	Boiled, baked, mashed	days/week	0-7
Fried potatoes	Chips or fried (from shop); chips or fried (cooked at home); roast potatoes	days/week	0-7
Vegetables	Green vegetables, salad; carrots; parsnips, swedes, turnips, beetroot, other root vegetables; onions; tomatoes	days/week	0-7
Legumes	Baked or butter beans, lentils, peas, chickpeas, sweetcorn	days/week	0-7
Fruit	Apples; pears; oranges; bananas; other fruits	pieces/week	0-60
Pasta and rice	Spaghetti and other pasta; rice (all types except pudding rice)	days/week	0-7
Breakfast cereal	Grapenuts, porridge, Ready brek, Special K, Sugar Puffs, Rice Crispies; Cornflakes, muesli, Shredded Wheat, Sultana Bran, Weetabix; Bran Flakes, Puffed Wheat; All Bran, Wheat Bran; other cereal	days/week	0-7
White bread	White bread	days/week	0-7
Wholemeal bread	Brown bread; wholemeal bread	days/week	0-7
Full-fat cheese	e.g. cheddar, Leicester, stilton, brie, soft cheeses	days/week	0-7
Low-fat cheese	e.g. edam, cottage cheese, reduced fat cheeses	days/week	0-7
Full-fat milk	Full-fat milk	None; ≤ 0.5 pint; 0.5-1 pint; >1 pint/day	1-4
Semi-skimmed milk	Semi-skimmed milk	None; ≤ 0.5 pint; 0.5-1 pint; >1 pint/day	1-4
Skimmed milk	Skimmed milk	None; ≤ 0.5 pint; 0.5-1 pint; >1 pint/day	1-4
Other milk	Condensed milk, evaporated milk etc.	None; ≤ 0.5 pint; 0.5-1 pint; >1 pint/day	1-4
Biscuits and puddings	Digestive biscuits, plain biscuits; sweet biscuits, sponge cakes, scones, buns; ice-cream, sweet yoghurts, trifle; fruit cake, fruit bread, plum pudding; fruit tart, jam tart, fruit crumble; milk puddings (rice, tapioca); tinned fruit, jellies; sweet sauces (chocolate, custard)	days/week	0-7

Table 8.1 *Continued.* List of 34 food groups derived from items in the food frequency questionnaire, used in men aged 60-79 years in 1998-2000

Food group	Food items	Units	Range
Chocolate and sweets	Chocolate, chocolate bars, sweets (all types)	days/week	0-7
Eggs	Eggs (boiled, poached, fried, scrambled); eggs in baked dishes (e.g. flans, quiches, soufflés, egg custard etc.)	days/week	0-7
Fruit juice	Natural fruit juices (including tomato juice)	days/week	0-7
Soft drinks	Fizzy drinks, non-diet squashes; low calorie (diet) squashes and fizzy drinks	days/week	0-7
Tea and coffee	Tea; coffee; other hot drinks (hot chocolate, malted milk, Horlicks)	cups/day	0-34
Nuts	Nuts (e.g. salted or unsalted peanuts), nut butter	days/week	0-7
Savoury snacks	Potato crisps, corn chips, crackers	days/week	0-7
Sweet spreads	Jam, honey, marmalade, chocolate spread	days/week	0-7
Sauces and soups	Chutney, brown sauce, tomato sauce; soups (all kinds, home-made, tinned, packet)	days/week	0-7
Wine	Wine	single glasses/week	0-44
Beer	Beer, Lager, Shandy	pints/week	0-70
Spirits	Spirits	single glasses/week	0-84
Olive oil	Olive oil	mls/week	0-500
Butter	Butter	grams/week	0-1134

Table 8.2 Food group factor loadings for 'high fat/low fibre', 'prudent' and 'high sugar' dietary patterns, in men aged 60-79 years in 1998-2000

Food groups	'High fat/low fibre' dietary pattern	'Prudent' dietary pattern	'High sugar' dietary pattern
Variance explained (%)	7.9	7.1	5.8
Red meat	**0.33**	0.12	0.03
Poultry	0.03	**0.29**	-0.09
Meat products	**0.42**	0.08	-0.04
Fish	0.07	**0.38**	-0.08
Potatoes	0.05	0.12	0.12
Fried potatoes	**0.36**	0.01	0.02
Vegetables	-0.01	**0.26**	0.09
Legumes	0.14	**0.26**	0.01
Fruit	-0.13	**0.23**	0.04
Pasta and rice	0.00	**0.34**	-0.06
Breakfast cereal	-0.19	0.06	**0.28**
White bread	**0.34**	-0.19	0.04
Wholemeal bread	**-0.30**	**0.25**	0.07
Full-fat cheese	0.04	0.05	**0.25**
Low-fat cheese	-0.03	0.17	-0.03
Full-fat milk	0.04	-0.07	0.13
Semi-skimmed milk	0.03	-0.01	0.13
Skimmed milk	-0.13	0.10	-0.17
Other milk	0.07	0.03	-0.12
Biscuits and puddings	0.06	-0.03	**0.46**
Chocolate and sweets	0.06	-0.04	**0.41**
Eggs	**0.26**	**0.23**	0.09
Fruit juice	-0.13	0.17	0.12
Soft drinks	0.08	0.05	0.09
Tea and coffee	0.09	-0.06	0.12
Nuts	0.01	0.14	0.10
Savoury snacks	0.16	0.03	0.15
Sweet spreads	-0.12	0.06	**0.36**
Sauces and soups	0.17	**0.26**	0.18
Wine	-0.18	0.19	-0.04
Beer	**0.23**	0.09	**-0.31**
Spirits	0.01	0.10	-0.11
Olive oil	-0.08	**0.23**	-0.05
Butter	0.09	0.02	0.04

Factor loadings ≥ 0.20/≤ -0.20 are indicated in bold.

Table 8.3 Cardiovascular risk factors and dietary factors by quartiles of a 'high fat/low fibre' dietary pattern, in men aged 60-79 years in 1998-2000

	'High fat/low fibre' dietary pattern (quartiles)				P (trend)
	Q1	Q2	Q3	Q4	
n	807	806	807	806	
Socio-demographic/Behavioural variables					
Age (years)	68.0 (5.4)	68.5 (5.3)	68.4 (5.5)	68.1 (5.4)	0.81
Current smokers (%)	4.3	7.6	13.7	24.7	<0.001
Heavy drinkers (%)	1.3	1.3	3.0	5.8	<0.001
Physically inactive (%)	7.9	9.6	8.2	11.9	0.02
Manual social class (%)	32.5	41.8	53.4	69.4	<0.001
Living in southern England region (%)	37.3	37.8	34.2	27.4	<0.001
Body composition					
Obesity (BMI $\geq$ 30 kg/m^2) (%)	14.5	15.4	15.9	18.8	0.02
Waist circumference (cm)	95.8 (10.6)	97.1 (9.6)	97.2 (9.9)	97.8 (11.1)	<0.001
Mid-arm muscle circumference (cm)	26.6 (2.3)	26.7 (2.2)	26.6 (2.3)	26.4 (2.5)	0.06
Dietary variables					
Energy intake (kcal)	1861.8 (385.3)	2004.7 (420.2)	2175.2 (445.5)	2548.4 (591.3)	<0.001
Carbohydrates (% kcal)	54.9 (6.7)	52.5 (6.7)	51.9 (6.8)	50.2 (6.5)	<0.001
Protein (% kcal)	16.5 (2.3)	15.9 (2.3)	15.3 (2.2)	14.8 (2.0)	<0.001
Fat (% kcal)	26.8 (5.8)	29.8 (5.9)	31.2 (5.6)	33.5 (5.4)	<0.001
Saturated fat (% kcal)	10.5 (3.2)	12.2 (3.4)	13.0 (3.5)	14.1 (3.3)	<0.001
Fibre (g/day)	29.7 (8.6)	26.6 (8.7)	24.9 (8.0)	23.9 (8.0)	<0.001
Vitamin C (mg/day)	94.5 (38.8)	85.9 (36.2)	80.7 (35.9)	74.0 (34.5)	<0.001
Vitamin E (mg/day)	8.4 (4.6)	8.4 (4.8)	8.3 (4.4)	8.9 (5.5)	0.05
Iron (mg/day)	14.9 (5.5)	14.3 (5.5)	13.5 (4.6)	14.3 (5.0)	0.004
Daily fruit intake (%)	61.6	46.2	38.9	21.4	<0.001
Daily vegetable intake (%)	45.1	35.9	28.8	23.5	<0.001
Plasma vitamin C (µmol/L)	35.2 (26.3)	33.4 (23.5)	28.5 (26.3)	26.1 (30.9)	<0.001
Plasma vitamin E (µmol/L)	35.4 (12.4)	34.5 (11.7)	33.1 (12.2)	32.0 (11.5)	<0.001
Healthy Diet Indicator	3.4 (1.1)	3.0 (1.2)	2.8 (1.3)	2.4 (1.2)	<0.001
Elderly Dietary Index	26.6 (2.8)	24.6 (2.8)	23.6 (2.7)	22.1 (2.9)	<0.001

Table 8.3 *Continued.* Cardiovascular risk factors and dietary factors by quartiles of a 'high fat/low fibre' dietary pattern, in men aged 60-79 years in 1998-2000

	'High fat/low fibre' dietary pattern (quartiles)				P (trend)
	Q1	Q2	Q3	Q4	
Metabolic variables					
SBP (mmHg)	149.9 (24.5)	149.5 (23.7)	150.7 (23.0)	150.5 (24.3)	0.40
Triglycerides (mmol/L)	1.7 (0.9)	1.7 (0.9)	1.9 (1.1)	1.9 (1.3)	<0.001
HDL (mmol/L)	1.4 (0.4)	1.3 (0.3)	1.3 (0.3)	1.3 (0.4)	0.02
Glucose (mmol/L)	6.0 (1.9)	5.9 (1.6)	6.0 (1.9)	6.0 (1.8)	0.98
Diabetes (%)	8.2	6.9	5.2	5.4	0.01
Inflammatory/hemostatic markers					
CRP (mg/L)*	1.3 (0.6-2.7)	1.5 (0.7-2.7)	1.9 (0.9-3.8)	2.0 (1.0-4.0)	<0.001
t-PA (ng/mL)	10.0 (4.0)	10.5 (4.1)	11.4 (4.3)	11.3 (4.6)	<0.001
D-dimer (ng/mL)*	73.5 (45.0-105.0)	75.6 (46.0-114.0)	86.9 (51.0-127.0)	78.9 (48.0-119.0)	0.005
vWF (IU/dL)	132.7 (45.2)	135.5 (44.0)	139.2 (44.8)	139.3 (46.3)	0.001
Fibrinogen (g/L)	3.1 (0.7)	3.2 (0.7)	3.3 (0.8)	3.3 (0.7)	<0.001
IL-6 (pg/mL)*	2.0 (1.4-2.8)	2.2 (1.4-2.9)	2.6 (1.7-3.7)	2.6 (1.6-3.8)	<0.001
Homocysteine (µmol/L)*	11.4 (9.6-13.2)	12.1 (10.0-14.1)	12.8 (10.4-14.6)	13.6 (10.8-16.0)	<0.001

Values presented as mean (SD) unless otherwise stated.
BMI, body mass index; CRP, C-reactive protein; HDL, high density lipoprotein; IL-6, interleukin 6; SBP, systolic blood pressure; t-PA, tissue plasminogen activator; vWF, von Willebrand factor.
*Log transformed - geometric mean and interquartile range presented.

Table 8.4 Cardiovascular risk factors and dietary factors by quartiles of a 'prudent' dietary pattern, in men aged 60-79 years in 1998-2000

	'Prudent' dietary pattern (quartiles)				P (trend)
	Q1	Q2	Q3	Q4	
n	807	806	807	806	
Socio-demographic/Behavioural variables					
Age (years)	68.8 (5.4)	68.4 (5.5)	67.9 (5.2)	68.0 (5.5)	0.001
Current smokers (%)	21.4	13.0	9.5	6.4	<0.001
Heavy drinkers (%)	3.0	3.0	1.8	3.5	0.85
Physically inactive (%)	14.4	9.5	7.0	6.8	<0.001
Manual social class (%)	62.3	52.7	46.7	35.4	<0.001
Living in southern England region (%)	36.1	33.8	32.6	34.4	0.40
Body composition					
Obesity (BMI $\geq$ 30 kg/m^2) (%)	15.5	16.5	16.9	15.8	0.82
Waist circumference (cm)	97.1 (10.4)	97.4 (10.2)	96.7 (10.6)	96.8 (10.2)	0.38
Mid-arm muscle circumference (cm)	26.4 (2.5)	26.5 (2.2)	26.6 (2.3)	26.7 (2.2)	0.002
Dietary variables					
Energy intake (kcal)	1944.4 (461.7)	2132.3 (495.9)	2174.9 (514.8)	2335.7 (578.5)	<0.001
Carbohydrates (% kcal)	52.3 (7.0)	52.1 (7.0)	52.9 (6.7)	52.2 (6.9)	0.54
Protein (% kcal)	14.7 (2.2)	15.4 (2.2)	15.8 (2.1)	16.5 (2.3)	<0.001
Fat (% kcal)	32.2 (6.1)	31.0 (6.0)	29.6 (5.8)	28.5 (6.2)	<0.001
Saturated fat (% kcal)	13.7 (3.5)	12.9 (3.5)	11.9 (3.3)	11.3 (3.6)	<0.001
Fibre (g/day)	19.2 (5.6)	24.8 (6.4)	28.5 (7.5)	32.6 (8.5)	<0.001
Vitamin C (mg/day)	57.8 (24.3)	76.9 (30.6)	91.7 (36.2)	108.7 (35.8)	<0.001
Vitamin E (mg/day)	7.3 (4.7)	8.3 (4.7)	8.9 (4.9)	9.5 (4.7)	<0.001
Iron (mg/day)	11.0 (3.5)	13.4 (4.3)	15.0 (4.7)	17.6 (5.7)	<0.001
Daily fruit intake (%)	22.4	34.8	49.8	60.9	<0.001
Daily vegetable intake (%)	17.5	29.9	36.4	49.5	<0.001
Plasma vitamin C (µmol/L)	26.6 (28.8)	28.8 (22.6)	32.7 (29.1)	35.1 (26.6)	<0.001
Plasma vitamin E (µmol/L)	31.7 (11.7)	34.1 (12.4)	34.5 (11.8)	34.7 (12.0)	<0.001
Healthy Diet Indicator	2.9 (1.3)	3.0 (1.3)	3.0 (1.2)	2.7 (1.3)	0.001
Elderly Dietary Index	21.7 (3.2)	23.6 (2.7)	25.0 (2.6)	26.3 (2.4)	<0.001

Table 8.4 *Continued.* Cardiovascular risk factors and dietary factors by quartiles of a 'prudent' dietary pattern, in men aged 60-79 years in 1998-2000

	'Prudent' dietary pattern (quartiles)				P (trend)
	Q1	Q2	Q3	Q4	
Metabolic variables					
SBP (mmHg)	149.7 (23.9)	150.5 (23.9)	149.4 (23.8)	150.9 (23.9)	0.50
Triglycerides (mmol/L)	1.9 (1.1)	1.9 (1.2)	1.8 (1.0)	1.8 (0.9)	0.004
HDL (mmol/L)	1.3 (0.3)	1.3 (0.3)	1.3 (0.3)	1.4 (0.3)	<0.001
Glucose (mmol/L)	5.9 (1.9)	6.0 (1.7)	6.0 (1.7)	6.1 (2.0)	0.20
Diabetes (%)	5.2	5.0	7.7	7.8	0.007
Inflammatory/hemostatic markers					
CRP (mg/L)*	2.0 (0.9-4.0)	1.7 (0.8-3.6)	1.5 (0.7-3.0)	1.4 (0.7-2.6)	<0.001
t-PA (ng/mL)	11.0 (4.3)	11.0 (4.5)	10.7 (4.2)	10.5 (4.1)	0.02
D-dimer (ng/mL)*	83.9 (49.0-127.0)	79.8 (50.0-115.0)	76.9 (45.0-113.0)	74.0 (44.0-112.0)	0.001
vWF (IU/dL)	140.7 (45.8)	140.2 (46.7)	134.7 (43.3)	131.0 (44.0)	<0.001
Fibrinogen (g/L)	3.3 (0.7)	3.3 (0.7)	3.2 (0.7)	3.1 (0.7)	<0.001
IL-6 (pg/mL)*	2.6 (1.7-3.9)	2.4 (1.5-3.4)	2.2 (1.5-3.1)	2.1 (1.4-3.0)	<0.001
Homocysteine (μmol/L)*	13.6 (10.9-16.2)	12.7 (10.2-15.0)	12.0 (9.9-13.9)	11.5 (9.7-13.3)	<0.001

Values presented as mean (SD) unless otherwise stated.
BMI, body mass index; CRP, C-reactive protein; HDL, high density lipoprotein; IL-6, interleukin 6; SBP, systolic blood pressure; t-PA, tissue plasminogen activator; vWF, von Willebrand factor.
*Log transformed - geometric mean and interquartile range presented.

Table 8.5 Cardiovascular risk factors and dietary factors by quartiles of a 'high sugar' dietary pattern, in men aged 60-79 years in 1998-2000

	'High sugar' dietary pattern (quartiles)				P (trend)
	Q1	Q2	Q3	Q4	
n	807	806	807	806	
Socio-demographic/Behavioural variables					
Age (years)	67.1 (5.1)	68.0 (5.2)	68.6 (5.4)	69.3 (5.7)	<0.001
Current smokers (%)	17.6	12.2	10.4	10.1	<0.001
Heavy drinkers (%)	7.3	2.7	1.0	0.4	<0.001
Physically inactive (%)	10.5	10.6	9.7	6.8	0.01
Manual social class (%)	56.4	51.6	47.2	42.0	<0.001
Living in southern England region (%)	29.7	33.6	34.5	39.0	<0.001
Body composition					
Obesity (BMI $\geq$ 30 kg/m^2) (%)	21.2	17.2	15.4	10.8	<0.001
Waist circumference (cm)	98.4 (10.8)	97.9 (10.0)	96.4 (9.9)	95.3 (10.3)	<0.001
Mid-arm muscle circumference (cm)	26.7 (2.4)	26.5 (2.3)	26.6 (2.3)	26.4 (2.3)	0.06
Dietary variables					
Energy intake (kcal)	1855.3 (461.8)	1995.1 (434.2)	2200.2 (456.4)	2535.1 (514.3)	<0.001
Carbohydrates (% kcal)	50.3 (8.2)	52.3 (6.9)	53.0 (6.0)	53.7 (5.8)	<0.001
Protein (% kcal)	16.5 (2.6)	15.9 (2.2)	15.5 (2.0)	14.5 (1.8)	<0.001
Fat (% kcal)	29.2 (7.4)	30.1 (6.4)	30.6 (5.4)	31.5 (5.1)	<0.001
Saturated fat (% kcal)	11.7 (4.2)	12.4 (3.8)	12.6 (3.1)	13.1 (3.0)	<0.001
Fibre (g/day)	22.8 (8.6)	25.1 (8.2)	27.2 (7.9)	30.0 (8.2)	<0.001
Vitamin C (mg/day)	73.9 (39.3)	79.4 (36.7)	85.5 (33.0)	96.2 (35.7)	<0.001
Vitamin E (mg/day)	7.5 (4.8)	7.9 (4.1)	8.6 (4.8)	9.9 (5.2)	<0.001
Iron (mg/day)	11.9 (4.4)	13.5 (4.8)	14.7 (4.8)	16.8 (5.4)	<0.001
Daily fruit intake (%)	35.6	42.4	43.5	46.7	<0.001
Daily vegetable intake (%)	28.6	29.7	33.5	41.5	<0.001
Plasma vitamin C (µmol/L)	28.4 (22.3)	30.9 (23.7)	32.2 (30.0)	31.8 (31.0)	0.008
Plasma vitamin E (µmol/L)	33.6 (11.8)	34.2 (12.5)	34.4 (12.5)	32.8 (11.1)	0.26
Healthy Diet Indicator	2.9 (1.4)	2.9 (1.3)	2.9 (1.3)	3.0 (1.2)	0.16
Elderly Dietary Index	23.7 (3.8)	24.2 (3.3)	24.4 (3.0)	24.5 (2.8)	<0.001

Table 8.5 *Continued.* Cardiovascular risk factors and dietary factors by quartiles of a 'high sugar' dietary pattern, in men aged 60-79 years in 1998-2000

	'High sugar' dietary pattern (quartiles)				P (trend)
	Q1	Q2	Q3	Q4	
Metabolic variables					
SBP (mmHg)	151.3 (22.8)	150.1 (23.9)	149.6 (24.3)	149.6 (24.6)	0.13
Triglycerides (mmol/L)	1.9 (1.0)	1.9 (1.1)	1.9 (1.2)	1.7 (0.9)	0.01
HDL (mmol/L)	1.4 (0.4)	1.3 (0.3)	1.3 (0.3)	1.3 (0.3)	0.004
Glucose (mmol/L)	6.1 (1.9)	6.0 (1.8)	5.9 (1.6)	5.9 (1.9)	0.04
Diabetes (%)	9.5	6.7	5.4	4.0	<0.001
Inflammatory/hemostatic markers					
CRP (mg/L)*	1.8 (0.9-3.7)	1.7 (0.9-3.4)	1.6 (0.7-3.2)	1.5 (0.7-2.9)	<0.001
t-PA (ng/mL)	11.3 (4.6)	10.9 (4.1)	10.6 (4.0)	10.4 (4.4)	<0.001
D-dimer (ng/mL)*	75.1 (46.0-111.0)	75.7 (46.0-109.0)	81.5 (49.0-121.0)	82.3 (49.0-125.5)	0.005
vWF (IU/dL)	135.9 (47.2)	137.9 (42.7)	136.0 (44.7)	136.8 (45.8)	0.91
Fibrinogen (g/L)	3.2 (0.7)	3.3 (0.7)	3.2 (0.7)	3.2 (0.7)	0.47
IL-6 (pg/mL)*	2.4 (1.6-3.5)	2.3 (1.5-3.3)	2.4 (1.5-3.3)	2.2 (1.4-3.1)	0.02
Homocysteine (µmol/L)*	12.7 (10.3-14.6)	12.2 (9.9-14.2)	12.5 (10.2-14.7)	12.4 (10.1-14.4)	0.41

Values presented as mean (SD) unless otherwise stated.
BMI, body mass index; CRP, C-reactive protein; HDL, high density lipoprotein; IL-6, interleukin 6; SBP, systolic blood pressure; t-PA, tissue plasminogen activator; vWF, von Willebrand factor.
*Log transformed - geometric mean and interquartile range presented.

Table 8.6 Hazard ratios (95% CI) for CHD events, CVD events, CVD mortality and all-cause mortality by quartiles of a 'high fat/low fibre' dietary pattern in men aged 60-79 years in 1998-2000

	'High fat/low fibre' diet quartiles	Cases (n)	Rate (per 1,000 person years)	Model 1	Model 2	Model 3	Model 4
All-cause mortality	Q1	187	22.65	1.00	1.00	1.00	1.00
	Q2	199	24.62	1.06 (0.87-1.30)	1.01 (0.82-1.25)	1.07 (0.85-1.33)	1.10 (0.88-1.38)
	Q3	239	30.59	1.32 (1.09-1.60)*	1.16 (0.94-1.43)	1.12 (0.90-1.40)	1.11 (0.88-1.39)
	Q4	274	35.69	1.63 (1.36-1.97)*	1.40 (1.11-1.76)*	1.43 (1.12-1.82)*	1.44 (1.13-1.84)*
	p-trend			<0.001	0.002	0.005	0.007
CVD mortality	Q1	62	7.51	1.00	1.00	1.00	1.00
	Q2	80	9.90	1.27 (0.91-1.78)	1.28 (0.89-1.83)	1.38 (0.94-2.01)	1.45 (0.99-2.12)
	Q3	81	10.37	1.32 (0.95-1.84)	1.11 (0.76-1.61)	1.10 (0.74-1.63)	1.10 (0.74-1.64)
	Q4	93	12.11	1.67 (1.21-2.30)*	1.40 (0.94-2.10)	1.36 (0.89-2.09)	1.39 (0.90-2.14)
	p-trend			0.002	0.19	0.34	0.35
CVD events	Q1	133	16.95	1.00	1.00	1.00	1.00
	Q2	139	17.84	1.02 (0.81-1.30)	1.00 (0.78-1.30)	1.00 (0.76-1.30)	1.02 (0.78-1.33)
	Q3	146	19.51	1.12 (0.88-1.42)	1.01 (0.77-1.31)	0.95 (0.72-1.25)	0.95 (0.72-1.25)
	Q4	151	20.55	1.23 (0.97-1.55)	1.04 (0.78-1.40)	0.95 (0.70-1.29)	0.95 (0.69-1.30)
	p-trend			0.06	0.80	0.69	0.64
CHD events	Q1	70	8.66	1.00	1.00	1.00	1.00
	Q2	72	9.05	1.02 (0.73-1.41)	1.00 (0.70-1.42)	1.00 (0.69-1.44)	1.02 (0.71-1.48)
	Q3	77	10.04	1.13 (0.82-1.56)	1.01 (0.70-1.44)	0.94 (0.64-1.36)	0.92 (0.63-1.35)
	Q4	82	10.97	1.28 (0.93-1.76)	1.09 (0.73-1.62)	0.97 (0.63-1.47)	0.95 (0.62-1.46)
	p-trend			0.10	0.69	0.80	0.72

CHD, coronary heart disease; CVD, cardiovascular disease.
Model 1: Age adjusted. Model 2: Adjusted for model 1 + energy intake, smoking, alcohol, physical activity, social class and BMI. Model 3: Adjusted for model 2 + HDL, SBP and diabetes. Model 4. Adjusted for model 3 + CRP and vWF.
*P <0.05

Table 8.7 Hazard ratios (95% CI) for CHD events, CVD events, CVD mortality and all-cause mortality by quartiles of a 'prudent' dietary pattern in men aged 60-79 years in 1998-2000

	'Prudent' diet quartiles	Cases (n)	Rate (per 1,000 person years)	Model 1	Model 2	Model 3	Model 4
All-cause mortality	Q1	280	36.66	1.00	1.00	1.00	1.00
	Q2	214	26.64	0.72 (0.60-0.86)*	0.76 (0.63-0.93)*	0.76 (0.62-0.93)*	0.77 (0.63-0.95)*
	Q3	202	25.15	0.76 (0.63-0.91)*	0.88 (0.72-1.07)	0.89 (0.72-1.10)	0.93 (0.75-1.14)
	Q4	203	24.97	0.72 (0.60-0.86)*	0.81 (0.66-1.00)*	0.78 (0.62-0.98)*	0.83 (0.66-1.04)
	p-trend			0.001	0.13	0.11	0.28
CVD mortality	Q1	95	12.44	1.00	1.00	1.00	1.00
	Q2	66	8.22	0.66 (0.48-0.90)*	0.68 (0.48-0.95)*	0.66 (0.46-0.94)*	0.68 (0.47-0.98)*
	Q3	78	9.71	0.91 (0.67-1.23)	0.99 (0.71-1.37)	0.98 (0.69-1.39)	1.03 (0.72-1.47)
	Q4	77	9.47	0.81 (0.60-1.10)	0.92 (0.64-1.30)	0.87 (0.60-1.27)	0.94 (0.64-1.37)
	p-trend			0.47	0.89	0.96	0.74
CVD events	Q1	158	21.64	1.00	1.00	1.00	1.00
	Q2	140	18.39	0.85 (0.68-1.07)	0.92 (0.72-1.17)	0.90 (0.70-1.16)	0.93 (0.72-1.21)
	Q3	133	17.21	0.87 (0.69-1.10)	0.92 (0.71-1.18)	0.91 (0.70-1.19)	0.93 (0.71-1.21)
	Q4	138	17.63	0.85 (0.68-1.07)	0.93 (0.72-1.22)	0.90 (0.68-1.19)	0.94 (0.71-1.25)
	p-trend			0.22	0.63	0.50	0.68
CHD events	Q1	87	11.65	1.00	1.00	1.00	1.00
	Q2	79	10.12	0.87 (0.64-1.18)	0.97 (0.70-1.34)	0.95 (0.68-1.34)	0.99 (0.70-1.40)
	Q3	70	8.87	0.83 (0.61-1.14)	0.90 (0.64-1.27)	0.89 (0.61-1.28)	0.92 (0.64-1.34)
	Q4	65	8.10	0.73 (0.53-1.01)	0.82 (0.56-1.18)	0.81 (0.55-1.20)	0.86 (0.58-1.27)
	p-trend			0.06	0.26	0.27	0.40

CHD, coronary heart disease; CVD, cardiovascular disease.
Model 1: Age adjusted. Model 2: Adjusted for model 1 + energy intake, smoking, alcohol, physical activity, social class and BMI. Model 3: Adjusted for model 2 + HDL, SBP and diabetes. Model 4. Adjusted for model 3 + CRP and vWF.
*P <0.05

Table 8.8 Hazard ratios (95% CI) for CHD events, CVD events, CVD mortality and all-cause mortality by quartiles of a 'high sugar' dietary pattern in men aged 60-79 years in 1998-2000

	'High sugar' diet quartiles	Cases (n)	Rate (per 1,000 person years)	Model 1	Model 2	Model 3	Model 4
All-cause mortality	Q1	219	27.32	1.00	1.00	1.00	1.00
	Q2	222	28.00	0.94 (0.78-1.14)	1.00 (0.82-1.23)	1.04 (0.84-1.29)	1.06 (0.85-1.31)
	Q3	214	26.56	0.81 (0.67-0.98)*	0.85 (0.68-1.05)	0.89 (0.71-1.12)	0.91 (0.72-1.15)
	Q4	244	31.18	0.88 (0.73-1.05)	0.89 (0.70-1.13)	0.96 (0.75-1.24)	1.00 (0.77-1.29)
	p-trend			0.08	0.18	0.53	0.71
CVD mortality	Q1	64	7.98	1.00	1.00	1.00	1.00
	Q2	73	9.21	1.04 (0.74-1.45)	1.07 (0.75-1.53)	1.10 (0.75-1.63)	1.13 (0.76-1.66)
	Q3	75	9.31	0.91 (0.66-1.29)	0.91 (0.62-1.33)	0.95 (0.63-1.43)	0.97 (0.64-1.47)
	Q4	104	13.29	1.18 (0.86-1.61)	1.07 (0.71-1.61)	1.27 (0.82-1.96)	1.32 (0.84-2.05)
	p-trend			0.39	0.94	0.40	0.33
CVD events	Q1	112	14.50	1.00	1.00	1.00	1.00
	Q2	139	18.34	1.17 (0.91-1.50)	1.26 (0.97-1.65)	1.22 (0.92-1.62)	1.27 (0.95-1.68)
	Q3	139	18.00	1.07 (0.83-1.37)	1.10 (0.83-1.46)	1.08 (0.80-1.46)	1.10 (0.81-1.50)
	Q4	179	24.04	1.32 (1.04-1.67)*	1.33 (0.98-1.81)	1.40 (1.01-1.93)*	1.47 (1.06-2.04)*
	p-trend			0.05	0.16	0.09	0.06
CHD events	Q1	59	7.48	1.00	1.00	1.00	1.00
	Q2	67	8.61	1.08 (0.76-1.53)	1.11 (0.76-1.61)	1.13 (0.76-1.68)	1.15 (0.77-1.72)
	Q3	79	10.00	1.18 (0.84-1.65)	1.24 (0.85-1.82)	1.21 (0.80-1.83)	1.20 (0.79-1.83)
	Q4	96	12.60	1.40 (1.01-1.94)*	1.42 (0.93-2.16)	1.52 (0.97-2.38)	1.57 (1.00-2.46)
	p-trend			0.04	0.09	0.07	0.06

CHD, coronary heart disease; CVD, cardiovascular disease.
Model 1: Age adjusted. Model 2: Adjusted for model 1 + energy intake, smoking, alcohol, physical activity, social class and BMI. Model 3: Adjusted for model 2 + HDL, SBP and diabetes. Model 4. Adjusted for model 3 + CRP and vWF.
*P <0.05

CHAPTER 9 Implications and conclusions

9.1. Summary

This chapter reviews the implications of the findings of this thesis in relation to public health and future epidemiological studies. Findings from analyses conducted for this thesis demonstrate that body composition (both obesity and low muscle mass) and poor diet quality are important risk factors for cardiovascular disease (CVD) and mortality in men, which persist in older age. The particular findings of potential public health importance are: i) that it is important to consider both adiposity and muscle mass as determinants of CVD and all-cause mortality in older adults; ii) that efforts are needed to maintain muscle mass and prevent sarcopenia in older age; iii) that further efforts are needed to prevent and reduce obesity in older age; and iv) that specific efforts are needed to improve diet quality in older age. These results have implications for future epidemiological studies, which include: 1) the need to carry out larger studies when examining the effects of sarcopenia and obesity on the risk of CVD and mortality, and to replicate findings in women and different ethnic groups; 2) to further explore the causal mechanistic pathways leading to sarcopenia; 3) the need for a universal consensus definition of sarcopenia and sarcopenic obesity to be adopted in order to make valid comparisons across studies; 4) the need to examine whether the effects of dietary patterns on the risk of CVD and mortality observed in this thesis are also beneficial in other older populations, including women and different ethnic groups; and 5) the need for further large studies on dietary patterns and the risk of CVD and mortality in older populations with prevalent CVD.

9.2. Introduction

9.2.1. Key findings

The research in this thesis has addressed several important questions on the cross-sectional associations between measures of body composition (adiposity and muscle mass) and dietary patterns in relation to cardiovascular risk factors, and the prospective associations between measures of body composition and dietary patterns in relation to risk of CVD and

mortality, using a representative population based cohort of older men from the British Regional Heart Study (BRHS), aged 60-79 years, over 11 years of follow-up.

Findings from Chapter 4 suggest that several established and emerging cardiovascular risk factors are related to low muscle mass based on consistent associations with both mid-arm muscle circumference (MAMC) and fat-free mass index (FFMI), and that sarcopenic obesity is associated with the highest levels of inflammatory and haemostatic markers. Chapter 5 showed that it is important to consider both muscle mass and adiposity as determinants of CVD mortality and all-cause mortality in older adults. Men who were sarcopenic, obese or sarcopenic obese had higher risks of all-cause mortality and CVD mortality compared to those who were non-sarcopenic, non-obese, with sarcopenic obese individuals having the highest risk of all-cause mortality. Using a combination of anthropometric measures of central adiposity (waist circumference [WC] or waist-to-hip ratio [WHR]) and muscle mass (MAMC) to define sarcopenic obesity appeared to be the strongest predictors of cardiovascular mortality and all-cause mortality in older men.

Findings from Chapter 6 and Chapter 8 showed that diet quality is an important determinant of the risk of CVD and mortality in older adults. Chapter 6 specifically suggested that higher adherence to either the Healthy Diet Indicator (HDI) or the Elderly Dietary Index (EDI) was associated with the least adverse cardiovascular risk profile. Men with higher adherence to the EDI had a 25% lower risk of all-cause mortality, a 37% lower risk of CVD mortality and a 34% lower risk of coronary heart disease (CHD) events, which was independent of socio-demographic, behavioural and cardiovascular risk factors. However, the HDI score was not significantly associated with any of the outcome measures. Encouraging older adults to adhere to a dietary pattern close to that defined in the EDI criteria may therefore reduce the risk of all-cause mortality, CVD mortality and CHD events and hence have public health benefits. Chapter 7 showed that social inequalities in diet quality, as measured by the EDI, persist in older age and that diet quality is influenced by both childhood and adulthood socioeconomic factors, in addition to marital status and habitation. Findings from Chapter 8 suggested that encouraging older adults to adopt a diet which avoids ‘high fat /low fibre’ components (including red meat, meat products, fried

potato and white bread) and 'high sugar' components (including biscuits, puddings, chocolate, sweets and sweet spreads) may be beneficial to reduce the risk of cardiovascular events and all-cause mortality in older adults.

9.2.2. **Novelty of the present findings**

Although there is already some evidence that sarcopenia is associated with established and emerging cardiovascular risk factors in older age[137;153-159], whether sarcopenic obese individuals have the worst cardiovascular risk profile is uncertain[154;155;160-173], as discussed in Chapter 2 (section 2.4.7). The results presented in Chapter 4 have provided additional evidence that low muscle mass (as measured by both MAMC and FFMI) is associated with physical inactivity, higher mean levels of insulin resistance and higher levels of inflammatory and hemostatic markers including C-reactive protein (CRP), fibrinogen and von Willebrand Factor (vWF). Findings also revealed that lower muscle mass was less likely in individuals with a high percentage of energy intake from carbohydrates, and to my knowledge this is the first study to show this. Results in Chapter 4 also showed that sarcopenic obese individuals had significantly higher levels of inflammatory and haemostatic markers (CRP, vWF and fibrinogen) compared to the sarcopenic only, obese only or non-sarcopenic, non-obese groups.

There is a paucity of prospective evidence on the associations between sarcopenic obesity and the risk of CVD[177] (Chapter 2, section 2.4.8) and mortality[190-194] (Chapter 2, section 2.4.9). To my knowledge, only one prospective study has examined the association between sarcopenic obesity groups and CVD[177]. The results reported in Chapter 5 add to the limited literature on the prospective associations between sarcopenia and sarcopenic obesity in relation to the risk of CVD and mortality, showing that sarcopenic obesity in older men (defined by WC and MAMC) is associated with an increased risk of all-cause mortality, an increased risk of CVD mortality, although non-significant, but is not associated with CVD events or CHD events.

Chapter 2 also highlighted the paucity of studies relating dietary patterns to the risk of CVD and mortality in older adults, especially in British populations. The examination of the associations between *a priori* dietary patterns and the risk of CVD and mortality in older adults has mainly focused on Mediterranean diet scores[32], but whether this type of diet is applicable to an older UK population is questionable[223] and there are limited studies in elderly populations on other *a priori* defined dietary patterns[232] (Chapter 2, section 2.5.3). Results from Chapters 6 and 7 add to the limited literature on the relationships between *a priori* dietary patterns, cardiovascular risk factors and the risk of CVD and mortality in older British adults. Specifically, this thesis describes the first application of the EDI, a modified Mediterranean diet score[233], to a non-Mediterranean population. The results emphasize that the EDI is applicable to an older British population and higher adherence is associated with the least adverse cardiovascular risk profile and a lower risk of all-cause mortality, CVD mortality and CHD events. Chapter 7 also highlights the influence of socioeconomic circumstances on diet quality, as measured by the EDI, in older age. To my knowledge, the findings in Chapter 7 are the first to confirm that the influences of childhood social class on diet quality can persist in older populations.

There are also a limited number of studies that have used *a posteriori* methods to define dietary patterns in relation to CVD and mortality risk in older adults[255;256], with a paucity of studies in British populations (Chapter 2, section 2.5.4). Only one study was identified in an older British population which has examined the association between dietary patterns, defined by principal component analysis, and risk of all-cause and CVD mortality[257]. Findings presented in Chapter 8 add to the limited literature on the associations between *a posteriori* dietary patterns and the risk of CVD and mortality in older adults, and to my knowledge no other study to date has analysed the association between dietary patterns defined by principal component analysis and the risk of CHD in an older British population. Findings therefore need to be replicated in other older British populations.

The coherence of these findings in relation to existing research and the strengths and limitations of these findings were discussed in each of the results chapters. In the

subsequent sections of this chapter, the potential implications of the findings in terms of public health and future epidemiological research are discussed.

9.3. Public health implications of findings

9.3.1. Considering both adiposity and muscle mass as determinants of CVD and all-cause mortality in older age

This thesis has shown that both obesity and sarcopenia are associated with CVD and all-cause mortality in older age. The strength and temporality of these associations provide strong evidence of causality as highlighted in the Bradford Hill criteria[401]. The public health implications of these findings are that it is important that both these elements of body composition are measured in older age to assess the risk of CVD and mortality, and that prevention efforts should focus on both maintaining muscle mass and preventing obesity.

It has been suggested previously that future research is needed to identify surrogate anthropometric indices of sarcopenic obesity[18] and results from this thesis suggest that such indices may include combined measures of central adiposity (WC or WHR) and muscle mass (MAMC). Although anthropometric measurements such as WC, WHR and MAMC require training to locate the correct anatomical positions for measurement, they are still sufficiently valid as well as simpler, quicker and cheaper than more invasive and expensive as well as more accurate measurements of adiposity and muscle mass such as computerised tomography scanning, magnetic resonance imaging, or dual x-ray absorptiometry[111]. Such anthropometric measures may therefore be much more readily available in both clinical and non-clinical settings and represent a practical alternative approach to defining sarcopenic obesity, in order to predict the risk of cardiovascular mortality and all-cause mortality in older adults. A further discussion on the implications of defining sarcopenia and sarcopenic obesity for future research will be given in section 9.4.1.

9.3.2. **Potential strategies to maintain muscle mass and prevent sarcopenia in older age**

Sarcopenia is not well recognised as a major public health problem and this is supported by the fact that to date no International Classification of Disease (ICD) codes or standard treatment guidelines for sarcopenia exist[145;402]. Public health efforts are needed in the UK to maintain muscle mass and prevent sarcopenia to reduce the risk of CVD and mortality in older age groups. Sarcopenia has a multifactorial aetiology[134;136;403] which may therefore present several opportunities for intervention. Findings from this thesis suggested that physical inactivity, a low percent of energy intake from carbohydrates and metabolic and inflammatory pathways were implicated in sarcopenia (Chapter 4). However, whether targeting these risk factors would provide opportunities for intervention is unclear from this thesis as associations observed were cross-sectional and hence causality cannot be established. Therefore, further understanding of the aetiology of sarcopenia and sarcopenic obesity in older age is needed (see section 9.4.1 for a further discussion).

Evidence from existing literature suggests that increased physical activity and improved nutrition appear to be the fundamental components of interventions to prevent sarcopenia[144;145;404;405] and hence to reduce the risk of CVD and mortality in older age. Physical activity, both aerobic and resistance, is a modifiable lifestyle behaviour, which can partially reverse age-associated skeletal dysfunction[306]. Evidence has shown that resistance training in particular is effective in increasing muscle strength, lean body mass and physical function in older adults[406;407]. The World Health Organization's (WHO) globally recommended physical activity levels for adults aged 65 years and above are at least 150 minutes of moderate-intensity aerobic physical activity per week or at least 75 minutes of vigorous-intensity aerobic physical activity per week, as well as muscle-strengthening activities, involving major muscle groups, on 2 or more days a week[408]. The National Service Framework for Older People included physical activity as a health promotion activity that is of specific benefit to older people, but a large proportion of people aged over 50 are sedentary (take less than half an hour of moderate intensity physical activity a week) and few people take the WHO recommended levels of activity for improving health[1;409].

This highlights the need for interventions and health promotion activities to increase physical activity, particularly resistance based activity, in older adults in the general population in order to reduce the risk of sarcopenia.

It has also been suggested that optimizing diet and nutrition through the life course may be key to preventing sarcopenia[132;145;410]. Although findings from this thesis did not show an association between protein intake and low muscle mass (Chapter 4), possibly due to the limitations of the cross-sectional methodology used, other literature has shown that dietary protein is a key nutrient in older age which helps to maintain lean mass since amino acids are required for muscle protein synthesis[133;410]. Existing evidence from trials has also shown that supplementation of the diet with essential amino acids improves lean body mass, strength and physical function[411] and that supplementing regular meals with leucine, in particular, may also improve muscle protein synthesis in older adults[412]. This has important public health implications for increasing protein intake in the elderly to reduce the risk of sarcopenia and hence to lower the risk of CVD and mortality. However, further studies are needed to define optimal intakes of protein in older ages[410]. A novel finding from this thesis showed that, cross-sectionally, lower muscle mass was less likely in individuals with a high percentage of energy intake from carbohydrates. However, the consensus in the literature on optimal carbohydrate intake is still very conflicting[413], with some studies showing that a low-carbohydrate diet decreases body weight and improves cardiovascular risk factors[414] and others showing that a low-carbohydrate diet is associated with a higher risk of all-cause mortality[415]. Further prospective studies are therefore needed to elucidate any causal associations between dietary carbohydrate intake and the risk of sarcopenia. Existing evidence from other studies also highlights the importance of older adults consuming a diet of adequate quality to ensure sufficient intakes of vitamin D, antioxidants and omega-3 polyunsaturated fatty acids which may help to preserve muscle mass and function[132;133;410]. Efforts to improve overall dietary quality in older age therefore have important public health implications for reducing the risk of sarcopenia, and policy efforts to improve diet quality in older age will be discussed below in section 9.3.4.

Several pharmacological agents have also been suggested in the treatment of sarcopenia[402] including: testosterone therapy, which may increase muscle strength and size but may also be associated with some adverse effects[416]; growth hormone, which stimulates the development of skeletal muscle and the breakdown of fat[417]; selective androgen receptor modulators; and myostatin inhibitors, a protein which inhibits muscle formation[130]. However, none of these interventions have proven to be as efficacious as exercise in combination with nutrition[402], which highlights the public health importance of interventions in physical activity and improved diet quality to reduce the risk of sarcopenia.

9.3.3. **Efforts to prevent and reduce obesity in older age**

Overweight and obesity are already well recognised as a major public health problem as they are well established as being strongly associated with cardiovascular morbidity and mortality in adult populations, and obesity prevalence in middle-aged and older adults is continuing to rise over time[10;11]. Therefore, public health prevention efforts to reduce the risk of obesity in the UK are already in place in both middle-aged and older adults[1;418]. The Department of Health announced 'A call to action on obesity in England' in 2011, with a national ambition of a downward trend in the level of excess weight averaged across all adults by 2020[11]. Existing health promotion efforts include increasing physical activity and improving diet and nutrition, and these are recognised as having specific benefits to older people[1;418]. Detailed efforts to improve diet quality, and hence reduce excessive calorie consumption and obesity will be discussed in section 9.3.4. Continuing these population-wide efforts to reduce levels of obesity in older age is therefore needed, especially since visceral obesity is also associated with sarcopenia and sarcopenic obesity[18-21]. Ongoing public health efforts to reduce obesity in combination with new efforts to reduce the risk of sarcopenia, as discussed above in section 9.3.2, would therefore reduce the risk of sarcopenic obesity in the population.

9.3.4. **Efforts to improve diet quality in older age**

This thesis has shown that poor diet quality is associated with CVD and all-cause mortality in older age. The strength and temporality of the associations between dietary patterns and

outcomes observed here provide strong evidence for causality as highlighted in the Bradford Hill criteria[401]. The public health implications of the findings from this thesis are therefore that efforts should be made to improve diet quality in older age in the UK in order to reduce the risk of CVD and mortality. Although socioeconomic position is not a modifiable lifestyle risk factor, amelioration of diet quality in population groups with lower diet quality would help to reduce social inequalities in diet.

Much focus has recently been on public health policy efforts to improve the overall diet quality of the population in the UK[419] and it has been suggested that the most powerful interventions are policies which effectively address affordability, availability and acceptability of diet[420]. One such policy is the NHS 'Change4Life' programme which is aimed at increasing the acceptability of a higher diet quality by giving people advice on a healthy diet[421]. This is England's first ever social marketing campaign to reduce obesity by encouraging individuals to adhere to six healthy behaviours including cutting back on fat and swapping sugars. The Department of Health's Public Health Responsibility Deal, which was launched in 2011, has also aimed to improve diet quality within England by encouraging businesses and organisations to sign up to voluntary pledges in order to help people eat more healthily[422]. These pledges include reformulation of food products and recipes to reduce total calories and harmful ingredients such as saturated fat and salt; encouraging people to eat more fruit and vegetable to help reach the 5-a-day target; and out of home food labelling and putting calorie information on menus. Also, new consistent front of pack nutritional labelling on food and drink was launched in the UK in 2013. The system combines red, amber and green colour-coding and nutritional information on how much total fat, saturated fat, salt, sugar and calories food products contain in order to help people make healthy choices about their diet[423].

The National Service Framework for Older People, included improved diet and nutrition as a health promotion activity which is of specific benefit to older people[1], but the above public health policy efforts in the UK are aimed at the general population and do not target older adults specifically. One way of improving the diet of older adults and of reducing

social inequalities in diet in older age could be to introduce food subsidies for the most socioeconomically disadvantaged group of older adults, since subsidising healthier foods is shown to be effective in modifying dietary behaviour[424]. One such food subsidy already in existence in the UK is 'Healthy Start'[425]. Women who are pregnant or families with a child under four years old and who are on certain benefits, and all pregnant women under 18 years, qualify to receive weekly food vouchers to spend on milk, plain fresh and frozen fruit and vegetables, and infant formula milk. A food subsidy for older adults specifically is also in operation in the United States of America - the Senior Farmers' Market Nutrition Program provides low-income older adults with vouchers that can be exchanged for eligible foods (fruits, vegetables and fresh-cut herbs) at farmers' markets, roadside stands, and community-supported agriculture programs[426]. However, no such food subsidy exists for disadvantaged groups of older adults in the UK and future modelling and simulation studies may therefore provide evidence for policy makers on the potential benefits of such a food subsidy[427].

There has also been much recent debate surrounding the topic of food taxes on unhealthy foods, including a fat tax and a sugar-sweetened beverage tax, as public health measures to limit the consumption of unhealthy foods[428-431]. Such taxes could in theory have the potential to improve diet quality in older age and hence reduce the risk of CVD and mortality, and also to reduce social inequalities in diet quality in older age. Food taxes are currently already in place in some European countries, but the debate as to whether to introduce such taxes in the UK continues[428-432].

9.4. Implications for future epidemiological research

This thesis has addressed several important questions on the role of body composition (adiposity and low muscle mass) and dietary patterns on the risk of CVD and mortality in older men aged 60 to 79 years from the BRHS. However this is a broad topic and therefore some unanswered questions remain, and in addition, some new questions have arisen as a result of the findings. In addition the findings from this thesis have some limitations, which were discussed in each of the preceding results chapters. In this section the implications for future epidemiological studies are summarised.

9.4.1. **Investigating sarcopenia and sarcopenic obesity with the risk of CVD and mortality in older age**

This thesis has examined the cross-sectional associations between measures of adiposity and muscle mass with cardiovascular risk factors (Chapter 4), and has also examined the prospective associations between combined measures of adiposity and muscle mass in relation to cardiovascular outcomes and mortality (Chapter 5). Although this study has the strengths of using data from a moderately large population-based, geographically and socioeconomically representative, cohort of older British men with very high follow-up rates[35;264] and comparing a wide range of body composition measures (as discussed in Chapters 4 and 5), there are still some limitations and considerations which call for a need to extend these investigations to future epidemiological studies in other populations.

At the initiation of the BRHS in the mid-1970s, the risk of CVD was lower in women in middle age, which would have required a very large number of female subjects in order to ensure adequate number of cardiovascular endpoints, which would have caused considerable logistic and financial problems. It was therefore decided that the study would include only men[34]. Also, towns were selected which did not have appreciable population movement and hence had a small proportion of non-white ethnic minority groups. Therefore, the data presented in this thesis are based on older men predominantly of white European ethnic origin[264]. There is considerable variation in body composition and the prevalence of sarcopenia with age, between genders and across different ethnic groups[151;433]. Future epidemiological studies are therefore important to replicate the findings from this thesis in other large populations including women, different ethnic groups and in younger people. Such studies would provide evidence of whether the associations observed between sarcopenic obesity and CVD and all-cause mortality were consistent in other populations and would also add to the sparse existing literature on the prospective associations between sarcopenic obesity and CVD and mortality.

The aetiology of sarcopenia is multifactorial and is not fully understood[134;136;403]. Chapter 4 provided some evidence of associations between measures of sarcopenia and cardiovascular risk factors; findings suggested that physical inactivity, a high percent of energy intake from carbohydrates and metabolic and inflammatory pathways were implicated in sarcopenia. However, a major limitation of these findings is that analysis was cross-sectional and hence causality could not be established. Therefore, there is a need for further exploration and understanding of the aetiological factors involved in sarcopenia and sarcopenic obesity in older age. In particular, studies analysing the prospective associations between changes in muscle mass and cardiovascular risk factors would be useful and would help to identify the reasons for the excess risk of CVD in sarcopenic older men and the excess risk of all-cause mortality in sarcopenic obese men, as observed in Chapter 5.

A key challenge in future epidemiological studies on sarcopenia in older age is defining sarcopenia and sarcopenic obesity. It has been suggested that current research on both the plausible mechanisms leading to sarcopenia and the functional consequences of sarcopenia are hindered by a lack of consensus definition and standardised assessment methodology[20;434]. A consensus definition of sarcopenia is essential in order to make valid comparisons of findings across sarcopenia studies, but to date there is no universally adopted definition of sarcopenia. However, a number of consensus definitions have been proposed, as discussed in Chapter 2 (Section 2.4.6). In 2009, the European Working Group on Sarcopenia in Older People (EWGSOP) proposed a definition of sarcopenia which includes the presence of both low muscle mass and low muscle function (either low strength e.g. handgrip strength, and/or low physical performance e.g. gait speed)[17]. In 2011, a similar definition was proposed by the International Working Group on Sarcopenia (IWGS), who suggested that diagnosis is based on a low whole-body or appendicular fat-free mass in combination with poor physical functioning[134]. For the purpose of this thesis data were only available on muscle mass and not muscle strength or physical performance so therefore the EWGSOP or IWGS definitions could not be applied. Since the onset of this thesis, another clinical definition of sarcopenia has also been suggested in 2014 by the Foundation for the National Institutes of Health (FNIH) Sarcopenia Project. This definition

has recommended specific cut points for muscle weakness (grip strength <26kg for men and <16kg for women) and for low lean mass (appendicular lean mass adjusted for body mass index <0.789 for men and <0.512 for women)[435]. Future epidemiological studies investigating the association between sarcopenic and risk of CVD and mortality should therefore use the proposed standardised consensus sarcopenia definitions (EGWSOP, IWGS and FNIH). Using all three proposed definitions within a study would allow for a comparison of which definition is most effective in predicting the risk of CVD and mortality over time. Future epidemiological studies should also examine both measures of muscle mass and muscle function to address the question of whether muscle mass or strength is most important in predicting the risk of CVD and mortality.

Sarcopenia is the term used to refer to the age-associated loss of skeletal muscle mass and function[140]. However, at the initiation of this thesis data were unavailable on the decline in muscle mass over time so the assessment of sarcopenia was based on low muscle mass, measured at one time point only, as is the case for several previous studies[17-19]. Future epidemiological studies should therefore seek to examine the change in muscle mass over time in relation to the risk of CVD and mortality, providing a more accurate measure of sarcopenia than just using data from one time point.

9.4.2. **Investigating diet quality and the risk of CVD and mortality in older age**

This thesis has examined the prospective associations between *a priori* dietary scores in relation to the risk of cardiovascular outcomes and mortality (Chapter 6), the cross-sectional associations of social circumstances and *a priori* dietary scores (Chapter 7) and the prospective associations between *a posteriori* dietary patterns, derived by principal component analysis, in relation to the risk of cardiovascular outcomes and mortality (Chapter 8). This study has the strengths of using data from a moderately large population-based, geographically and socioeconomically representative, cohort of older British men with very high follow-up rates[35;264]. The dietary intake of BRHS participants used in this thesis, collected via a food frequency questionnaire, is broadly comparable with the intake

in the National Diet and Nutrition Survey[339] so results are therefore generalisable to older men in the UK. However, for reasons given in section 9.4.1, the BRHS does not include women[34]. Since gender differences exist in dietary intake[383;384] it is therefore important to examine whether the dietary patterns explored in this thesis are also beneficial in large cohorts of older women in the UK. Similarly, the BRHS is comprised of men predominantly of white European ethnic origin, so results may not be applicable to non-white ethnic groups and further studies are needed to examine whether the dietary patterns observed here are also beneficial in other ethnic groups.

Results from this thesis have been the first to show that adherence to the EDI is associated with a lower risk of all-cause mortality, CVD mortality and CHD events and that this dietary score is applicable to older British men (Chapter 6). In order to provide further evidence on the effectiveness of adherence to the EDI on lowering the risk of CVD and mortality in a UK population, a nutritional intervention trial could be carried out in older adults, with the intervention group receiving education or encouragement to adhere to components of the EDI[233] in comparison to a control group of existing dietary intake. This would help to inform policy efforts on the recommendation of dietary intake in older adults in the UK.

Dietary intake can vary greatly by region and country[223;436], so although results in this thesis are applicable to the UK, they may not be applicable to other parts of Europe or other countries outside of Europe. *A priori* methods of defining dietary patterns in particular have the limitation that they may be culturally or regionally specific and may not be universally applicable[30;204]. Future studies would therefore need to be carried out in other countries to assess whether the EDI is a valid measure of diet quality and related to the risk of CVD and mortality in other populations. *A posteriori* methods of defining dietary patterns have the advantage over *a priori* methods of making no prior assumptions about dietary patterns, instead using an empirical, data-driven approach to derive typical patterns of dietary intake[30]. However, the results observed in Chapter 8 are therefore geared specifically to the dataset from which they were derived, and likely to apply only to older British men.

Dietary patterns, identified by principal component analysis, are likely to differ according to different populations studied and further studies in other European populations are needed to see if patterns similar to those in this thesis are derived, and to compare these patterns with the associated risks of CVD and mortality.

Results from this thesis were based on the assessment of diet at one time point at the twenty year re-examination in 1998-2000, so it is possible that dietary patterns may have changed over time. The recently completed re-examination of BRHS participants, in 2010 to 2012, has collected dietary data via a food frequency questionnaire and further exploratory analyses would allow assessments to be made about whether the overall diet quality of BRHS participants had improved or worsened over time. This would provide important information on whether diet is stable in older age groups over time.

Analyses in this thesis related to the prospective associations between dietary patterns and risk of CVD and mortality excluded men with prevalent MI, stroke and heart failure since dietary changes may have occurred in these individuals following diagnosis and also no measure of the severity of CVD was available for these participants. Further large epidemiological studies are therefore needed in populations with controlled prevalent CVD (e.g. CHD, stroke or heart failure) in order to provide evidence of whether the dietary patterns studied in this thesis, such as the EDI, are effective in the secondary prevention of CVD.

9.5. Concluding statement

The population in the UK is ageing due to a steady increase in life expectancy over time. Since the 1930s, the number of people aged over 65 years in the UK has more than doubled[1]. CVD remains the main cause of mortality in the UK, accounting for nearly a third of all deaths in both men and women, and is a major contributor to morbidity and disability[4]. Results from this thesis have demonstrated that body composition and dietary patterns are two important and potentially modifiable risk factors for CVD and mortality, which persist in older age. Sarcopenic men and obese men have a significantly increased

risk of CVD mortality and all-cause mortality, and men with both sarcopenia and obesity have the highest all-cause mortality risk. Adherence to high quality dietary patterns, measured using both *a priori* dietary scores and *a posteriori* dietary patterns were associated with a decreased risk of CVD and all-cause mortality, emphasizing the importance of adopting a dietary pattern inherent in the Elderly Dietary Index criteria and avoiding 'high fat /low fibre' and 'high sugar' components. These results emphasize the potential of population-wide public health measures to prevent sarcopenia and obesity and also to improve overall diet quality in older adults in the UK, in order to decrease the risks of CVD and all-cause mortality in older age.

APPENDIX I Conference oral presentations (peer-reviewed abstracts)

1. **Atkins JL**, Whincup PH, Morris RW, Wannamethee SG. Dietary patterns in older men: Influence of early life social circumstances and area of residence. Society for Social Medicine (Brighton, September, 2013).

2. **Atkins JL**, Whincup PH, Morris RW, Wannamethee SG. Dietary patterns in older British men: the influence of early life social circumstances and area of residence. Nutrition Society Summer Meeting (Newcastle, July, 2013).

3. **Atkins JL**, Whincup PH, Morris RW, Lennon LT, Papacosta O, Wannamethee SG. Dietary patterns and the risk of cardiovascular disease and mortality: a population-based cohort study of older British men. Nutrition Society Summer Meeting (Newcastle, July, 2013).

4. **Atkins JL**, Whincup PH, Morris RW, Lennon LT, Papacosta O, Wannamethee SG. Sarcopenic-obesity and risk of mortality and cardiovascular disease in older men. NIHR School for Primary Care Research Showcase (London, October, 2012)

APPENDIX II Conference poster presentations (peer-reviewed abstracts)

1. **Atkins JL**, Whincup PH, Morris RW, Lennon LT, Papacosta O, Wannamethee SG. Principal component analysis of dietary patterns and the risk of cardiovascular disease and mortality in older British men. Longitudinal Studies: Maximising their value for ageing research (Cambridge, July, 2015).

2. **Atkins JL**, Whincup PH, Morris RW, Lennon LT, Papacosta O, Wannamethee SG. Principal component analysis of dietary patterns and the risk of cardiovascular disease and mortality in older British men. EPI/Lifestyle (Baltimore, USA, March, 2015).

3. **Atkins JL**, Whincup PH, Morris RW, Wannamethee SG. Sarcopenic obesity and the risk of cardiovascular disease and mortality: a population-based cohort study of older men. European Congress on Obesity (Liverpool, May, 2013).

4. **Atkins JL**, Whincup PH, Morris RW, Wannamethee SG. Dietary patterns in the elderly: Influence of early life social circumstances and area of residence. European Congress on Obesity (Liverpool, May, 2013).

5. **Atkins JL**, Whincup PH, Morris RW, Wannamethee SG. Sarcopenic obesity and risk of all-cause and cardiovascular mortality in older men. Society for Social Medicine (London, September, 2012).

APPENDIX III General Practice medical record review form used for biannual morbidity follow-up

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>

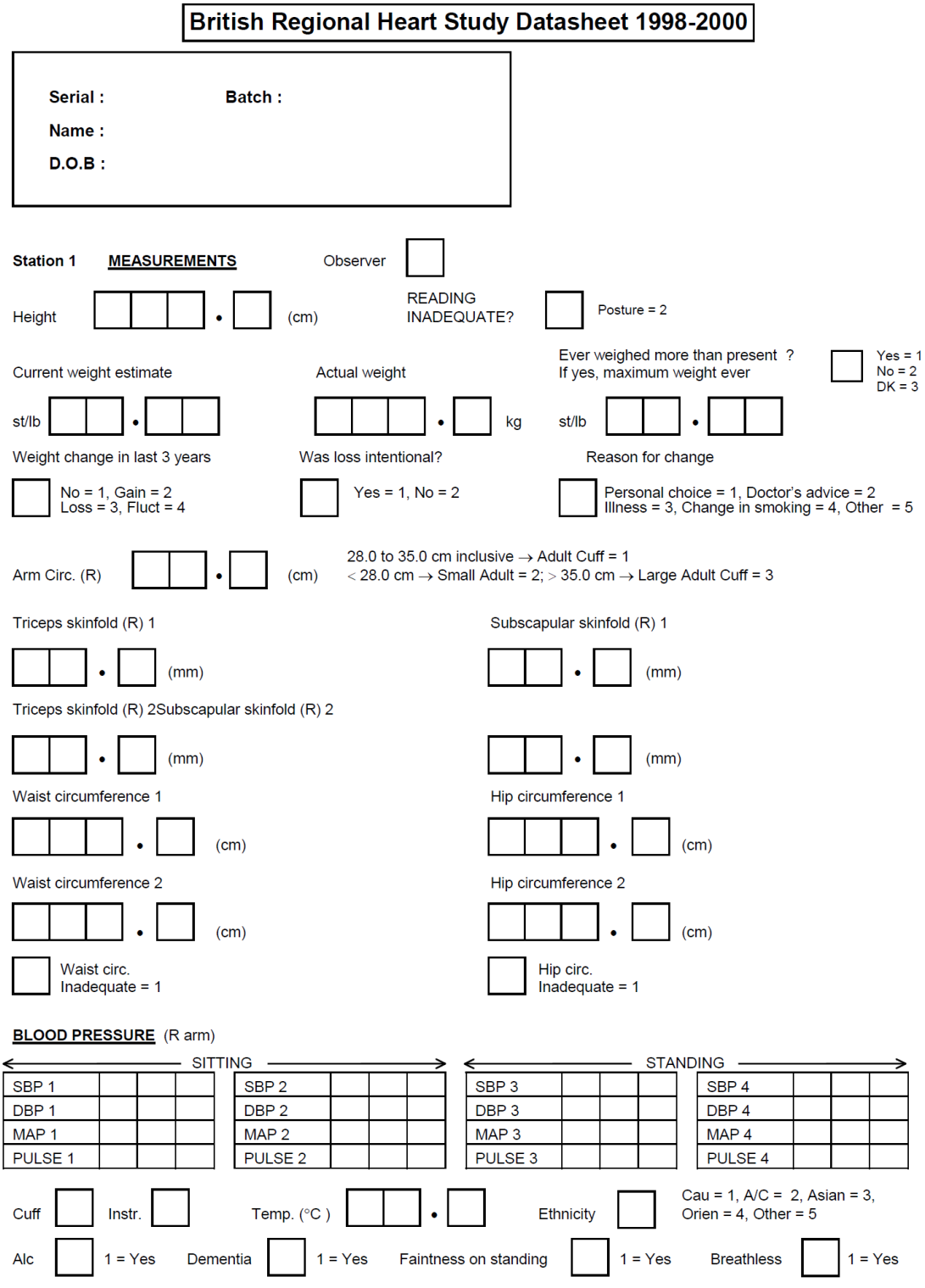
NHS No: <NHS>

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: .....
		YES	NO	
4	Has he been referred to a Consultant for any new cardiovascular condition?	☐	☐	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: .....
		YES	NO	
6	Has he had a Cancer diagnosis?	☐	☐	Date: .....
	Site:			

1.

APPENDIX IV 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 ? ___ Yes = 1, No = 2, DK = 3
If yes, maximum weight ever st/lb ___ • ___

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) 2 ___ • ___ (mm)

Subscapular skinfold (R) 2 ___ • ___ (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				SITTING				STANDING				STANDING			
	SBP 1				DBP 1				MAP 1				PULSE 1			
	SBP 2				DBP 2				MAP 2				PULSE 2			
	SBP 3				DBP 3				MAP 3				PULSE 3			
	SBP 4				DBP 4				MAP 4				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

Ankle oedema ☐ Yes = 1, No = 2
Leg ulcer ☐ Sole = 1, Ankle = 2, Shin = 3

Pulses
Dorsalis Pedis ☐ Yes = 1, No = 2
Post Tibial ☐ Yes = 1, No = 2

Pacemaker ☐ Yes = 1, No = 2
↓
Impedance ☐☐☐

RIGHT SIDE

Ankle oedema ☐ Yes = 1, No = 2
Leg ulcer ☐ Sole = 1, Ankle = 2, Shin = 3

Pulses
Dorsalis Pedis ☐ Yes = 1, No = 2
Post Tibial ☐ Yes = 1, No = 2

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 V Questionnaire in 1998-2000 at twenty-year follow-up

Study Number : ☐☐☐☐☐☐☐☐

BRITISH REGIONAL HEART STUDY

20 YEAR FOLLOW-UP SURVEY

Thank you for attending this follow-up survey. It would be very helpful if you could complete this questionnaire, which will bring us up to date with your health and lifestyle.

Most questions can be answered simply by ticking the correct box ☑

All information will be treated as **strictly confidential**.

The Research Nurse will help you with any problems.

Thank you for your help.

Conditions affecting the heart or circulation

1.0 Have you **ever** been told by a doctor that you have or have had any of the following conditions ?

		Yes	No	If after 1996, please give year
(a)	Heart attack (coronary thrombosis or myocardial infarction)	☐	☐	19_____
(b)	Heart failure	☐	☐	19_____
(c)	Angina	☐	☐	19_____
(d)	Other heart trouble	☐	☐	19_____
(e)	High blood pressure	☐	☐	19_____
(f)	Aortic Aneurysm	☐	☐	19_____
(g)	Narrowing or hardening of the leg arteries (including claudication)	☐	☐	19_____
(h)	Deep Vein Thrombosis (clot in the deep leg vein)	☐	☐	19_____
(i)	Pulmonary Embolism (clot on the lung)	☐	☐	19_____

Treatment for heart trouble

2.0 Have you **ever** had any of the following **TREATMENTS** for chest pain or heart disease ?

		Yes	No	If **Yes,** please give year of treatment	
(a)	Angioplasty of coronary arteries ('balloon treatment')	☐	☐	19_____	19_____
(b)	Coronary artery bypass graft (CABG) operation	☐	☐	19_____	19_____

Stroke

		Yes	No	Year of first diagnosis
3.0	Have you **ever** been told by a doctor that you have had a stroke ?	☐	☐	19_____
(a)	**If Yes,** did the symptoms last for more than 24 hours ?	☐	☐	

Cancer

4.0 Have you **ever** been told by a doctor that you have or have had Cancer ? Yes ☐ No ☐

If Yes, please give the following information:-

OFFICE USE

(a) Cancer Site_____ ☐☐ Year first diagnosed 19_____

Diabetes

Please answer all the questions

5.0 Have any of your close 'blood' relatives (your parents, brothers or sisters) **ever** had diabetes ? Yes ☐ No ☐

If Yes, please list any of these relatives who have had diabetes and if possible their age when they were first diagnosed: OFFICE USE

(a) Mother _____ ☐☐

(b) Father _____ ☐☐

(c) Brothers _____ ☐ ☐☐

(d) Sisters _____ ☐ ☐☐

5.1 Have you **ever** been told by a doctor that you have (or have had) diabetes? Yes ☐ No ☐

(a) **If Yes,** in what year was your diabetes first diagnosed ? 19_____

Chest pain

6.0 Do you ever have any pain or discomfort in your chest ?

Yes ☐

No ☐ → If **No**, go to Question 7.0 on the next page

6.1 Do you know the cause of the pain ? Yes ☐ No ☐

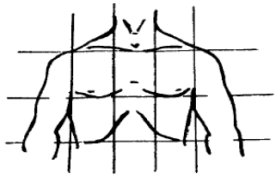
OFFICE USE

(a) **If Yes**, please state: ☐

_____

(b) Where do you get this pain or discomfort ?

Please mark **X** on the appropriate places



YOUR RIGHT SIDE

YOUR LEFT SIDE

OFFICE USE ☐☐☐

(c) When you walk at an ordinary pace on the level does this produce the chest pain ?

Yes ☐1
No ☐2
Unable to walk on level ☐3

(d) When you walk uphill or hurry does this produce the chest pain ?

Yes ☐1
No ☐2
Unable to walk on level ☐3

Chest pain continued

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

Yes	☐1
No	☐2
Continue at the same pace	☐3

		Yes	No
(f)	Does the pain or discomfort in your chest go away if you stand still?	☐	☐

(g) How long does it take to go away ?

10 minutes or less	☐1
More than 10 minutes	☐2

(h) Overall is the chest pain

Becoming more frequent	☐1
Staying about the same	☐2
Becoming less frequent	☐3

Previous Chest Pain

		Yes	No
7.0	Have you previously had chest pain, which has stopped because of an operation?	☐	☐

(a) If **Yes,** please give details: OFFICE USE

_____

Severe chest pain

8.0 Have you **ever** had a **severe** pain across the front of your chest lasting for half an hour or more ?

Yes☐ No☐ ➔ If **No**, go to question 9.0 on the next page

(a) If **Yes**, what year did this happen ? 19_____

		Yes	No
(b)	Did you see a doctor because of this pain?	☐	☐

OFFICE USE

(c) If **Yes**, what were you told was the cause_____

Leg pain

9.0 Do you get pain or discomfort in your leg (or legs) when you walk?

Yes	☐1
No	☐2
Unable to walk	☐3

➔ If **No** or **Unable to walk**, go to question 10.0, on the next page

		Yes	No
9.1	Do you know the cause of the pain ?	☐	☐

OFFICE USE

(a) If **Yes,** please state: -

_____

		Yes	No
(b)	Does this pain ever begin when you are standing still or sitting ?	☐	☐

(c) Do you get the pain if you walk uphill or hurry?

Yes	☐1
No	☐2
Unable to walk	☐3

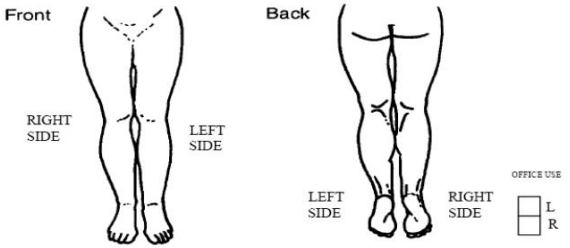
(d) Do you get the pain walking at an ordinary pace on the level?

Yes	☐1
No	☐2
Unable to walk	☐3

(e) What happens to the pain if you stand still?

Usually continues more than 10 minutes	☐1
Usually disappears in 10 minutes or less	☐2

(f) Please mark on the diagram below where you get the pain.



Smoking

10.0 Have you **ever** smoked cigarettes regularly (at least 1 a day) ?

Yes ☐1
No ☐2 ➔ If **No**, go to question 10.3 below

10.1 Do you smoke cigarettes at present?

Yes ☐1
No ☐2

(a) **If Yes**, how many cigarettes do you smoke a day at present ? ☐☐

(If hand-rolled, how much tobacco do you use a week ? ☐☐ oz /
☐☐☐ grams)

(b) **If No**, at what age did you give up ? ☐☐ years

10.2 Have you changed your cigarette smoking habits over the last three years ?

No ☐1
Yes, increased ☐2
Yes, decreased ☐3
Yes, given up ☐4

Pipe & Cigar Smoking

10.3 Have you **ever** regularly smoked a pipe ? Yes ☐ No ☐

(a) **If Yes**, do you currently smoke a pipe ? Yes ☐ No ☐

(b) **If Yes,** how much tobacco do you smoke per week? ☐☐ oz /
☐☐☐ grams

10.4 Have you **ever** regularly smoked cigars ?

Yes ☐1
No ☐2 ➔ If **No**, go to question 10.5 below

(a) **If Yes**, do you currently smoke cigars ? Yes☐ No☐

(b) **If Yes,** how many cigars do you smoke per week ? ☐☐

Other exposure to Cigarette smoke

10.5 Does your wife / partner smoke cigarettes ?

Yes ☐1 ➔Number per day ☐☐
Ex -Smoker ☐2
No ☐3
Does not apply ☐4

10.6 For about how many hours each day are you exposed to other people's cigarette smoke ?

(a) at home ☐☐ (hours)

(b) outside the home ☐☐ (hours)

(c) Tick here if rarely exposed to cigarette smoke ☐1

Alcohol

11.0 Would you describe your present alcohol intake as

Daily/most days	☐1
Weekends only	☐2
Occasionally (once or twice a month)	☐3
Special occasions only	☐4
None	☐5

One drink is **HALF** a pint of beer /cider, a **SINGLE** whisky, gin, etc. or **ONE GLASS** of wine or sherry

11.1 How much do you usually drink on the days when you drink alcohol ?

More than 6 drinks	☐1
3-6 drinks	☐2
1-2 drinks	☐3
None	☐4

11.2 How many alcoholic drinks do you have during an average week ? ☐☐☐

11.3 What type of drink do you usually take?

Beers, Lagers	☐1
Wines, Sherry	☐2
Spirits	☐3
Variety of Beers, Wines or Spirits	☐4
Low alcohol drinks	☐5

	Yes	No	If **Yes**, glasses per week
(a) Do you drink white wine ?	☐	☐	☐☐
red wine ?	☐	☐	☐☐

11.4 Is the alcohol which you drink usually taken (tick whichever applies) :-

before meals	☐1
with meals	☐1
after meals	☐1
separate from meals	☐1

11.5 Have you changed your alcohol intake in the last three years?

No	☐1
Yes, increased	☐2
Yes, cut down	☐3
Yes, given up	☐4

11.6 If you have **CUT DOWN** or **GIVEN UP**
Was this due to (tick which ever apply):-

Personal choice	☐1
Doctor's advice	☐1
Illness or ill health	☐1
Health precaution	☐1
Being on medication	☐1
Financial reasons	☐1
Other	☐1

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 ☐☐

Your Health Overall

Please indicate which statements best describe your health **TODAY**
(Do not tick **more than one** box in each group)

13.0 General Health:-
- Excellent ☐1
- Good ☐2
- Fair ☐3
- Poor ☐4

13.1 Pain / Discomfort:-
- I have no pain or discomfort ☐1
- I have moderate pain or discomfort ☐2
- I have extreme pain or discomfort ☐3

13.2 Usual Activities (e.g. work, study, housework, family or leisure activities):-
- I have no problems with performing my usual activities ☐1
- I have some problems with performing my usual activities ☐2
- I am unable to perform my usual activities ☐3

13.3 Self Care:-
- I have no problems with washing and dressing ☐1
- I have some problems with washing and dressing myself ☐2
- I am unable to wash or dress myself ☐3

13.4 Mobility:-
- I have no problems in walking about ☐1
- I have some problems in walking about ☐2
- I am confined to a chair / wheelchair ☐3

13.5 Anxiety /Depression:-
- I am not anxious or depressed ☐1
- I am moderately anxious and /or depressed ☐2
- I am extremely anxious and /or depressed ☐3

13.6 Your Memory:- compared to five years ago, is your memory
- improved ☐1
- the same ☐2
- almost as good ☐3
- worse ☐4
- much worse ☐5

13.7 Health Scale

We have drawn a health scale (rather like a thermometer) on which perfect health is 100 and very poor health is 0. Please put a cross (**X**) on the scale to reflect how good or bad your health is today.

Worst Imaginable Health State — Best Imaginable Health State

0 • 10 20 30 40 50 60 70 80 90 • 100

OFFICE USE

Disability

		Yes	No
14.0	Do you have any long-standing illness, disability or infirmity ?	☐	☐

('long-standing' means anything which has troubled you over a period of time or is likely to do so)

	If Yes,	Yes	No
(a)	Does this illness or disability limit your activities in any way?	☐	☐
(b)	Do you receive a disability allowance ?	☐	☐

14.1 Do you currently have difficulty carrying out any of the following activities on your own as a result of a long term health problem?

		Yes	No	Date started	Cause of problem	OFFICE USE
(a)	Difficulty going up / down stairs	☐	☐	19_____	_____	
(b)	Difficulty bending down / straightening up	☐	☐	19_____	_____	
(c)	Falling or having great difficulty keeping balance	☐	☐	19_____	_____	
(d)	Difficulty walking for a quarter of a mile on the level	☐	☐	19_____	_____	

14.2 Is your present state of health causing problems with any of the following ?

		Yes	No	Cause of problem	OFFICE USE
(a)	Job at work (paid employment)	☐	☐	_____	
(b)	Household chores	☐	☐	_____	
(c)	Social life	☐	☐	_____	
(d)	Interests and hobbies	☐	☐	_____	
(e)	Holidays and outings	☐	☐	_____	
(f)	Family relationships	☐	☐	_____	

Contact with relatives and friends

15.0 How often do you see or speak to :-

	Every week 1	Every month 2	Every few months 3	Every Year 4	Rarely or Never 5	Does not apply 6
Your Children						
Brothers / Sisters						
Friends						
Neighbours						

15.1 Is the amount of contact you have with each of these:-

	Too little 1	About right 2	Too much 3	Does not apply 4
Your Children				
Brothers / Sisters				
Friends				
Neighbours				

Present Circumstances

16.0 Are you at present :- Please give year

- single ☐1
- married ☐2 ↘
- widowed ☐3 → 19 _____
- divorced or separated ☐4 ↗
- other ☐5

16.1 Are you at present :-

- living alone ☐1
- living with a partner or spouse ☐2
- living with other family member(s) ☐3
- living with other people ☐4

16.2 Your accommodation

Are you :-

- an owner occupier ☐1
- renting from the local authority ☐2
- renting privately ☐3
- other (please give details)_____ ☐4

OFFICE USE

Present Circumstances continued

		Yes	No
16.3	Do you have a car available for your own use ?	☐	☐
16.4	Do you have a pet ?	☐	☐

OFFICE USE

(a) **If Yes**, what kind of pet do you own :- _____

16.5 **Heating**

Please tick the fuels you use to heat your home:-

Natural gas	☐1	Oil	☐1	Wood	☐1
Calor gas	☐1	Coal	☐1		
Electricity	☐1	Other	☐1	please specify	_____

OFFICE USE

16.6 Does your home have:-

	Yes	No	
Central heating	☐1	☐2	
Open fires	☐1	☐2	
Double Glazing	☐1	☐2	In part ☐3

16.7 Please tick the fuels you use for cooking:-

- Natural gas ☐1
- Electricity ☐1
- Other ☐1 (Please specify) _____

OFFICE USE

Work and Retirement

17.0 At present are you :-

retired	☐1	age at retirement ☐☐
employed, full time	☐2	
employed, part time	☐3	
unemployed, seeking work	☐4	
unemployed, not seeking work	☐5	

(a) If you are **retired**, did you retire because of:-

normal retiring age	☐1
early retirement, voluntary	☐2
early retirement, compulsory	☐3
retirement, medical grounds	☐4
other reasons	☐5

17.1 Please give details of your current occupation **or** the last job you held before retiring: -

OFFICE USE

(a) What kind of work do you / did you do_____

(b) Type of business or industry_____

(c) How many years have you done or did you do that kind of work ? _____

18.0 Are you on any regular medication ?

Yes ☐

No ☐ ➔ If **No**, go to question 18.3 on the next page

For Research Nurse use only	
Actual medications	☐1
Prescription Card (repeat)	☐2
Other list	☐3
No formal documentation	☐4

18.2 Which medications (including tablets, medicines, inhalers, sprays, injections) you are taking ? Please list medications below:

Medication	Dose	Frequency	Reason for taking	OFFICE USE BNF CODE	ICD CODE

Aspirin

18.3 Do you take aspirin regularly ? Yes ☐ No ☐ ➔ If **No**, go to question 18.3(b) below

(a) If Yes , year started 19 ☐☐

Dose ☐☐☐ mg

Frequency / week ☐

Reason for use _____

On Prescription Yes ☐ No ☐

OFFICE USE ☐☐☐

18.3 (b) If **No**, have you taken aspirin regularly in the past ? Yes ☐ No ☐

If Yes , year started 19 ☐☐

year stopped 19 ☐☐

Reason for taking _____

On Prescription Yes ☐ No ☐

OFFICE USE ☐☐☐

Warfarin

18.4 Have you taken warfarin regularly at any time ? Yes ☐ No ☐

If Yes , year started 19 ☐☐

Duration in months ☐☐

Reason for taking _____

OFFICE USE ☐☐☐

GTN

18.5 Have you ever taken GTN tablets under the tongue (or spray) to relieve pain in the chest ?

Yes ☐ No ☐

(a) **If Yes,** when was the last time you used them ? ☐☐☐ mths ago

Vitamins & Minerals

18.6 Do you regularly take any vitamin or mineral tablets? Yes ☐ No ☐

(a) **If Yes**, please give details :-

Name of vitamin / mineral	Daily Dose	Year Started
		19_____
		19_____
		19_____
		19_____

Blood Cholesterol Test

19.0 Have you ever had your blood cholesterol measured ? Yes ☐ No ☐

(a) **If Yes**, were you told that the result was
High ☐1
Normal ☐2
Low ☐3
Not told ☐4

(b) **If High**, have you been advised to take any particular action ? (please give details)

Diet ☐1
Drugs ☐1

Eating and drinking

20.0 What time did you last have something to eat or drink other than water ?

☐☐ . ☐☐ hours If yesterday please tick ☐1

21.0 **Consent to follow up studies**

An important part of this study is to observe the future health of the people taking part. We are therefore seeking your permission to receive specific information related to heart disease and stroke, particularly from the records held by your general practitioner. All these details would be treated in **absolute confidence** by the Research Team.

Do you agree to us following your future health through your health records ?

☐1 Agreed ☐2 Not Agreed

We will arrange to have your blood sample checked for cholesterol and other factors which are important for heart disease risk. The results of these tests will be sent back to your doctor in the next four to five weeks. If any of the results give cause for concern, you will be asked to make an appointment with your doctor.

Do you agree to us passing the test results to your doctor ?

☐1 Agreed ☐2 Not Agreed

Part of your blood sample will be frozen and kept for special scientific studies of factors affecting heart disease risk, which may help us to understand how to prevent heart disease in the future. Among the factors we may need to study will be the way in which genetic factors affect heart disease risk.

Would you allow us to use your sample in this way ?

☐1 Agreed ☐2 Not Agreed

I agree to allow the Research Team to continue to study my health in accordance with the criteria above. I understand that any details recorded will be treated in complete confidence.

Signed: _____

Date: _____

APPENDIX VI Postal dietary questionnaire in 1998-2000

Study Number : | | | | | | | | |

BRITISH REGIONAL HEART STUDY

20 YEAR FOLLOW-UP SURVEY

QUESTIONNAIRE ON PHYSICAL ACTIVITY AND DIET

We should be very grateful if you would complete this questionnaire which asks about your physical activities and diet. Please return it to us with your appointment reply card in the reply paid envelope provided. You may wish to seek help from others with some of the questions on diet, especially if you do not do your own cooking. If you have any difficulties in completing this questionnaire, please phone us on 0171 830 2335 and leave your telephone number so that we can call you back and answer your queries.

All information will be treated as **strictly confidential**.

Thank you for your help.

British Regional Heart Study
Department of Primary Care & Population Sciences
Royal Free Hospital School of Medicine
Rowland Hill Street
London NW3 2PF

PART I : PHYSICAL ACTIVITY

These questions are designed to find out how physically active you are in everyday life, both inside and outside your home. Please try to answer all questions, describing your usual activities **OVER THE LAST YEAR**.

Getting About

1.0 Which of the following forms of transport do you use most often? (tick only one box)

- Car ☐ 1
- Public transport ☐ 2
- Walking or Cycling ☐ 3

Walking

1.1 How many miles do you walk in total in an average week ? ___ ___ miles / week

1.2 How many journeys of at **least a mile** do you walk each week ? ___ ___ journeys

(Please write '0' if none)

2.0 **Household Activities**

About how many hours each week do you usually spend on the following household activities ? (please tick one box for each question)

	None 1	Less than 1 hour a week 2	1 to 3 hours a week 3	3 to 6 hours a week 4	6 to 10 hours a week 5	More than 10 hours a week 6
Light Activities (eg preparing food, cooking, washing up, dusting)						
Moderate Activities (eg cleaning, sweeping, hoovering washing floors, shopping)						
Heavy Activities (eg scrubbing floors, walking with heavy shopping)						

3.0 **Climbing Stairs**

How many flights of stairs do you climb up each day ? (a flight of stairs = 10-15 stairs)

	None 1	1 to 5 flights 2	6 to 10 flights 3	11 to 15 flights 4	More than 15 flights 5
On a weekday					
On a weekend day					

4.0 **Other Activities in the past year**

Please indicate how often you did these activities **during the past year.**
If you didn't do a particular activity at all, simply write 'X' in the first column.

	How many times each month ? □□	→	How many months of the year? □□	→	Average time on each occasion? Hours □□	Minutes □□
Walking on specific journeys (eg to shops, errands)		→		→		
Rambling / Hiking		→		→		
Cycling		→		→		
Light gardening (eg watering the lawn/garden)		→		→		
Moderate gardening (eg planting, cutting grass)		→		→		
Heavy gardening (eg digging, shovelling)		→		→		
DIY (eg home / car maintenance, carpentry)		→		→		
Swimming		→		→		
Jogging		→		→		
Exercises (stretching, bending, keep fit, etc)		→		→		
Dancing		→		→		
Bowling (indoor, lawn, tenpin)		→		→		
Golf		→		→		
Tennis / Badminton		→		→		
Fishing		→		→		
Other exercises (please specify)		→		→		
		→		→		

OFFICE USE □

□

5.0 Did you do any of these activities vigorously enough to cause sweating, breathlessness or fast heartbeat ? Yes □ No □

5.1 **If Yes,** for about how many minutes did you do such vigorous activities each week ? ___ ___ ___ (mins)

5.2 Compared with your level of activity three years ago, are you doing

more □1
about the same □2
less □3

5.3 **If less**, please give the reason

_____ OFFICE USE □

PART II : YOUR DIET

1. Are you on any special diet (eg vegetarian , low fat, diabetic) ? Yes □ No □ OFFICE USE □

If Yes, please give details _____

How to fill in the diet questionnaire

The following questions are mostly about how often you **USUALLY** eat different sorts of food each **week**.

If you usually eat a food **every day**, ring **7** days a week

If you usually eat a food on **three days a week**, ring **3**, and so on

For foods which you eat **less than once a week** :-

Ring **M** if you eat it **at least** once a month

Ring **R** if you eat it **less than** once a month, or if you **never** eat it at all

Please ring **one** answer for each of the foods listed. Remember to circle **R** if you never eat a food.

Example

	Number of days each week							Monthly	Rarely/ Never
Food eaten every day (7 days a week)	(7)	6	5	4	3	2	1	M	R
Food eaten on three days a week	7	6	5	4	(3)	2	1	M	R
Food eaten less often than once a week but at least once a month	7	6	5	4	3	2	1	(M)	R
Food eaten never or less than once a month	7	6	5	4	3	2	1	M	(R)

Please ring the correct number or letter for every food item (one circle only per line)

			Number of days each week							0 Monthly	8 Rarely/ Never
2.	**Meat**										
(a)		Beef (including minced beef, beef burgers)	7	6	5	4	3	2	1	M	R
(b)		Lamb	7	6	5	4	3	2	1	M	R
(c)		Pork, bacon, ham, salami	7	6	5	4	3	2	1	M	R
(d)		Chicken, turkey, other poultry	7	6	5	4	3	2	1	M	R
(e)		Tinned meat (all types, corned beef, etc)	7	6	5	4	3	2	1	M	R
(f)		Pork Sausages	7	6	5	4	3	2	1	M	R
(g)		Beef Sausages	7	6	5	4	3	2	1	M	R
(h)		Meat Pie, Pasties	7	6	5	4	3	2	1	M	R
(i)		Liver, kidney, heart	7	6	5	4	3	2	1	M	R
3.	**Fish**										
(a)		White fish (cod, haddock, hake, plaice, fish fingers, etc)	7	6	5	4	3	2	1	M	R
(b)		Kippers, herrings, pilchards, tuna, sardines, salmon, mackerel (including tinned)	7	6	5	4	3	2	1	M	R
(c)		Shellfish	7	6	5	4	3	2	1	M	R
4.	**Vegetables (fresh, tinned, dried, frozen)**										
(a)		Potatoes: boiled, baked, mashed	7	6	5	4	3	2	1	M	R
(b)		Potatoes									
		(i) chips or fried (from shop)	7	6	5	4	3	2	1	M	R
		(ii) chips, fried or (cooked at home)	7	6	5	4	3	2	1	M	R
		(iii) roast potatoes	7	6	5	4	3	2	1	M	R
(c)		Green vegetables, salads	7	6	5	4	3	2	1	M	R
(d)		Carrots	7	6	5	4	3	2	1	M	R
(e)		Parsnips, swedes, turnips, beetroot, and other root vegetables	7	6	5	4	3	2	1	M	R
(f)		Baked or butter beans, lentils, peas, chickpeas, sweetcorn	7	6	5	4	3	2	1	M	R
(g)		Onions (cooked, raw, pickled)	7	6	5	4	3	2	1	M	R
(h)		Garlic	7	6	5	4	3	2	1	M	R
(i)		Spaghetti and other pasta	7	6	5	4	3	2	1	M	R
(j)		Rice (all types except pudding rice)	7	6	5	4	3	2	1	M	R
(k)		Tomatoes (fresh, tinned, pureed)	7	6	5	4	3	2	1	M	R
		How often do you eat fresh vegetables in :									
(l)		**summer**	7	6	5	4	3	2	1	M	R
(m)		**winter**	7	6	5	4	3	2	1	M	R

Please remember to circle ⑧ if you never eat a food

			Number of days each week							0 Monthly	8 Rarely/ Never
5.	**Fresh fruit**										
	How often do you eat fresh fruit in :										
(a)		**summer**	7	6	5	4	3	2	1	M	R
(b)		**winter**	7	6	5	4	3	2	1	M	R
(c)		Number of apples eaten a week ___ ___									
(d)		Number of pears eaten a week ___ ___									
(e)		Number of oranges or grapefruit eaten a week ___ ___									
(f)		Number of bananas eaten a week ___ ___									
(g)		Number of other fruits eaten a week (please give name and quantity)									

Name	Quantity	Name	Quantity
.....	.....	.....	.....
.....	.....	.....	.....
.....	.....	.....	.....

OFFICE USE ☐☐

			Number of days each week							0 Monthly	8 Rarely/ Never
6.	**Cheese**										
	Full- fat cheese (eg Cheddar, Leicester, Stilton, Brie, soft cheeses)		7	6	5	4	3	2	1	M	R
	Low-fat cheese (eg Edam, Cottage cheese, reduced fat cheeses)		7	6	5	4	3	2	1	M	R
7.	**Bread**										
(a)		White bread	7	6	5	4	3	2	1	M	R
(b)		Brown bread	7	6	5	4	3	2	1	M	R
(c)		Wholemeal	7	6	5	4	3	2	1	M	R
(d)		Bread rolls	7	6	5	4	3	2	1	M	R
(e)		Crispbread (Ryvita, cream crackers, etc)	7	6	5	4	3	2	1	M	R

please give name of crispbread etc.....

(f) Further details about your bread

	How many slices or rolls a day ?	Are the slices thick, medium or thin? Circle your answer.		
(i) White Bread	___ ___	thick 1	medium 2	thin 3
(ii) Brown Bread	___ ___	thick	medium	thin
(iii) Wholemeal Bread	___ ___	thick	medium	thin
(iv) Bread Rolls	___ ___	large	medium	small

Please remember to circle ⑧ if you never eat a food

			Number of days each week							0 Monthly	8 Rarely/ Never
8.	**Breakfast Cereals**										
	(a)	Grapenuts, Porridge, Ready Brek, Special K, Sugar Puffs, Rice Crispies	7	6	5	4	3	2	1	M	R
	(b)	Cornflakes, Muesli, Shredded Wheat, Sultana Bran, Weetabix	7	6	5	4	3	2	1	M	R
	(c)	Bran Flakes, Puffed wheat	7	6	5	4	3	2	1	M	R
	(d)	All Bran, Wheat Bran	7	6	5	4	3	2	1	M	R
	(e)	Another Cereal	7	6	5	4	3	2	1	M	R
		please give name									
9.	**Biscuits, puddings and sweets**										
	(a)	Digestive biscuits, plain biscuits	7	6	5	4	3	2	1	M	R
	(b)	Sweet biscuits, sponge cakes, scones, buns	7	6	5	4	3	2	1	M	R
	(c)	Ice cream, sweet yoghurts, trifle	7	6	5	4	3	2	1	M	R
	(d)	Fruit cake, fruit bread, plum pudding	7	6	5	4	3	2	1	M	R
	(e)	Fruit tart, jam tart, fruit crumble	7	6	5	4	3	2	1	M	R
	(f)	Milk puddings (rice, tapioca)	7	6	5	4	3	2	1	M	R
	(g)	Tinned fruit, jellies	7	6	5	4	3	2	1	M	R
	(h)	Sweet sauces (chocolate, custard)	7	6	5	4	3	2	1	M	R
	(i)	Chocolate, chocolate bars, sweets (all types)	7	6	5	4	3	2	1	M	R
10.	**Eggs**										
	(a)	Eggs (boiled, poached, fried, scrambled)	7	6	5	4	3	2	1	M	R
	(b)	Eggs in baked dishes (eg flans, quiches, soufflés, egg custard, etc)	7	6	5	4	3	2	1	M	R
11.	**Other foods**										
	(a)	Soups (all kinds, home-made, tinned, packet)	7	6	5	4	3	2	1	M	R
	(b)	Nuts, nut butter (eg salted or unsalted peanuts)	7	6	5	4	3	2	1	M	R
	(c)	Savoury snacks (eg potato crisps, corn chips, crackers)	7	6	5	4	3	2	1	M	R
	(d)	Chutney, brown sauce, tomato sauce	7	6	5	4	3	2	1	M	R
	(e)	Sweet spreads (eg jam, honey, marmalade, chocolate spread)	7	6	5	4	3	2	1	M	R
12.	**Drinks and Juices (non-alcoholic)**										
	(a)	Natural fruit juices (including tomato juice)	7	6	5	4	3	2	1	M	R
	(b)	Fizzy drinks and Non-diet squashes	7	6	5	4	3	2	1	M	R
	(c)	**Low calorie** (diet) squashes and fizzy drinks	7	6	5	4	3	2	1	M	R

Please remember to circle ® if you never eat a food

13. **Milk**

(a) Roughly how much milk do you drink a day in tea, coffee, milky drinks or cereals ? (Tick only one box)

1 ☐ none at all
2 ☐ half pint or less
3 ☐ between half and one pint
4 ☐ more than one pint

(b) What kind of milk do you usually use? (Tick only one box)

1 ☐ full fat milk, fresh or dried
2 ☐ semi-skimmed milk, fresh or dried
3 ☐ fully skimmed milk, fresh or dried
4 ☐ other kinds of milk, eg condensed, evaporated

14. **Fats**

(a) What do you usually spread on bread ? OFFICE USE

1 ☐ butter Give brand name .....
1 ☐ full-fat soft margarine Give brand name ..... ☐
1 ☐ low-fat soft margarine Give brand name ..... ☐
1 ☐ hard margarine Give brand name .....

(b) How do you normally spread the fat ?

1 ☐ thinly 2 ☐ average 3 ☐ thickly

(c) How often do you eat home-fried food (including chips), cooked with :-

	Number of days each week							0 Monthly	8 Rarely/ Never	
Lard, dripping, solid vegetable oil	7	6	5	4	3	2	1	M	R	
Give brand name and type										☐
Liquid vegetable oil	7	6	5	4	3	2	1	M	R	
Give brand name and type										☐

15. **Salt**

(a) How much salt is added to your food, on cooking ?
1 ☐ a lot 2 ☐ a little 3 ☐ none

(b) How much salt is added to your food on your plate ?
1 ☐ a lot 2 ☐ a little 3 ☐ none

Please remember to circle ® if you never eat a food

16. **Your household**

How many people normally eat in your household ?

Number of adults (including yourself) ___ ___ Number of children 1 to 4 years old ___ ___

Number of children 5 to 16 years old ___ ___ Number of babies under 1 year old ___ ___

17. How much of the following foods does **your household** use on average **each week** (including cooking and baking)? If you live on your own, please give the amounts which you yourself eat a week.

	If rarely or never used tick here			
Butter	☐1	___ ___ lbs	___ ___ozs	or ___ ___ ___ grams
Margarine (all types)	☐1	___ ___ lbs	___ ___ozs	or ___ ___ ___ grams
Lard and solid vegetable oil	☐1	___ ___ lbs	___ ___ozs	or ___ ___ ___ grams
Liquid vegetable oil (eg Sunflower, Corn, Groundnut oil)	☐1		___ ___ozs	or ___ ___ ___ ml
Olive Oil	☐1		___ ___ozs	or ___ ___ ___ ml
Cream	☐1		___ ___ozs	or ___ ___ ___ ml
Full- fat cheese (eg Cheddar, Leicester, Stilton, Brie, and soft cheeses)	☐1	___ ___ lbs	___ ___ozs	or ___ ___ ___ grams
Low-fat cheese (eg reduced fat cheddar, reduced fat soft cheeses, Edam)	☐1	___ ___ lbs	___ ___ozs	or ___ ___ ___ grams
Sugar	☐1	___ ___ lbs	___ ___ozs	or ___ ___ ___ grams

18. **Hot drinks**

Coffee

(a) How many cups of **coffee** do you have a day ? ___ ___ cups a day

Is this ☐1 ground coffee ☐2 instant coffee

Is it decaffeinated ? ☐1 Yes ☐2 No

(b) How many teaspoons of sugar do you take in each cup ? ___ teaspoons
(Do not count artificial sweeteners)

Tea

(c) How many cups of **tea** do you have a day ? ___ ___ cups a day

(d) How many teaspoons of sugar do you take in each cup ? ___ teaspoons
(Do not count artificial sweeteners)

Other Hot Drinks

(e) How many cups of other hot drinks (eg drinking hot chocolate, malted milk, Horlicks) do you have a day ? ___ ___ cups a day

19. **Alcoholic drinks**

		Yes	No	Seldom
(a)	Have you ever consumed alcoholic drinks ?	☐1	☐2	
(b)	Do you take alcoholic drinks at present ?	☐1	☐2	☐3

(c) Think back carefully over the last seven days.
Please write the number of alcoholic drinks you have consumed on each day during the past week. It may help if you try to remember where you were and who you were with on each day.

For each day, write in how much you have drunk:

(i) the **number** of **pints** of non-alcoholic beer, lager, etc
(ii) the **number** of **pints** of low-alcohol beer, lager, etc
(iii) the **number** of **pints** of beer, lager, shandy, cider, stout, etc
(iv) the **number** of **single glasses** of whisky, vodka, gin, rum, etc
(v) the **number** of **single glasses** of wine, sherry, martini, port, etc

	(i) Pints of Non-alcoholic Beer ☐☐	(ii) Pints of Low-alcohol Beer ☐☐	(iii) Pints of Beer, Lager, Shandy ☐☐	(iv) Single glasses of Spirits ☐☐	(v) Single glasses of Wine ☐☐
Monday					
Tuesday					
Wednesday					
Thursday					
Friday					
Saturday					
Sunday					

		Yes	No
(d)	Would you say last week was fairly typical of what you usually have to drink in one week ?	☐1	☐2

		More	Less
(e)	If last week was not typical, would you normally drink more or less in a week ?	☐1	☐2

20. **Birth Weight**

Recent research has suggested that circumstances around the time of birth, and particularly birthweight, may influence the heart and circulation many years later.

If you can tell us about your birthweight and the birthweight (s) of your children (asking other family members if necessary) this would be very helpful :-

(a) **Your birth weight:** ___ ___ lb ___ ___ oz Not known ☐1

(b) **The birthweight of your children:-**

			Boy	Girl	Not known	☐1
First Child	___ ___ lb	___ ___ oz	☐1	☐2	Does not apply	☐1
Second Child	___ ___ lb	___ ___ oz	☐1	☐2		
Etc	___ ___ lb	___ ___ oz	☐1	☐2		
	___ ___ lb	___ ___ oz	☐1	☐2		
	___ ___ lb	___ ___ oz	☐1	☐2		

Thank you for your help with this questionnaire.

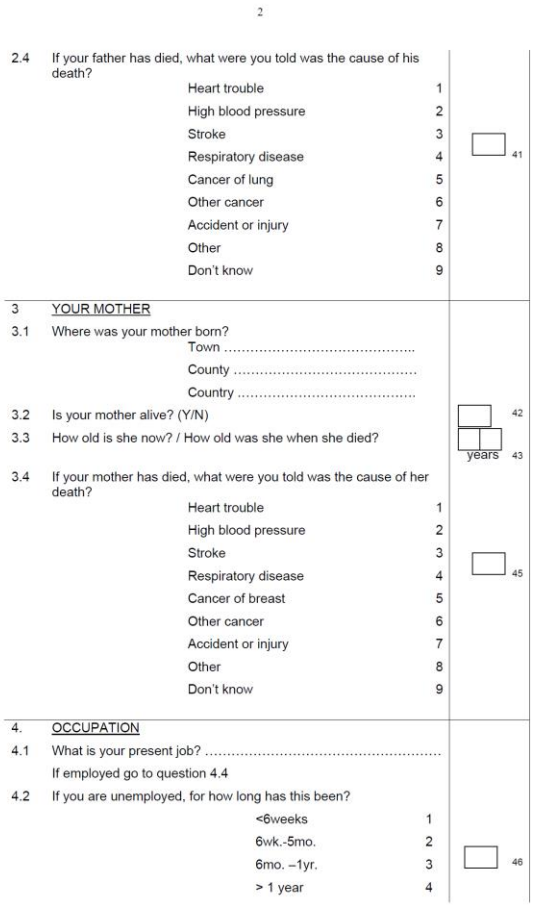
Please check that you have answered all questions and return the questionnaire to us in the envelope provided.

No stamp is required.

For comments:

APPENDIX VII Baseline questionnaire in 1978-80

Selected question used in this thesis on occupation:



2

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	
Respiratory disease	4	41
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?

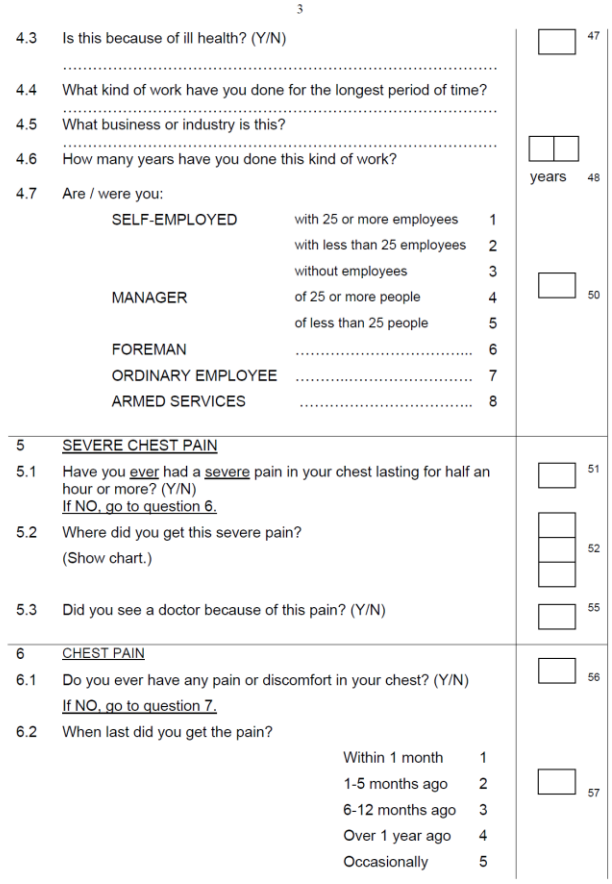
Heart trouble	1	
High blood pressure	2	
Stroke	3	
Respiratory disease	4	45
Cancer of breast	5	
Other cancer	6	
Accident or injury	7	
Other	8	
Don't know	9	

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	



3

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	
	with less than 25 employees	2	
	without employees	3	
MANAGER	of 25 or more people	4	50
	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?

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

APPENDIX VIII Postal questionnaire in 1996

Selected question used in this thesis on education and pension status:

Present Circumstances (continued)

23.2 Are you at present

- living alone ☐1
- living with a partner or spouse ☐2
- living with other family member(s) ☐3
- living with other people ☐4

23.3 Your accommodation

Are you

- an owner occupier ☐1
- renting from the local authority ☐2
- renting privately ☐3
- other (please give details)_____ ☐4

office use ☐

		Yes	No
23.4	Do you have a car available for use in your household ?	☐	☐

23.5 Please state the age at which your full time education ended _____

23.6 At present are you

- retired ☐
- employed, full time ☐
- employed, part time ☐
- unemployed, seeking work ☐
- unemployed, not seeking work ☐

23.7 If you are **retired**, is this due to

- normal retiring age ☐
- early retirement, voluntary ☐
- early retirement, compulsory ☐
- illness/disability ☐
- other reasons ☐

Please give the year in which you retired 19 _____

If you are **unemployed**, is this due to

- redundancy ☐1
- illness/disability ☐2
- other reasons ☐3

23.8 What type of financial support do you have or will you have on retirement ?

- state pension only ☐
- occupational pension, fixed amount ☐
- occupational pension, index linked ☐
- private pension ☐

APPENDIX IX Postal questionnaire in 1992

Selected question used in this thesis on father's occupation and childhood amenities:

Employment continued

21.4 What job have you done for the longest period of time?

office use

21.6 Would you describe this work as

Manual ☐ 1
Non-manual ☐ 2

21.5 What job did you father do for the longest period of his working life?

office use

21.6 Would you describe this work as

Manual ☐ 1
Non-manual ☐ 2

22.0 *When you were a child (up to 10 years old)*

		Yes	No
22.1	Did you have a bathroom in your house?	☐	☐
22.2	Did you have a hot water tap in the house?	☐	☐
22.3	Did you share a bedroom with brothers or sisters?	☐	☐
22.4	Did your family own a car?	☐	☐

23.0 *At present*

		Yes	No
23.1	Do you have access to a telephone in your house?	☐	☐
23.2	Have you made a personal phone call in the last week?	☐	☐
23.3	Have you written a personal letter in the last week?	☐	☐
23.4	Do you take a weekly or monthly magazine or journal?	☐	☐
23.5	Do you attend religious services or meetings?	☐	☐
23.6	Did you vote in the last general or local elections?	☐	☐
23.7	Have you been on holiday in the last year?	☐	☐
23.8	Are you planning to go on holiday next year?	☐	☐
23.9	Do you use the public library?	☐	☐
23.10	Are you a member of any club, society or group?	☐	☐
23.11	If YES, In the past month have you attended a meeting of a club, society or group?	☐	☐

Thank you for you help

All your answers will be treated in complete confidence and will not be identifiable. Please you would check that you have answered all the questions you can, and then return the form in the envelope provided, NO STAMP IS NEEDED.

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