CARDIOVASCULAR HEALTH IN ADVANCED AGE

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ABSTRACT

New Zealand's population is ageing. Cardiovascular disease (CVD) may account for 53% of death in people aged 85+. Nevertheless, little is known about the cardiovascular health status of those in advanced age.

The aim of the study is to assess cardiovascular health and examine the relationships between cardiovascular risk factors and presence of clinically manifest CVD in people of advanced age.

This thesis reports a cross-sectional study of 108 participants aged 85 years (75-79 for Māori) from three locations (urban and rural) in New Zealand. Demography, medical history, nutritional risk and physical activity levels were established by interview. Height, weight, blood pressure, body composition, ultrasound of the carotid intima-media thickness (CIMT) and echocardiography were completed. Fasting blood samples were collected.

Two-thirds of the sample (n=72) had clinically manifest CVD. The level of physical activity measured by the PASE scale was inversely associated with CVD [OR (95% CI): 0.990 (0.982–0.999), p=0.028] controlling for sex, age-ethnicity, and smoking status.

High-density lipoprotein level was inversely associated with CVD after adjusting for sex, age-ethnicity, smoking status and waist circumference [OR (95% CI): 0.291 (0.086–0.986), p=0.047]. The study did not find an association between inflammatory markers and CVD. One-quarter of the sample has increased CIMT (≥1.206mm). Almost all of the participants (94%) had abnormal echocardiographic measures: 38% had left ventricular (LV) hypertrophy; 68% had enlarged left atrial area; and 5% had abnormal LV systolic function. The echocardiography results suggest that subclinical CVD may be prevalent among the very old.

Findings from this study have to be interpreted with caution due to the cross-sectional nature of the study and the small sample size. However, this thesis forms the basis for ongoing longitudinal study and these results suggest that, in contrast to those in middle age, HDL appear to be more closely related to CVD than LDL.

In this sample of those in advanced age, two-thirds have CVD. Level of physical activity and HDL concentration seems to be important risk factors associated with CVD. Larger prospective

studies are needed to confirm these results. The clinical significance of increased CIMT and abnormalities of echocardiographic measures need to be determined in longitudinal studies.

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25-OH D	25-hydroxyvitamin D
aCVD	Atherosclerotic cardiovascular disease
AS	Aortic stenosis
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BF%	Body fat percentage
BMI	Body mass index
BNP	Brain natriuretic peptide
BP	Blood pressure
CABG	Coronary artery bypass surgery
CAD	Coronary artery disease
CHD	Coronary heart disease
CHF	Congestive heart failure
CI	Confidence interval
CIMT	Carotid intima-medial thickness
CRP	C-reactive protein
CV	Cardiovascular
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DEXA	Dual energy x-ray absorptiometry
DM	Diabetes mellitus
ECG	Electrocardiogram
E/E'	Ratio of mitral E velocity to mitral annular E velocity
ESR	Erythrocyte sedimentation rate
FM	Fat mass
FS	Fractional shortening
GDP	Gross Domestic Product
HDL	High-density lipoprotein
HF	Heart failure
HTN	Hypertension
HR	Hazard ratio
ICD-9	International Classification of Disease, Ninth Revision
IHD	Ischemic heart disease
IL	Interleukin
IL-6	Interleukin-6
IQR	Interquartile range
LDL	Low-density lipoprotein
LV	Left ventricular / Left ventricle
LVID	Internal diameter of the left ventricle
LVM	Left ventricular mass
Max	Maximum
Min	Minimum
MR	Mitral regurgitation
N or n	Number
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association

NZHF	New Zealand Heart Foundation
NZHIS	New Zealand Health Information System
PAI-1	Plasminogen activator inhibitor-1
PASE	Physical Activity Scale for the Elderly
PCI	Percutaneous coronary intervention
PLP	Pyridoxal 5' phosphate (vitamin B_6)
PWT	Posterior wall thickness
RA	Rheumatoid arthritis
RR	Relative risk
SBP	Systolic blood pressure
SCREEN II	Seniors in the community: risk evaluation for eating and nutrition, version II
TC	Total cholesterol
TG	Triglycerides
TNF-α	Tumour necrosis factor-alpha
SD	Standard deviation
SWT	Septal wall thickness
WAT	White adipose tissues
WC	Waist circumference
WHO	World Health Organisation
WHR	Waist-to-hip ratio

PUBLICATION

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CHAPTER ONE: INTRODUCTION

1.1 Background

The world's population is ageing. In 2005, 10% of the world's population was aged 60 years and above. This figure is expected to double over the next 45 years, reaching 22% in 2050 (i.e. 2 billion elderly persons over 60 years). According to the United Nations, the number and proportion of persons aged 80 years and above is the fastest growing segment of the world population. (1) In New Zealand, those aged 85 years and above (also known as people of advanced age) made up 1.3% of the 2004 total population. (2) It is projected that in 2051, people of advanced age will represent 6.4% of New Zealand's total population. In other words, between 2004 and 2051, there will be a 507% increase in the population of those living to advanced age (Figure 1-1). (3)

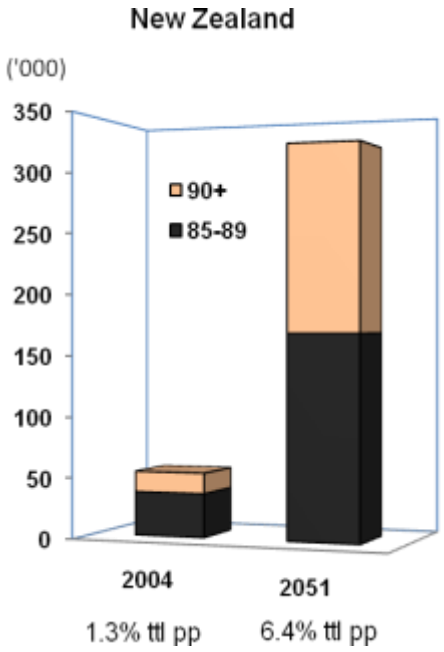


Figure 1-1: Population growth of those aged 85+ between 2004 and 2051
Abbreviations: **ttl pp:** total population

The ageing population is not an urgent crisis but if the health and welfare sectors are not prepared, its effects will be profound. The biennial report from the Paris-based Organisation for Economic Co-operation and Development (OECD) identified a trio of problems facing the New Zealand government's financial accounts; the ageing population was one of them. One implication of the ageing population is a higher healthcare (and superannuation) cost. The projected spending will add an additional 8.2% to the GDP by mid 21st century, a growth that is faster than in the OECD as a whole. (4) In 2004, the percentage of those in advanced age (1.3%) consumed 10% of the

Vote Health Expenditure for health and disability support services. (2) The Ministry of Health projects that this age group will consume 15% of the Vote Health Expenditure for health and disability support services in 2021. (5)

Cardiovascular disease (CVD) is the leading cause of death and disability in developed countries, including New Zealand. (6-8) CVD prevalence increases with age. In the United States of America, the average age of an American having first angioplasty and coronary artery bypass surgery (CABG) is 63 and 65 years old, respectively. (9) In New Zealand, the average age of a Māori and NZ European having their first stroke is 61 and 76 years old, respectively. (10) It was estimated that between 2001 and 2003, 53% of deaths in those of advanced age was attributable to CVD. (3)

The burden of disease and years lost to disability in relation to CVD is substantial. (7) Ischemic heart disease (IHD) accounted for 40% of all hospitalisations for CVD, and the hospitalisation rate for IHD increased exponentially from age 45 onward. (7) Adults aged 75 years and above have the highest rate of hospital admissions related to heart failure (HF), taking up to two-thirds of all bed-days. (11) Additionally, the length of hospital stays increased with age. (11) Stroke is a major cause of severe disability, accounting for approximately 5% of the burden of severe disability and 3% of the burden of all dependent disability in the adult population. (7)

The cost related to CVD in older adults is mirrored in expenditure on health and disability support services. The per capita health expenditure for men and women increased from $4,224 and $3,647 for those aged between 65 and 74 years to $13,467 and $15,158 for those aged 85+. (5) A substantial proportion of total health expenditure is devoted to CVD. In the early 1990's it was estimated that the direct cost of coronary heart disease (CHD) and stroke amounted to NZ$179 million and NZ$93 million per annum, respectively. These figures are not inclusive of indirect and intangible costs. (12, 13)

Cardiovascular health tends to deteriorate with ageing. With ageing, the percentage of individuals with no risk factors decreases, from over 80% in young adults to practically zero in the very old (90+ years). (14) Age is the common denominator in assessing CVD risk profile.

Findings from the Framingham Heart Study identified - besides age - male sex, cigarette smoking, hypertension, type 2 diabetes, obesity, total cholesterol, HDL and LDL as conventional

risk factors associated with CVD morbidity and mortality. All these risk factors, except for age and sex, are closely related to lifestyle behaviour. Prospective studies found conventional CV risk factors do not always present in patients with CHD. (15, 16) In the Women's Health Study of more than 27,900 participants with an average age of 55 years, 77% of first CV events occurred among women with LDL levels below 4.1 mmol/L and 46% occurred among those with LDL levels below 3.4 mmol/L. (17) This epidemiological evidence indicates that there are other variables responsible for CVD beyond the conventional risk factors.

Atherosclerosis was understood as a lipid storage problem. With the progress in medical science, we now understand better the mechanism responsible for the atherosclerotic process. The inflammatory response was identified as an important process which involved from the inception of atherosclerosis to the clinical manifestation of CVD. (18, 19)

In the Women's Health Study (mentioned above), irrespective of LDL levels, increasing C-reactive protein (CRP) levels were associated with increased risks of CV events. (17) CRP is one of the inflammatory markers produced during the acute phase of the inflammation response. Many studies have been carried out investigating the relationships between inflammatory markers (e.g. tumour necrosis factor-alpha, interleukin-6, fibrinogen and erythrocyte sedimentation rate) and CVD risk.

One of the mechanisms between inflammatory markers and CVD risk is related to the thickness of the artery wall. Intima-media thickness, the distance between the lumen-intima interface and the media-adventitia interface (20), is an indicator of the total atherosclerotic burden. (21) The probable consequence of increased atherosclerotic burden is CHD. CHD is the underlying cause of heart failure. Left ventricular dysfunction, which is closely related to left ventricular structure, is likely to precede heart failure. Therefore, the role of the inflammatory response, through the development of atherosclerosis, is linked to the clinical manifestation of CVD.

Ageing leads to physiological changes. Lifestyle behaviour in old age may relate differently to CV risk factors than in younger age groups. Inadequate dietary intake in older adults may be a more pressing concern than overeating. The benefit of physical activity may be more important for CV health in people of advanced age than in younger age groups.

Individuals who live past the average life expectancy may have differing risk factor profiles for initial and recurrent CVD. Increased body weight is associated with CVD risk. Generally, the linear incremental increase in body weight in every decade plateaus at about 75 years, and then weights decline. (22, 23) Similarly, total cholesterol increases with age up to 65 years, and then cholesterol begins to decline. (24-27) Risk of CVD continues to increase with age despite this fall in body weight and cholesterol levels. In older men (age between 73 and 94 years, mean age 78 year), Framingham risk score does not predict all-cause and CVD mortality. (28) Conventional CV risk factors in the Framingham risk score did not accurately predict CVD mortality in people aged 85 years with no CVD history. (29) Inflammatory markers increase with age (30-32), and a linear relationship with CVD seems to persist into advanced old age. (33-36) Hence, inflammatory markers may be of greater significance to CVD for those living to advanced age. Cumulative exposure to CV risk factors and ageing of the cardiomyocytes most likely suggests that those living to advanced age will likely to have had greater atherosclerotic burden and remodelling of the left ventricle taken place. Atherosclerosis and structural changes of the left ventricles are associated with impaired heart function. Intima-media thickness and left ventricular structure and function (determined by echocardiography) may provide better predictive values for CVD risk in advanced age.

Little is known about the cardiovascular health status in the very old. Most studies, abroad or in New Zealand, involve few people in advanced age. This study aims to determine the cardiovascular health status and CV risk factors, and to investigate the relationship between CV risk factors and CVD in advanced age. Findings from this study will extend the existing New Zealand and international evidence on CVD beyond that available for those up to 75 years old. This extension of evidence into advanced age will assist in the development of an intervention programme to improve CVD outcomes in those living to advanced age.

1.2 Structure of the thesis

This thesis is divided into ten chapters: introduction, literature review, methods, pilot study, response rate and demographic, nutritional risk and physical activity, cardiovascular risk factors, carotid intima-media thickness and echocardiographic measures, associations between CVD and cardiovascular risk factors and, lastly, the conclusions.

The introductory chapter (Chapter One) has presented the study background. The comprehensive literature review (Chapter Two) sets the thesis within the wider context of what is known in literature about conventional and emerging cardiovascular risk factors from the young to the elderly population. The existing biomedical evidence and the possible interactions between lifestyle factors and CV risk factors impacting CV health in advanced age is conceptualised, and the study rationale is presented in the last section of Chapter Two. The methods chapter (Chapter Three) specifies study objectives and details the study design and methods to address the study objectives. The pilot study chapter (Chapter Four) reports the feasibility of recruitment and data collection procedures set out in the methods chapter. The thesis presents results in five chapters followed by discussion: Chapters Five (response rate and demographic); Six (nutritional risk and physical activity); Seven (cardiovascular risk factors); Eight (carotid intima media-thickness and echocardiographic measures); and Nine (associations between CVD and cardiovascular risk factors). Key findings and implications from this study are brought together in Chapter Ten.

CHAPTER TWO: LITERATURE REVIEW

This chapter aims to review the existing literature on cardiovascular disease (CVD) and its risk factors from young to the older population. As most of the cardiovascular (CV) risk factors are closely linked to lifestyle behaviour, this chapter will firstly present nutritional risk and physical activity relating to cardiovascular health. This is followed by conventional CV risk factors and inflammatory markers. The impact of these risk factors is then linked to the changes in the carotid arteries (thickening of the artery wall) and changes in the left ventricular (LV) structure and function. The chapter will conclude with an overview of the pathways for CVD and rationale for future investigations.

Literature reviews were completed on every aspect of CVD and risk factors. These literature searches were performed using Medline, Journals@Ovid Full Text, Cochrane Database of Systematic Reviews, and Google Scholar. News articles pertaining to the CV health in the general and older population, and in relation to nutrition and physical health and well-being from the media websites, e.g. International Herald Tribune, BBC, CNN, Yahoo!News, and Senior Journal were referenced back to the source article for detailed information. E-mail alerts were subscribed for updated research findings. Initial searches were limited to review articles published from year 2000 onwards. References cited in the articles were explored for additional studies. For longitudinal studies, searches for earlier publications were done to gain insight into the background and baseline information, e.g. study design and characteristic of study samples. The searches were carried out using the following subject headings and combinations: *cardiovascular disease, cardiovascular risk factors, aged, nutritional status, nutritional risk, malnutrition, physical activity, exercise, diabetes, serum glucose, hypertension, blood pressure, body composition, obesity, vitamins, antioxidants, inflammatory markers, carotid intima-media thickness, natriuretic peptides, and left ventricular mass/structure/function*. Updated statistical information on the older populations and mortality or morbidity attributed to CVD was obtained from New Zealand and relevant international websites: World Health Organisation http://www.who.int; New Zealand Ministry of Health http://www.moh.govt.nz; New Zealand Guideline Group http://www.nzgg.org.nz; Statistics New Zealand http://www.stats.govt.nz.

2.1 The ageing population and cardiovascular disease

The world's population is ageing, particularly in developed countries. Among the developed countries, it was projected that France, Germany, United Kingdom and Japan will have more than 5% of the population age 80 years and above in 2020. (37) In New Zealand, this age group will make up 3.5% of the New Zealand population. (37) This indicates the New Zealand population may be less old than expected compared to other developed countries. There are two possible reasons for this observation. First, the smaller proportion of those 80 years and above in the New Zealand population may be due to a higher net migration rate in New Zealand in recent decades (2.46 migrants/1,000 population, 2009 estimate) than France (1.48), Germany (2.19), United Kingdom (2.16) (38) and Japan (0 migrant/1000 population, 2011 estimate). (39) Another reason that the New Zealand population may be not as old as it would otherwise be is the effects of an earlier influx of younger people into Europe than New Zealand, who are now experiencing rapid ageing. Despite a less old population compare to other developed countries, the New Zealand population is ageing.

In New Zealand, between 1950-52 and 2004-06, life expectancy at age 65 increased from 12.8 years to 17.8 years for men and 14.8 to 20.5 years for women. (3) In other words, the population is ageing, more so among the older population. In 1951, 3.9% of the New Zealand population aged 65 years and above were people aged 85 years or more. This proportion rose to 11.7% in 2006 and is projected to increase to 24% in 2051. In absolute figures, there were 53,100 people aged 85 years or above in 2004 and this number is projected to be 322,400 in 2051, i.e. an increase of 507%. (3)

Despite longer life expectancy, an 85-year-old man is expected to spend 24% of his total life expectancy with moderate mobility limitation; this figure is 13.4% when applied to a woman. (40) This could partly explain why those aged 85 years or more consume the highest yearly per capita expenditure ($12,144 for men and $13,640 for women). (41) Another contributor to the greater utilisation of national health expenditure at greater age would be ischemic heart disease (IHD), as the rate of IHD increases with age. Cardiovascular diseases contribute the highest percentage of all deaths in New Zealand and stroke is an important cause of severe disability. (7, 42) Heart failure is the most common cause of hospitalisation among the elderly. (11) Older people with heart failure have a poorer prognosis than younger groups with 30-day and 1-year mortality rates of 20% and

40% respectively. (43) In New Zealand, between 2001 and 2003, 53% of deaths in the 85+ age range were attributed to CVD. (3)

2.2 Advanced age

The demographic shift towards an older population implies that health care professionals will encounter more elderly requiring medical attention. While it is projected that the 85+ population will be growing faster than other age groups, epidemiological studies to date consists of a small number of participants aged 85 years and above. Physiological changes occur with ageing. It is uncertain if those in advanced age (85+) have similar or different CV risk factors than those observed in the younger population. Would lifestyle behaviours have a similar or different impact on CV health in advanced age? People of advanced age are also under-represented in clinical trials. (44, 45) Would treatment intervention for the younger population be as efficacious for those in advanced age or will there be a different treatment emphasis for this age group? The following sections will present findings from the literature pertaining to cardiovascular risk factors and their association with CVD from the younger elderly to those living to advanced age.

2.3 Nutritional risk

Nutritional status has a crucial role in cardiovascular (CV) health. Four of the five conventional CV risk factors (diabetes, hypertension, obesity, and dyslipidemia) are related to nutritional status. Overnutrition, leading to obesity, is one of the main risk factors for CVD. Obesity is linked to development of type 2 diabetes (46, 47) and hypertension. (48, 49) Evidence from studies had been consolidated to develop dietary guidelines to combat these risk factors. For example, the American Heart Association has a dietary guideline for sugar intake (50, 51), and the DASH diet (Dietary Approaches to Stop Hypertension) to control hypertension. (52, 53) Depending on the severity of the disease outcome, adults with CVD are encouraged to adhere to therapeutic diets or are put on a dietary restriction. For older adults with CVD, dietary restriction may narrow the variety of food choices leading to an imbalance of dietary intake. Their nutritional status will be affected more considerably if the CVD condition results in impaired physical function, which may affect food procurement, food preparation and food intake, subsequently, predisposing older adults to undernutrition.

Undernutrition is common among the elderly. It proceeds from prolonged exposure to the risk of undernutrition (nutritional risk). The prevalence of undernutrition in hospitalised elderly patients was estimated to range between 14% and 45%. (54) The wide ranges were due to different methods of assessment administered in different studies. While the prevalence of undernutrition in community-living elderly is uncertain, the prevalence of nutritional risk is widespread. It was estimated that 44% of healthy, community-dwelling older people are at nutritional risk. (55, 56) In one study of vulnerable[1] older adults (mean age 79 years old) living in the community, the prevalence of nutritional risk was 69%. (57) In Christchurch, New Zealand, 54% of relatively healthy[2] community-living older adults (mean age 80 years) were at nutritional risk. (58) These studies showed nutritional risk are prevalent among older adults, particularly those with impaired physical function.

Nutritional risk factors in elderly persons encompass physiological changes, health status, psychological, and socioeconomic factors. Physiological changes with ageing impacting dietary intake include: decrease in taste acuity and smell leading to reduced appetite (59, 60); loss of natural teeth and poorly fitted dentures causing chewing difficulties (56, 61); decrease in saliva production with ageing affects the formation of the food bolus (62); dysphagia (61); increase in cytokines levels with ageing (63-65) may have a role in undernutrition as increased cytokines levels (IL-1, IL-6, TNF-α, and serotonin) were found to suppress appetite (61, 66); and changes in gastrointestinal function may lead to malabsorption of certain micronutrients (e.g. vitamin B_{12}, vitamin D, calcium, zinc, magnesium, and iron). (62) Presence of chronic health conditions (whether psychologically or physically, or both) exacerbate the risk of undernutrition. Cognitive impairment, perception of deterioration in health, recent hospitalisation, and functional limitations were found to be important determinants of malnutrition risk among older adults (mean age 74 years) living at home. (67) Depression was shown to be associated with negative effects on eating behaviours and is one of the common causes of nutritional risk. (56, 59, 61) Clinical depression is prevalent among patients with heart failure (68), stroke (69) and myocardial ischemia. (70) Stroke patients suffering from swallowing problems had poorer nutritional status than those with no swallowing problems. (71) In addition, heart failure patients may have reduced physical function

[1] This Canadian study defined vulnerable older adults (n=367) as those who may be at increased risk for adverse health outcomes who tend to have dependency in daily activities (basic or instrumental activity of daily living, or had mobility/transportation difficulties) (54)

[2] The Christchurch, New Zealand study (n=158) excluded the elderly with dementia, palliative care patients, and those who had already been referred for dietetic intervention or were receiving prescribed protein and energy supplements.

and stroke-related disability is common. (72-75) Reduced physical function or physical disability means accessibility to food (shopping for food, preparing food, or eating meals) is affected. Additionally, sun exposure is the major source of vitamin D in older adults in New Zealand. The level of vitamin D may also be affected by limited outdoor activities among older people. The situation of nutritional risk may be aggravated by socioeconomic factors such as living alone (76, 77) and financial constraint (food insufficiency or limitation of food choices). (78) These factors are likely to present synchronously predisposing older adults to be at nutritional risk.

Indicators of nutritional risk in older adults consists of both clinical (anthropometry and weight) and sub-clinical (nutritional biomarkers) aspects. The initial clinical manifestation of undernutrition is weight loss. (79, 80) In older adults above 65 years old, CVD patients with lower body mass index (BMI) had increased risk of death (81) and had slower recovery from illness and surgery. (82) This relationship of low BMI and adverse health outcomes may be related to reduce energy reserves require for recovery. BMI is an indication of energy reserves. (83) Besides the recovery process, older adults at nutritional risk are likely to have inadequate key nutrients for maintenance of good CV health. BMI is an important clinical indicator of nutritional risk in older adults. However, it is yet to be determined whether nutritional risk indicators (e.g. low BMI) represent ageing factors or do in fact represent undernutrition.

Micronutrients are essential for maintenance of CV health. Plasma vitamin antioxidants are related to CV morbidity and mortality. In the Boston Puerto Rican Healthy Study, a longitudinal study which recruited 1,222 adults aged 45-75 years (mean age 52 years), low vitamin B_6 status, measured as plasma pyridoxal 5'-phosphate (PLP) concentration, was observed to be associated with inflammation (higher C-reactive protein levels, CPR), higher oxidative stress (reflected by a higher concentration of the urinary DNA damage markers) and metabolic conditions (metabolic syndrome, diabetes, or obesity). (84) In the InChianti study, plasma PLP was inversely associated with CRP and interleukin-6 (IL-6) receptors; meaning, low vitamin B_6 was correlated with a pro-inflammatory state. (85) In older adults (mean age 68 years), low vitamin B_6 status was associated with increased risk of stroke and transient ischemic attack (TIA), independent of other CV risk factors, vitamin supplements used, and homocysteine level. (86) Low concentration of plasma vitamin C was associated with low-grade inflammation (87), which in turn is associated with atherosclerosis and stroke. (18, 88-90) The cardioprotective role of vitamin D has been studied

extensively, and studies found that serum 25-hydroxyvitamin D (25-OH D, a measure of vitamin D in serum) was inversely associated with CVD risk and mortality. (91-98) The relationship between low concentrations of serum vitamin and risk of CVD is partly mediated by the inflammatory process.

In addition to vitamins, essential fatty acids are also related to CV health. Regular consumption of fish or fish products provides the essential fatty acids, such as n–3 polyunsaturated fatty acids (PUFAs), which have been found to be cardioprotective. (21) This was evidently observed in Alaskan natives, who had a higher dietary intake of n–3 PUFAs and had lesser fatty streaks and lower raised plaques, than non-natives who had a lower dietary intake of n–3 PUFAs. (99) This may be because fish oil (which contains n–3 PUFAs) improves lipid profile (reducing triglyceride levels and increasing HDL levels). (100) Other proposed mechanisms for the protective role of essential fatty acids include: decreased expression of adhesion molecules, reduced activation of nuclear factor-κβ (a transcription factor that is central to the mechanism of vascular inflammation), inhibition of vascular smooth muscle proliferation, suppression of vascular calcification, down regulation of pro-inflammatory cytokines, and up regulation of anti-inflammatory cytokines. (21, 93) This research area requires further investigation.

Nutritional risk, as mentioned earlier, is prevalent among older adults living in the community. It predicts hospitalisation among adults aged over 65 years. (101) In a prospective cohort study which recruited more than 10,300 British men and women from the General Practice Research Database (mean age 66 years), CVD patients with poor nutritional status were associated with sharply increased risks of hospital admission and increased rates of GP consultation and prescription. (81) This may be because elderly people who are at nutritional risk may have inadequate nutrients and lower energy reserves for recuperation from adverse health conditions. (102) Furthermore, physical function of older adults at nutritional risk is likely to be affected. (82, 103) In a cross-sectional study which recruited 1,010 adults aged 60 years and older, nutritional risk is positively related to activities of the daily living. (79) The directional relationship between nutritional risk and physical function is yet to be determined. Older adults at nutritional risk presumably will have less energy for physical activity as the maintenance of vital organ functions consumes proportionally more energy. (104) Therefore, reduce physical activities and inadequacy

of micronutrients consequences of nutritional risk in older adults may exacerbate the existing CV health conditions.

In short, nutritional risk is common among older adults. It is attributed to physiological changes, interlinked with health status and socioeconomic factors. Nutritional risk can have a profound impact on the cardiovascular health of those in advanced age. Inadequate vitamin antioxidants may: hasten the progression of atherosclerosis, prolong the recovery duration thus increasing medical care, and constrain physical function or physical activity. This chain of relationships may contribute to a downward spiral of CV health. Assessment of nutritional risk in those of advanced age will enable investigation of the impact of nutritional risk on CV health. An understanding of this relationship would offer further opportunity for research in aiming to prevent deterioration of CV health in those of advanced age.

2.4 Physical activity

There is compelling evidence for the benefits of regular physical activity on cardiovascular (CV) health. A sedentary lifestyle is a risk factor for cardiovascular disease (CVD). The beneficial effects of physical activity are observed in asymptomatic men and women as well as those with established CVD. (105) There also appears to be a dose-response relationship between the effect of physical activity and the risk of CVD. (105) Improvements in physical fitness, even in previously inactive people, are associated with a significant reduction in risk of hypertension, type 2 diabetes mellitus, obesity, and dyslipidemia. (105, 106) It is likely through reduction of these risk factors that physically active adults have a reduced risk of premature death. In middle-aged adults, physical activity was associated with a 30-50% reduction in risk of CV mortality. (107, 108) The benefit of physical activity on the CV system continues in septuagenarians who engage in regular exercise. (109-111)

One of the probable mechanisms of the effect of physical activity on cardiovascular health may be related to the effect of physical activity on biomarkers HDL and vitamin D, which both are found to be related to CVD risk (93, 95, 112, 113). In an observational study of 70 adults above age 60 years, those who regularly participate in non-vigorous physical activity (lawn bowls or an exercise class) had significantly higher high-density lipoprotein (HDL) levels than frailer adults who did very low intensity physical activity (slow walking or a range of movement exercises). (111) In the

Longitudinal Aging Study Amsterdam (LASA), serum vitamin D was also found to be positively associated with physical activity levels. (114) These studies unanimously indicate a strong association between physical activity and reduced CVD risk, and the effect is observed into the seventh decade of life. Nevertheless, both the above mentioned studies did not examine the interaction between physical function and physical activity on HDL and vitamin D levels. Older adults with better physical function may perform a higher level of physical activity. The relationship between physical function, physical activity and HDL/Vitamin D levels in the elderly needs further investigation.

In the ageing process, the aerobic capacity (estimated as peak oxygen consumption) declines between 5 and 10% per decade in untrained individuals. (115) It was observed that declining aerobic capacity accompanies the lower level of physical activity observed among older adults. (116-118) Older adults with CVD could be affected to a greater extent than their counterparts without CVD. The clinical consequences of heart failure include dyspnoea, fatigue and exercise intolerance (119); as for stroke, the clinical consequences include neurological disorders (hemiplegia, spasticity, and aphasia). (120) These physical function impairments lead to reduced activity and aerobic capacity. For example, the peak oxygen consumption rate in chronic stroke patients is about half that of age-matched healthy individuals. (121) Therefore, older adults with CVD are more likely to have lower levels of physical activity than their otherwise healthy counterparts. Inability to participate in physical activity creates a vicious circle causing a reduction in CV health status and physical function of older people.

Studies have shown that exercise intervention elicits significant clinical benefits in patients with clinically manifest CVD. (120, 122) In patients with stable coronary artery disease (stenosis of more than 75%) randomised to a two-year regular exercise training versus percutaneous intervention, patients in the exercise training group had a significantly lower rate of CV events than patients who received percutaneous intervention during the 24-month follow-up period. (123) The exercise group also had a significant increase in HDL levels and a significant decrease in inflammatory markers (CRP decreased by 41% and IL-6 decreased by 18%). (123) A review and meta-analysis on the impact of exercise training in patients with heart failure (HF) shows that exercise training improves maximum heart rate, maximum cardiac output, peak oxygen consumption, anaerobic threshold (119, 122), and many vascular and skeletal features, including increasing blood supply to support

skeletal muscle through enhancement of endothelial function and modification of the underlying tissue inflammation. (119) For stroke patients, exercise training improves peak oxygen consumption and workload, improves submaximal exercise blood pressure response, improves sensorimotor function, improves walking performance, improves CV fitness, and increases peak left ventricular ejection fraction and HDL levels, while reducing submaximal energy expenditure, resting heart rate and total serum cholesterol. (120, 124) These effects are likely to reduce the risk of recurrent stroke and CV events. Additionally, a randomised clinical trial shows that exercise programmes (versus control) reduced hospitalisation rates in patients with HF. (125) Take note that the average age of participants in these studies (in the meta-analyses) was 60 years old with a limited number of people in advanced age. (122, 124, 126)

The benefits of physical activity extend beyond CV health in older adults. In the Jerusalem Longitudinal Cohort Study, continuation or initiation of physical activity in older adults aged 70 years and above delayed functional losses and improved survival (127). It may be argued that reverse causality is at work and that physical activity served as a proxy for good health. (127) To address this, the authors further analysed the association between physical activity and survival, eliminating data from early deaths and controlling for comorbidities, functional status and self-rated health status; the significant association remained. This rather convincing finding of the Jerusalem Longitudinal Cohort Study is not without limitation. The study is limited, firstly by the diminishing size of the sample during follow-up, which thus introduced an inherent healthy survivor bias. Secondly, the physical activity questionnaire was not validated and the reliability of the questionnaire was not assessed. The non-specific nature of question about self-reported physical activity would therefore increase the variability in the intensity of physical activity between participants, hence reducing the power of the study to show the effect of physical activity. A validated questionnaire may address this issue. Nonetheless, the study indicates physical activity have a positive impact on physical function of older adults aged 70 years and above.

A probable rationale for physical activity in delaying functional loss is that physical activity can prevent the onset of sarcopenia (loss of muscle mass). (128, 129) The aetiology of sarcopenia is multifactorial; modification of the inflammatory state with ageing is one of the causes. (130) Ageing is accompanied by increased levels of inflammatory markers and is associated with chronic low-grade inflammation. (63-65) Low-grade inflammation is associated with the atherosclerotic process,

leading to increased CVD risk. (18, 88, 131, 132) Older adults with elevated inflammatory markers (CRP, IL-6, and TNF-α) also have increased risk of low muscle strength and muscle mass loss. (133, 134) Given that CVD risk and progression of sarcopenia is linked to inflammation, and physical activity has an anti-inflammatory role (65, 128, 135, 136), the prescription of physical activity to reduce CVD risk and to maintain or improve physical function in older adults is a promising therapeutic intervention.

Research on the effect of exercise in the very old (85 years and above) is sparse. In the Aging and Longevity study in the Sirente Geographic Area (ilSIRENTE study), which recruited 248 octogenarians and followed up for 24 months, it was observed that participants who walk one hour or more per day have a better survival chance than those walking less than one hour per day. (137) The underlying mechanism of the effect of physical activity in octogenarians is likely to be through improvement in aerobic fitness. In another observational study, active octogenarians who maintain regular physical activity (walking at least once a week, every week, eight months a year), were observed to have a higher aerobic capacity and functional capacity than age-matched sedentary elderly people. (138) Introduction of exercise training in healthy and frail octogenarians improved aerobic fitness, albeit the improvement was smaller when compared with middle-aged adults. (139, 140) The small improvement in aerobic fitness in this age group is probably due to the absence of cardiac remodelling, improvement of cardiac function, and improvement in arterial stiffness. (141) Reduced cardiac adaptation means limited capacity of the aged left ventricle to generate greater stroke volume, resulting in a smaller increase in peak cardiac output; cardiac output is a pivotal factor responsible for the increase in peak oxygen consumption. (141) These studies showed physical activity with moderate intensity was associated with improved aerobic fitness in the very old.

In a non-comparative intervention trial with ten healthy non-frail octogenarians, participants underwent a nine-month supervised high-intensity endurance exercise training (3 days a week, an hour a session with an intensity of 83% of peak heart rate). At the end of the intervention, there were improvement in insulin action, a reduction in total cholesterol (-8%) and low-density lipoprotein (-10%), and a significant decrease in fat mass. (140) This study suggests that high-intensity endurance exercise in healthy octogenarians improves not only aerobic fitness but also cardiovascular risk profile. However, this study is limited by the small sample size, has stringent

inclusion criteria and absence of control group. The cardiovascular health benefit of the similar exercise regimen is yet to be determined in a wider group of octogenarians with different physical function. To this point, the benefit of physical activity and cardiovascular health in the very elderly were drawn from observational studies; randomised controlled trials are needed.

Several randomised controlled trials were conducted to determine the influence of exercise on health in frail elderly, with mean age ranges between 78 and 84 years. (142) A review of these randomised controlled trials concluded that there is insufficient evidence to establish exercise benefits on health in frail older adults. (142) The ongoing randomised controlled study–Health Enhancing Strength Training in Nonagenarians (STRONG)[3] (143) will extend the existing evidence on the effect of physical activity intervention in community-dwelling nonagenarians.

Older adults, particularly the very old, experience not only physiological changes but also pathological changes related to disease states. Hence, aerobic fitness is likely to vary greatly among individuals of advanced age. Generally, older adults engage in lower levels of physical activity. Studies have shown the benefit of physical activity on CV health persists into advanced old age. As the beneficial effect of physical activity is dose-dependent, the blend between exercise frequency and intensity to achieve the maximal benefit, while minimising adverse events, in the very old remains under-researched. This is made more difficult with the heterogeneity in the advanced-age population. Furthermore, there is also consideration for different exercise training modalities. Perhaps resistance training may be more suitable for some people of advanced age as it was safer, with fewer orthopaedic complications e.g. joint pain or swelling (particularly in older adults with osteoarthritis), and was not associated with CV events (144) compared to aerobic training. (120) Studies have shown resistance training increased muscle mass. (145, 146) This led to the hypothesis that resistance training may be better for prevention of muscle loss and weakening observed in patients with congestive heart failure (CHF) compared to aerobic training. (119) In stroke patients, resistance training improves muscle strength, motor performance, balance, sensorimotor impairments, and functional ability. (120) Again, it is not certain if the benefits of resistance training can be extrapolated to the very old. There is a need to understand the physiological benefit conferred by physical activity in advanced age.

[3] The aim of the STRONG study is to assess the effectiveness of an eight-week aerobic and strength training programme for improvement of muscle strength, daily functional capacity and quality of life, and the effects of the intervention on physical activity levels and body composition

2.5 Conventional cardiovascular risk factors

"Cardiovascular risk factors" – the term coined by the first director of the Framingham Heart Study, Dr. William Kannel, is a list of factors that predispose an individual to the development of cardiovascular disease (CVD). (147) Since the Framingham Heart Study, a wealth of studies has been conducted, investigating risk factors for CVD. Subsequently, a list of conventional cardiovascular (CV) risk factors was generated. While in-depth understanding progresses on the role of conventional CV risk factors leading to CVD, new risk factors continue to unfold. Thus, the list of CV risk factors continues to grow. This section will discuss the modifiable and non-modifiable conventional CV risk factors and their association with CVD in ageing.

2.5.1 Age, sex and familial history

The non-modifiable risk factors are age, sex, and family history of CVD. In the Framingham risk score for predicting the 10-year absolute risk of a coronary heart disease (CHD) event, a person aged 70-74 years (the maximum age limit in the equation) carried the highest risk score. In studies investigating CV risk factors and CVD within the same study sample, cases (participants with asymptomatic or manifest CVD) are always older than controls (148-150), suggesting CV risk increases with age. Physiological changes that take place during ageing include, but are not limited to, changes in vascular structure and function (151), ageing of the cardiomyocytes (152) and immunosenescence (deterioration of the immune system). (153) Arterial ageing can be attributed to an increase in arterial stiffness and disturbed pressure wave reflection. (151) Changes in the vasculature, especially on the large arteries, affects the heart. (151) Cardiomyocytes undergo complex changes resulting in loss of contractile function and loss of endogenous protection against irreversible injury. (152) Deterioration of the immune function may contribute to the changes in vasculature and cardiac muscle. (153, 154) The CV system changes with normal ageing process.

Men and women carry different CV health profiles. Women below the age of 40 years have a negative risk score, but the risk score increases to be the equivalent of their male counterparts in the middle-aged group and eventually overtakes them in older ages. (155, 156) It is postulated that the endogenous sex hormone explains the different CV risk profiles between men and women. However, rather than a simplistic presumption, advance investigations on gene polymorphism led to the hypothesis that it was the biological effects of XX and XY chromosomes that are expressed

through sex hormones. (157) The issue of endogenous sex hormones and CVD risk remains an open question.

Parental history of CVD is closely related to the CVD risk of a person. Compared to adults with no parental history of myocardial infarction (MI), those with a maternal and paternal history of MI have a greater risk of CVD [relative risk (95% CI) for men: 1.85 (1.56–2.19); women 2.05 (1.51–2.79)]. (158) To date, there are more than 130 genes/gene-groups identified that are possibly related to CVD. (159) The areas of polymorphism investigation include atherosclerosis, hypertension, hyperlipidemia, MI, stroke, and thrombosis. (159) Individually, each polymorphism has a modest influence on the CV risk factor. Simultaneous interactions with other polymorphisms, and importantly the interaction with environmental factors, determine the manner of CVD manifestation.

The effect of age, sex and familial history on CVD will be included in the following sections discussing modifiable risk factors. The modifiable risk factors to be discussed are cigarette smoking, diabetes mellitus, hypertension, general and abdominal obesity, and dyslipidemia, which are important CV risk factors. (160)

2.5.2 Cigarette smoking

Cigarette smoking is the major contributor to cardiovascular disease and premature mortality. The expected years of life lost as a result of premature mortality due to smoking is higher in men than women. (161) Cardiovascular disease (CVD) is one of the leading causes of smoking-attributable expected years of life lost. (161) The average age of smoking attributable CVD death is 69 years for men and 75 years for women. The main CVDs related to cigarette smoking are ischemic heart disease, cerebrovascular disease, aortic aneurysm, and peripheral vascular disease. (162) The adverse effects of cigarette smoking on the cardiovascular system are mediated through increased insulin resistance, unfavourable lipid profiles, increased levels of inflammatory markers, impaired endothelium-dependent vasodilatation, increased arterial stiffness, and increased carotid intima-media thickness. (162-168) (Figure 2-1) These changes in the vessels lead to alteration of the structure and function of the heart (166, 169, 170) and symptoms are then manifested clinically. In short, cigarette smoking predisposes an individual’s vascular and heart cells to hypoxia and disrupts the biochemical equilibrium that leads to substantially increased risk of CVD.

2.5.3 Diabetes mellitus

In the year 2000, it was estimated that 171 million people lived with diabetes and this is projected to increase to 366 million by 2030. (171) Diabetes is associated with substantial morbidity from microvascular (retinopathy, nephropathy and neuropathy) and macrovascular complications (ischemic heart disease, stroke and peripheral vascular disease). Hyperglycaemia leading to the formation of advanced glycation end products was found to be an essential mediator in the pathogenesis of diabetic vasculopathy. (172) In the diabetic condition, binding of monocytes to vascular smooth muscle cells is enhanced, and subsequently, retentions of the monocyte in the subendothelial. This leads to accelerated monocyte differentiation which is associated with foam cell formation in the pathology of atherosclerosis. (172) Diabetes is a disproportionately expensive disease and has the greatest impact on cardiovascular event risk. (173, 174) Nevertheless, as many as one in every five older adults are unaware they have the disease. (175)

Pathogenesis of diabetes can be approached from two aspects – modifiable and non-modifiable factors. The non-modifiable factors are age and an inherited genetically linked risk. The onset age of type 2 diabetes is commonly 40 years and above (174), and by 75 years old, 20% of the population will have developed diabetes. (176) The higher prevalence of diabetes in certain ethnic groups implies that genetic factors play an important role. For example, the prevalence of diabetes in Native Hawaiian adults over 50 years old was more than twice that of the general population aged 50 to 59 years old, i.e. 40% vs. 13% for men and 36% vs. 12% for women. (176, 177) In twins, siblings of the affected patient have a higher chance of developing diabetes. (178) With regards to modifiable factors, lifestyle habits such as excessive consumption of food high in refined carbohydrate and saturated fat, coupled with physical inactivity, predispose a person to diabetes. (179) Adults who are inactive have a 52% increased likelihood of having diabetes compared to active adults, and this association is independent of BMI. (47) The Cardiovascular Health Study found that older adults with an average age of 73 years (range 65–98 years) who engaged in moderate physical activity in addition to a good dietary habit had a 46% lower incidence of diabetes. (180) The inter-relationships between a dietary habits and physical activity could synergistically predispose or prevent one from developing type 2 diabetes.

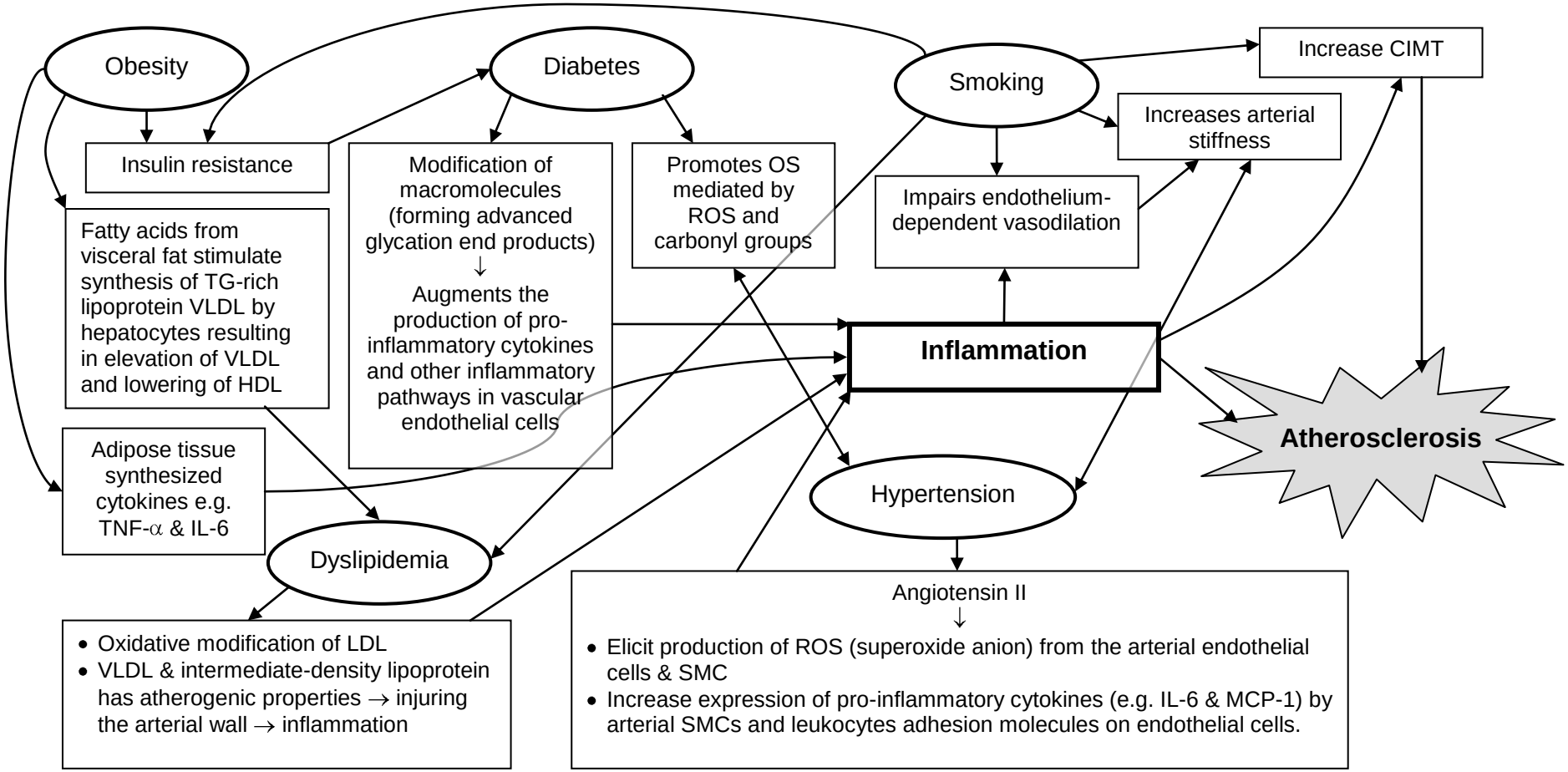


Figure 2-1: Pathophysiological pathways of atherosclerosis
(Adapted from references 89, 162, 181, 182)
Abbreviation: **CIMT**: carotid intima-media thickness; **HDL**: high-density lipoprotein; **IL-6**: interleukin-6; **LDL**: low density lipoprotein; **MCP-1**: monocyte chemoattractant protein-1; **OS**: oxidative stress; **ROS**: reactive oxygen species; **SMC**: smooth muscle cells; **TG**: triglycerides; **TNF-α**: tumour necrosis factor-alpha; **VLDL**: very low density lipoprotein

Individuals with diabetes have a markedly increased risk of atherosclerotic vascular disease and cardiovascular events. They not only have a two- to four-fold increased risk of developing peripheral artery disease (PAD) compared with their non-diabetic counterparts, they also develop a more severe disease and the disease progresses more aggressively. (183) In a population-based retrospective cohort study consisting of 379,000 adults with diabetes and 9,018,000 adults without diabetes living in Ontario, Canada, the study showed that diabetes was associated with an earlier manifestation of CVD, i.e. diabetic men and women were about 15 years younger than those without diabetes in the same Framingham risk algorithm category. (184) In addition, young adults with diabetes have 12 to 40 times higher rates of coronary heart disease (CHD) than those without diabetes. (184) In the Strong Heart Study, a population-based longitudinal study with 4,550 study participants aged between 45 and 75 years old[4] followed up for 12 years, individuals with diabetes had a 2.9 hazard ratio of CVD than those without diabetes. The hazard ratio increased to 3.7 if a diabetic participant had prehypertension. (185) In a group of nearly three thousand Danish men aged between 53 and 75 years old (mean age 63 years), followed up for 16 years, the study found that, irrespective of BMI, those with type 2 diabetes had a two-fold higher risk of all-cause mortality than men without diabetes. (186) Similar trends were observed in older adults with diabetes. In the Cardiovascular Health Study, a prospective community-based observational study of 5,888 participants ≥65 years (mean age 73 years), patients with diabetes had a relative risk of 1.74 (95% CI 1.38–2.19) for developing CHF over a median follow-up of 6.3 years. (34) From the Diva[5] study, patients with diabetes (and aged ≥85 years) were the independent determinants for case fatality at day-30 for both stroke and acute MI. (187) These studies, although carried out in different ethnic groups, are in agreement that diabetic patients develop CVD at a younger age, and have a higher risk of CVD and all-cause mortality than their counterparts without diabetes.

In addition to diabetes, which confers significant risk for CVD, increased fasting serum glucose in non-diabetic individuals also increases CVD risk. (188, 189) For increment of fasting serum glucose between 0.6mmol/L (10mg/dL) and 1mmol/L, the risk of heart failure increases between 8–14%. (190, 191) The impact of hyperglycaemia is sex-specific. The DECODE (Diabetes

[4] The Strong Heart Study is a cohort study of CVD in 13 American Indian tribes. The mean age was 54 years old for participants without diabetes and 56 years for participants with diabetes.

[5] The Dijon Vascular project (Diva) was based on the Dijon Stroke Registry and the registry of myocardial infarction of Dijon and Côte d'Or. The study population was 151,846 Dijon, France inhabitants. The city has less than 5% migration and 15% of the population aged 65 years or older.

Epidemiology: Collaborative analysis of Diagnostic criteria in Europe) study consists of 14 prospective European cohorts with 17,579 non-diabetic men and women aged 30 to 89 years with a median follow-up of 8.3 years. The DECODE study found the hazard ratios for CVD and all-cause mortality increased in both men and women with impaired glucose regulation[6], but the increased risk was higher in men than in women (hazard ratios for CVD mortality, men/women: 3.47 vs. 1.33; hazard ratios for all-cause mortality, men/women: 2.34 vs. 1.31). For newly-diagnosed diabetic participants, women had higher hazard ratios for CVD and all-cause mortality compared to diabetic men. (188) Hence, early intervention is warranted for individuals with hyperglycaemia to avert CVD.

Pharmacotherapy is commonly prescribed to improve glycaemic control in those with diabetes. This intervention aims to reduce CVD risk. Nevertheless, it remains to be confirmed that lowering serum glucose with pharmacological treatment will reduce CVD risk. (192) In the United Kingdom Prospective Diabetes Study (UKPDS), over a 10-year period, the difference in HbA1c concentration between those receiving intensive treatment (with sulphonlureas or insulin) and those on a diet (low-fat, high-carbohydrate, and high-fibre) was only 0.9%. Additionally, those in the intensive treatment group had more hypoglycaemic episodes than those in the diet group. (193) Hence, the UKPDS investigators suggested the concept of polypharmacy for treatment of type 2 diabetes to maximise efficacy and minimise side effects. (194) This regimen may be applicable in younger adults, but may not be appropriate for older adults because glycaemic control in older individuals is possibly multifaceted, depending on other factors including comorbidities and polypharmacy. (179) In view of this, the strategy may be to treat other cardiovascular risk factors. (179, 195) By and large, lifestyle improvement is the cornerstone of diabetes management. (192) Lifestyle intervention proven effective in younger adults needs to be tailored according to the needs of the very elderly. Dietary intervention that results in weight loss, found to improve glycaemic control in younger adults (196), may not be suitable for older persons as higher BMI was found to be a protective factor for all-cause mortality in older adults. (197) In short, glycaemia control in advanced age needs to be approached in a holistic manner.

These population-based studies collectively showed a positive association between diabetes and CVD. Nevertheless, these studies have limited numbers of older adults. (47, 184, 187, 188) The Cardiovascular Health Study is the first population-based longitudinal study of coronary heart

[6] DECODE study defined impaired glucose regulation as fasting plasma glucose 6.1– 6.99mmol/L and/or 2-hour plasma-glucose 7.8–11.02mmol/L

disease and stroke which recruited adults aged 65 years and older. The CHS found the relationships between lifestyle factors (participation in physical activity and good dietary habit), diabetes and CVD in older adults with an average age of 73 years were the same as those observed in the younger population-based studies. (34, 180) It is uncertain whether such relationships persist into advanced age. Assuming adults with diabetes would have premature mortality, we should ask 'what would be the prevalence of diabetes in people of advanced age?' What is the prognosis for people of advanced age with diabetes? The role of diabetes in CVD in people of advanced age has not been studied in sufficient detail to allow extrapolation of management strategies to those in advanced age with confidence.

2.5.4 Hypertension

Elevated blood pressure had been identified as the major cardiovascular (CV) risk factor. It affects 25-30% of the adult population and up to 60-70% of those beyond the seventh decade of life. (198) Epidemiological data showed that CV risk increases incrementally with blood pressure across all age groups in both men and women. Hypertension predisposes to clinical manifestation of coronary heart disease (CHD) and the chief hazard is stroke. (199) The complication of hypertension is ethnic- and age-specific, to some extent. Hypertensive middle-aged Europeans and Americans were predisposed to CHD, whereas in Asians and older individuals it is stroke. (198, 200)

Age and baseline blood pressure (BP) are closely related to the progression of hypertension. (48) In the Framingham Heart Study, compared to younger participants (35–64 years), older individuals (65–94 years) were twice as likely to become hypertensive on a 4-year follow-up. (48) Older individuals with high-normal BP[7] at baseline have the highest annual incidence rate of hypertension (16%); the lowest was in younger individuals with optimum BP[8] with an annual incidence rate of two-percent. (48) The age-related pattern of the effect of blood pressure on the cardiovascular system has been demonstrated by the Framingham Heart Study. (198) Under 50 years of age, diastolic BP was a strong predictor of CVD; age 50-59 years was a transition period where all three blood pressure indices (diastolic, systolic and pulse pressure) demonstrate similar

[7] According to the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, high-normal BP is defined as systolic BP 130–139mmHg or diastolic BP 85–89mmHg (201)
[8] According to the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, optimum BP is defined as SBP <120mmHg or DBP <80mmHg (201)

predictive values; and in those 60 years and above, pulse pressure became a superior predictor to systolic BP. (198) Three hemodynamic phases involved in the increase of blood pressure with age has been postulated. The increased vascular resistance was the main basis for a progressive rise in diastolic BP up to the age of 50 years. In the fifth decade, vascular resistance and large artery stiffness increased in parallel. From 60 years onwards, large artery stiffness is the key feature for hypertension. (202)

The risk of CVD increased incrementally with blood pressure, but pre-hypertension[9] alone was not a significant risk factor for CVD mortality. (203, 204) Weight gained/obesity is the main risk factor for progression to hypertension. In the Framingham study, a 5% weight gain during a four-year follow-up was associated with 20-30% increased likelihood of developing hypertension. (48) Similarly, the prospective study among middle-aged Japanese men found BMI to be an independent marker in predicting development of hypertension from pre-hypertension. (205) High BMI, together with diabetes, predisposed individuals with normal blood pressure (SBP 120–139mmHg or DBP 80–89mmHg) with pre-existing CVD[10] to a greater risk of CVD mortality. (185, 204, 206) Individuals with pre-hypertension and CVD have a nine-fold increased risk of CVD mortality [HR (95% CI): 9.3 (3.3–25.9)] than those with either pre-hypertensive or pre-existing CVD alone. (204) From a large health maintenance organisation with more than 57,500 patients aged 35 and above, hypertensive patients with comorbid diabetes have the highest relative risk of CV events over a six-year follow-up than those with BMI>30kg/m^2 [RR=1.00 (0.92–1.08)] or hyperlipidemia alone [RR=1.21 (1.10–1.32)]. (173) Findings from this study were obtained from a single health plan that provides prepaid health coverage. The regression models for this study controlled only for age, sex, and smoking status; family history of CVD and socioeconomic status, which are known to be closely related to CVD risk, were not adjusted for. (TABLE 2-1, page 28) These prospective studies showed that the presence of other CV risk factors magnified the impact of elevated BP on the risk of CVD.

Chronic low-grade inflammation has been recently identified as the hallmark of hypertension. (135) (Figure 2-1, page 20) C-reactive protein (CRP, an inflammatory marker) was found to be consistently positively associated with elevated blood pressure. Growing numbers of inflammatory

[9] Pre-hypertension is defined as SBP 120–139 mmHg ore DBP 80–89 mm Hg. According to the Seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC VII report (203)

[10] Pre-existing CVD included personal history of coronary artery disease or cerebrovascular accident

markers (e.g. cytokines) and vascular markers (endothelial cellular adhesion molecules) were discovered to be associated with hypertension. Nevertheless, the mechanism linking inflammation to hypertension is not well defined. In a study determining arterial stiffness in patients with chronic inflammatory diseases (systemic lupus erythematosus and rheumatoid arthritis), CRP is associated with arterial stiffness in patients, compared to healthy study participants. (131) Arterial stiffness disproportionately increases systolic blood pressure, thus causing increased pulse pressure and isolated systolic hypertension. (199) Bridging these two findings suggests CRP is associated with hypertension through the underlying vascular changes. CRP has been found to show a graded and continuous association with blood pressure (207, 208) (TABLE 2-1, page 28) and elevated CRP in normotensive individuals is a predictor of hypertension. (208, 209) Epidemiological studies showed that inflammatory markers are elevated with increasing blood pressure. (181) In brief, studies showed that elevated levels of inflammatory markers are linked to increased blood pressure. It is yet to be determined whether elevated inflammatory markers are a risk factor for, or marker of, hypertension.

Clinical trials on hypertension treatment often comprised only a small proportion of the very elderly (210) as they are often frail and have other diseases. (211) In a meta-analysis consisting only of octogenarians (13% of the overall population) from seven clinical trials comparing active drug therapy versus placebo versus no treatment, antihypertensive therapy was associated with lower rates of stroke (34%), heart failure (39%) and major CV events (22%). (44) Nonetheless, blood pressure management in the elderly can be more recalcitrant than in the younger population. Orthostatic hypotension becomes increasingly prevalent in older individuals and is a risk factor for falls. (202) Isolated systolic hypertension (ISH), which accounts for 65% of hypertension in the elderly (212), is associated with an increased risk of incident heart failure [HR (95% CI): 1.26 (1.04–1.51)]. (213) Yet Goodwin pointed out that two population studies (the Tempere Study and the Leiden 85+ Study) with the majority of study participants aged 85 years and older, showed those with increased systolic BP have better chances of survival than those with normal systolic BP. (214) So, would antihypertensive treatment benefit or impair the CV health of the elderly?

The Systolic Hypertension in the Elderly Program (SHEP) is the first double-blind randomised trial to test the efficacy of antihypertensive drug treatment[11] on clinical endpoints for persons with isolated systolic hypertension (SBP between 160 and 219mmHg and DBP<90mmHg). (215) (TABLE 2-2, page 30) The study reported that the 5-year incidence of stroke was 5.2 per 100 participants for active treatment and 8.2 per 100 for placebo. Adverse effects (such as chest pain or heaviness, trouble with memory or concentration, change in bowel habits, cold or numb hands, unusual joint pain etc) were greater in the active treatment group than in the placebo group. Findings from the SHEP study indicate treatment of ISH decreases morbidity and disability in adults aged 60 and above. However, it is uncertain if similar treatment efficacy can be extrapolated to adults 80 years and above since only 14% (n=648) of the SHEP study sample was of this age group. (215)

The HYpertension in the Very Elderly Trial (HYVET), the largest randomised, double-blind placebo-controlled trial in hypertensive patients aged 80 years and above had more than 3,800 participants. The HYVET study found, compared to the placebo group, that participants treated with idapamide 1.5mg ± perindopril 2–4mg had a significantly reduced risk of CVD and all-cause mortality. (202) (TABLE 2-2, page 30) This study would have a profound implication on the management of blood pressure in the very elderly who are considered "healthy"[12] but would similar results be observed in community-living people of advanced age?

In summary, it is not uncommon for a hypertensive individual to have increased abdominal adiposity, dyslipidemia and elevated blood glucose (199); which are closely related to lifestyle behaviour. Both the Joint National Committee VII report and the World Health Organisation/International Society of Hypertension guidelines unanimously advocate lifestyle modifications for the treatment of all hypertensive patients. (203, 216) Exercise, a part of lifestyle modification, is a well accepted as an effective antihypertensive treatment. Exercise interventions in hypertensive patients leads to a reduction in blood pressure in a dose-dependent manner. (217) Edwards *et al*. suggest exercise and diet interventions is perhaps more effective in reducing

[11] All participants were given a once-daily dose of either active drug treatment (chlorthalidone 12.5mg/d or matching placebo (step 1 medication). Drug dosage was doubles (including matching placebo) for participants failing to achieve the SBP goal at follow-up visit. If the ASP goal was not reached at the maximal dose of step 1 medication, atenolol 25mg/d, or matching placebo was added as the usual step 2 drug.

[12] Exclusion criteria for HYVET: Known accelerated hypertension; congestive heart failure requiring treatment with a diuretic or ACE inhibitor; renal failure (serum creatinine >150μmol/L); documented cerebral or subarachnoid haemorrhage in the past six months; condition expected to severely limit survival; known secondary hypertension (i.e. renal artery stenosis); gout; clinical diagnosis of dementia; residency in a nursing home; inability to stand or walk)

inflammation and its associated risk of hypertension compared to pharmacological interventions. (135) Since hypertension is infrequently occurs in isolation from other CV risk factors, interventions combining lifestyle modifications and pharmacotherapy in managing hypertension may be more appropriate for adults of advanced age. The effect of lifestyle and pharmacologic interventions for hypertension in people of advanced remained to be explored.

TABLE 2-1: Prospective studies investigating the association between blood pressure, hypertension and CVD
(listed according to increasing age)

Study (year of publication)	Mean age (range), years	Sample size Sex	Main findings
Framingham Heart Study (2001) (48)	52 (35–94)	9,845 both sexes	Non-hypertensive adults with high normal BP and normal BP frequently progress to HTN over a period of 4 years (models were adjusted for age, sex, BMI, percent change in weight over the 4-year interval, smoking status and heart rate). A 5% increase in weight over the 4-year interval (i.e. an increase of 4kg in men and 3kg in women) was associated with a 20-30% increased likelihood of being hypertensive on follow-up.
(Japanese cohort) (2009) (205)	42	777 men only	During the three-year observation period, baseline BMI>25.0 [adjusted OR (95% CI): 2.27 (1.25–4.13)] and baPWV>13.5m/s [adjusted OR (95% CI): 3.32 (1.79–6.15)] were significant predictors of future HTN among pre-hypertensive men, independent of BP, heart rate, triglyceride, fasting plasma glucose, alcohol, and metabolic syndrome.
The Singapore Cardiovascular Cohort Study (2009) (204)	NT (53%): 34 Pre-HTN (28%): 40 HTN (19%): 52	5,830 both sexes	During the observation period (median 12 years), pre-HTN was not an independent risk factor for mortality; but Pre-HTN is an increased risk for all-cause and CVD mortality in the presence of diabetes, smoking, and pre-existing CVD, i.e. adjusting the model for other CVD risk factors attenuated the statistical significant relationship between pre-HTN and all-cause as well as CVD mortality.
ARIC Study (2006) (206)	Optimal BP (63%): 53 Normal BP (23%): 54 High BP (14%): 55 (range: 45–64)	8,960 both sexes	During the follow-up period of an average of 11.6 years, compared to those with optimal BP levels, middle-aged adults with pre-hypertensive levels of BP have an increased risk of developing CVD; and the risk increased in the presence of diabetes and BMI>30kg/m^2. The Cox proportional hazards regression models were adjusted for study centre, conventional CVD risk factors, education level, sport index, lipid lowering medication, fibrinogen, von Willebrand factor, and white blood cell count.
The Strong Heart Study (2006) (185)	No DM (58%): 54 DM (42%): 56 (range: 45–74)	2,629 both sexes	During the 12 years follow-up, compared to those with normal BP and no DM, adults with both pre-HTN and DM had a higher risk of developing CVD [HR (95% CI)=3.7 (2.66–5.15)] than adults with pre-HTN [HR (95% CI): 1.8 (1.28–2.54)] and adults with DM alone [HR (95% CI): 2.9 (2.03–4.16)]. The Cox proportional hazard model was adjusted for age, sex, conventional CV risk factors and alcohol use.

TABLE 2-1 continued

Medical records from Kaiser Permanente Northwest, a not-for-profit, group-model health maintenance organisation (2007) (173)	60 (≥35)	57,573 both sexes	RR (95%CI) of CV events over 6 years among patients free from CVD with HTN and comorbidities (the Cox proportional hazards models were adjusted for age, sex, and smoking status): DM only: 2.07 (1.86–2.30) DM + hyperlipidemia: 2.20 (1.89–2.55) DM + BMI>30kg/m^2: 2.37 (2.15–2.61) DM + hyperlipidemia + BMI>30kg/m^2: 2.80 (2.48–3.17)
Women's Health Study (2003) (208)	Mean age range 51–54 (≥45)	20,525 women only	During a median follow-up of 7.8 years, baseline CRP levels were modestly but independently associated with an increased risk of incident HTN, even among those with very low initial systolic and diastolic BP (the Cox proportional hazards models were adjusted for age, conventional CV risk factors, exercise, alcohol intake, postmenopausal hormone use, parental history of MI<60 years, treatment with aspirin, vitamin E and beta-carotene)
Kuopio Ischemic Heart Disease (2004) (209)	(42–60)	379 men only	The risk of developing HTN over 11 years among normotensive middle-aged men was 2.8 times (95% CI 1.19–6.63) higher for those with CRP>3mg/L than CRP<1mg/L (the logistic regression models were adjusted for age, smoking status, socioeconomic status, leisure-time physical activity, CVD, intake of energy adjusted dietary factors, baseline systolic BP, waist circumference, concentrations of insulin, glucose, and HDL, and changes in waist circumference, cigarettes smoking per day and alcohol intake (g/day) during the 11-year period).
CARDIA Study (2006) (207)	32 (25–37)	3,919 both sexes	Compared to those with CRP<1mg/L, young adults with CRP>3mg/L had a 79% (95% CI 1.40–2.28) greater risk of incident HTN but the risk attenuated after adjusting for BMI [adjusted OR (95% CI) CRP<1mg/L (reference group) vs. CRP>3mg/L 1.14 (0.86–1.53)], a result contrasting with the findings in the older population

Abbreviations: **ARIC:** Atherosclerosis Risk in Communities; **baPWV:** brachial-ankle pulse wave velocity (a marker of arterial stiffness); **BMI:** body mass index; **BP:** blood pressure; **CARDIA:** Coronary Artery Risk Development in Young Adults; **CI:** confidence interval; **CRP:** C-reactive protein: **CVD:** cardiovascular disease; **HYVET:** HYpertension in the Very Elderly Trial; **DM:** diabetes mellitus; **HF:** heart failure; **HR:** hazard ratio; **HTN:** hypertension; **NT:** normotensive; **Ref:** reference; **OR:** odds ratio; **RR:** relative risk

TABLE 2-2: Randomised controlled trial investigating the effect of antihypertensive treatment on CVD and all-cause mortality
(listed according to increasing age)

Study (year of publication)	Mean age (range), years	Sample size Sex	Main findings
SHEP (1991) (215)	72 (≥60) Age group: 60-69=41.5% 70-79=44.8% ≥80=13.7%	4736 Both sexes	The cumulative stroke rates for the total period of follow-up (70 months) for the active treatment group vs. the placebo group per 100 participants were 5.5 vs. 9.2. The favourable effect of active treatment compared with placebo for stroke incidence was observed for all age groups: 60 to 69 years, 34 vs. 47 events; 70 to 79 years, 48 vs. 74 events; and ≥80 years, 21 vs. 38 events. With regards to combined nonfatal and fatal cardiovascular events, the active treatment group had 32% [RR (95% CI) 0.68 (0.58-0.79)] fewer events than the placebo group, with the 5-year absolute benefit estimated at 55 events per 1000 participants. It was not mentioned if the proportional hazards regression analysis was adjusted for confounders.
HYVET (2008) (202)	84 (≥80)	3,845 both sexes	Compared to the placebo group, participants treated with idapamide 1.5mg ± perindopril 2–4mg had a reduced risk of fatal and non-fatal stroke [HR (95% CI): 0.70 (0.49–1.01)]; fatal and non-fatal HF [HR (95% CI): 0.36 (0.22–0.58)]; and all-cause mortality [HR (95% CI): 0.79 (0.65–0.950)]. The proportional hazards analyses were adjusted for sex, age, baseline systolic BP, and previous CVD

Abbreviations: **BP:** blood pressure; **CI:** confidence interval; **HYVET:** HYpertension in the Very Elderly Trial; **HF:** heart failure; **HR:** hazard ratio; **SHEP:** Systolic Hypertension in the Elderly Program

2.5.5 BMI and body fat distribution

Obesity is defined as excessive accumulation of fat in adipose tissues. (218) This concept has been the subject of extensive research in exploring the relationship between obesity and adverse health conditions, often including CVD. (219) Obesity can be categorised into two groups: 1) android obesity, also known as abdominal fat distribution, is associated with an increased risk of CVD, and 2) gynoid fat distribution, where fat is distributed more evenly. (218) Not only is fat distribution associated with an adverse CVD risk, the types of adipose tissue also carry specific risk of future CV events. As opposed to brown adipose tissue, of which the primary function is heat production and has been linked to weight loss (220), white adipose tissue (WAT) is an emerging factor predicting immunity and inflammation. Current research is investigating the production of cytokines (IL-6 and TNF-α) by WAT in contributing to a chronic inflammatory state in those with visceral obesity. (221) Chronic inflammation is believed to be the fundamental element of atherosclerosis. (18) The relationship between adipose tissue and inflammatory markers is mentioned in Section 2.6 (page 39). As research on WAT is under way, this section will dwell on general obesity, determined by body mass index (BMI) and body fat distribution, measured by waist circumference (WC) and waist-to-hip ratio (WHR), in relation to atherosclerosis and CVD.

Obesity is a major risk factor for CVD. NHANES[13], a population-based longitudinal study with 2.3 million study participants, showed increased BMI (a measure of general obesity) was associated with CVD mortality. (219) Body fat distribution is also found to be closely related to the CV risk profile. The INTER-HEART study, with 27,100 participants from 52 countries, reported that abdominal obesity indexes (waist circumference and waist-to-hip ratio) showed a strong relation to myocardial infarction (MI) risk, a relationship stronger than BMI. (222) The Norfolk cohort study, with 24,500 participants, found abdominal obesity was a better predictor for coronary heart disease (CHD) than BMI. (223) The Dallas Heart Study, a population-based probability sample of 6,100 adults participants from Dallas County, found a similar finding – that WC and WHR were the preferred measures of cardiac risk associated with obesity. (224) These longitudinal studies unanimously agreed abdominal obesity increased CVD risk. (TABLE 2-3) On the other hand, these findings underscore an important limitation of BMI: its failure to make a distinction between different body compositions. BMI does not characterise excess abdominal obesity (218) and its value could

[13] **NHANES**: National Health and Nutrition Examination Survey

be erroneous for those with increased lean body mass. (225) Muscle mass, which is related to muscle strength and physical performance, is heavier than fat mass. Hence, a person with a high body fat-to-muscle mass ratio (possibly with a desirable BMI) will have a poorer physical performance, thus poorer physical fitness, than a person with a low body fat-to-muscle mass ratio (with a considerably high BMI). The NIH–AARP[14] Diet and Healthy Study of 243,500 participants found that persons with a normal BMI but large waist circumference (WC) had a 20% higher mortality risk than those with a normal BMI and normal WC. (226) The EPIC[15] study found that the association of WC and WHR with mortality risk seems to be stronger among participants with lower BMI than those with higher BMI. (227) Therefore, abdominal adiposity may be a better indicator for CV health profile and a better predictor for mortality risk than BMI.

The aptness of abdominal adiposity indexes (WC and WHR) in assessing the risk of adverse CV health outcomes and mortality, or all-cause mortality, remains inconclusive. This is partly due to less precision of these indexes in measuring body fat distribution. The more sophisticated technological measurements, such as the dual energy x-ray absorptiometry (DEXA) scan, can accurately quantify body fat percentage and distribution. Access to DEXA scan, however, is limited. WC and WHR are used in large population studies as a pragmatic choice in terms of time and money. (228)

The relationship between abdominal obesity, CV risk profile and mortality risk probably differs between the indexes (WC and WHR), and is sex-specific. (229) In the INTER-HEART study, WHR demonstrated a stronger association with MI risk compared to WC for both sexes, irrespective of smoking status, presence of dyslipidemia, diabetes or hypertension. (222) The Iowa Women's Health Study found WC was more strongly associated with CHD-related mortality than WHR; whereas WHR (not WC) was associated positively with other CVD-related mortality. (230) In the British Regional Heart study with male participants, WC was more strongly associated with all-cause mortality than WHR, after adjustment for muscle mass[16]. (231) In stratifying the relationships between abdominal obesity and adverse health outcomes for men and women, a Cochrane review article reported that abdominal adiposity was an independent risk factor for stroke for men but not women. (232) Analysis using data from the Physicians' Health Study and Women's Health Study

[14] **NIH–AARP**: National Institutes of Health–American Association of Retired Persons
[15] **EPIC**: European Prospective Investigation into Cancer and Nutrition
[16] The British Regional Heart Study assessed muscle mass with mid-arm muscle circumference

found positive associations between WC and WHR with CVD did not vary substantially although the associations seem weaker for WHR and MI among men. (233) These studies suggest that abdominal adiposity measurements are appropriate in the prediction of CVD risk and mortality, and that the disease-specific risk varies according to gender.

With advancing age, body composition changes. Lean body mass is replaced with fat mass and the fat appears to be redistributed to the abdominal region. (234) In other words, older adults are likely to have a higher body fat-to-muscle mass ratio than younger adults. These physiological changes indicate that the BMI value in the elderly population underestimates adiposity associated with an adverse health profile. (218) Thus, the use of BMI in geriatric research may not be a good indicator of obesity related to medical complications. The loss of muscle mass with ageing (235) and the increased prevalence of nutritional risk in the elderly (55, 56) may be related to decreasing weight after age 75. (22, 23) Loss of muscle mass and reduced energy reserves for recuperation (consequence of undernutrition) are related to worsening disability (235) and may lead to subsequent adverse health conditions. (102) Prospective studies found that a higher BMI (ranging between 27-31kg/m^2) is favourable for survival among adults over 75 years old. (236, 237) Among hospitalised individuals over 80 years old, low BMI is an important predictor of all-cause and CVD mortality. (238) Therefore, low BMI could be a more significant problem than being overweight in the elderly population. (236)

Contrary to the inverse relationship between BMI and risk of all-cause and CVD mortality, abdominal adiposity may continue to adversely impact the CV health of the elderly population. Adipose tissue is one of the sources that produce proinflammatory cytokines. (239) (Figure 2-1) It is not only the quantity of adipose tissue per se, but the fact that abdominal fat is strongly related to increase inflammatory markers. (239-241) Inflammatory markers are associated with CVD risk; this will be discussed further in Section 2.5. In the Cardiovascular Health Study with adults over 65 years old, a higher BMI value was associated with lower mortality risk, whereas a higher WC value was associated with higher mortality risk. (197) A U.K. study of 15,160 adults aged 75 years and above found a similar result – that BMI was inversely associated with mortality but WHR (instead of WC) was positively associated with circulatory mortality. (242) This suggests that in older adults, BMI (reflective of lean mass) is inversely associated with all-cause mortality, and WC and WHR (reflective of fat mass) is linearly associated with all-cause mortality. It remains an open question

as to whether one (WC or WHR) is better than the other in predicting CVD in older people. BMI, WC and WHR may have a specific predictive value in older adults.

In summary, numerous studies observed BMI, WC and WHR to be positively associated with the risk of CVD and all-cause mortality. Most epidemiological studies did not include adults living to advanced age, i.e. those aged 85 years or more. Studies showed that the increased gradient of risk across the increasing BMI categories diminishes with age. (238, 243, 244) Thus, using BMI as a measure of adiposity in the elderly may result in misclassification of risk in this population. In view of this, adding WC or WHR to BMI would enable accurate stratification of individuals into higher risk and lower risk categories. (197, 227) As to the relationships between abdominal adiposity and risk of CVD and all-cause mortality, again, most prospective studies involved a younger population, with a mean age range between 51 and 70 years. (222, 226, 227, 230, 231, 233) (TABLE 2-3) Therefore, it is clearly shown that there is a lack of evidence pertaining to general and abdominal adiposity and its relationship with CV health in the advanced age population. A distinct BMI, WC and WHR classification system is needed for very elderly adults.

TABLE 2-3: Longitudinal cohort studies investigated the association between BMI, WC and WHR, and CVD and all-cause mortality
(listed according to increasing age)

Study (year of publication)	Sex	Age range (mean), years	Sample size
Dallas Heart Study (2007) (224)	Both	18–65 (mean: 45)	6,101
NHANES (2007) (219)	Both	≥25	2.3 million
EPIC study* (2008) (227)	Both	25–70 (mean: 51.5)	359,387*
INTER-HEART study[#] (2005) (222)	Both	Men <55; Women <65 (mean: 57)	27,098[#]
Norfolk cohort (2007) (223)	Both	45–79 (mean: 60)	24,508
Physicians' Health Study (PHS) & Women's Health Study (WHS) (2008) (233)	Both	PHS: 40–84 (mean: 61) WHS: ≥ 45 (mean: 61)	PHS: 16,332 WHS:32,700
NIH-AARP Diet and Health Study (2008) (226)	Both	51–72 (mean: 63)	243,522
Iowa Women's Health Study (2000) (230)	Women	55–69 Varies within BMI quintile: 62–65 yrs; WHR quintile: 55–70 yrs	31,702
British Regional Heart Study (2007) (231)	Men	60–79	7,735
Cardiovascular Health Study (2005) (197)	Both	≥ 65 65–70 (42%); 71–76 (33%); 77–82 (18%); ≥83 (7%)	5,200

Abbreviations: **BMI:** Body mass index; **EPIC:** European Prospective Investigation into Cancer and Nutrition; **NHANES:** National Health and Nutrition Examination Survey; **NIH-AARP:** National Institutes of Health–American Association of Retired Persons; **WHR:** waist-to-hip ratio
* Participants from 10 European countries
[#] Participants from 52 countries

2.5.6 Dyslipidemia

Cholesterol is inherently related to CVD. However, not all cholesterol is bad; high-density lipoprotein is protective against CVD. Besides cholesterol, triglyceride levels are linearly related with CVD risk. The prevalence of dyslipidemia (disruption of cholesterol and triglyceride levels in the blood) ranges between 14% and 76%, depending on the study setting. (26, 27, 245) Despite the wide range of dyslipidemia across countries, these studies found the prevalence of dyslipidemia increased with age to the sixth and seventh decade of life. (26, 27, 245) The Reykjavik study is a population-based cohort study which enrolled more than 18,500 men and women with an average age of 52 (±9) and 53 (±9) years respectively, and a follow-up period of up to 28 years (mean 17.4 years). (246) The study found that for an increase of 1mmol/L fasting total cholesterol, the hazard ratio for myocardial infarction (MI) was 1.24 for women and 1.30 of men, independent of other MI

risk factors. (246) As for fasting triglyceride levels, both the Reykjavik and the EPIC-Norfolk studies reported that a 1 mmol/L increase was associated with a 19% increased risk of coronary heart disease (CHD). (246, 247) A similar trend was observed between non-fasting triglyceride levels and CVD. In the Copenhagen City Heart Study, a prospective cohort study with almost 14,000 men and women followed-up for an average of 26 years, every increase of 1 mmol/L in non-fasting triglyceride levels was associated with a 20% and an 18% increased risk of MI and all-cause mortality in women; and an 8% increased risk of all-cause mortality in men, independent of other CV risk factors. (248) The study chose to use non-fasting triglyceride levels because they are reflective of increased levels of remnant lipoproteins which may promote atherosclerosis. The size and density of the lipoprotein may be as important as the amount of lipoprotein.

Small and dense LDL is considered to be an atherogenic lipoprotein. (249) Compare to medium-sized LDL, the small LDL particles has an easier entry into the intima layer, are more susceptible to oxidation, have reduced antioxidant concentrations, retard metabolism, and decreased intra/extravascular equilibration. (249) These LDL related mechanisms potentially explain a part of the association between LDL concentrations, CV events and disease progression in both young and old adults. (249-251) In the Framingham Offspring Study, women with CHD had significantly higher mean levels of small dense LDL than women without CHD. The study also found that cholesterol-lowering medication did not affect small dense LDL levels. (250) It is still to be confirmed that there is a causal relationship between small, dense LDL and CVD. It may be that small, dense LDL particle is a part of the pathophysiology of metabolic syndrome which is associated with increased CVD risk. (249, 251)

Like other conventional risk factors, the causes of dyslipidemia can be attributed to familial and lifestyle factors. In 16 population-cohort, 22 loci (specific locations of a gene or DNA sequence on a chromosome) were identified to be associated with serum lipid metabolism, lipid transporter and response to nutrient levels. (252) In addition to serum lipid concentration, genetic factors contribute up to 67% of HDL and LDL subclasses. (253) This heritable trait is a feature of the metabolic syndrome and is an important prognostic factor for the manifestation and progression of CHD. (249, 250) A genetic risk score was constructed from the Northern Finnish Birth Cohort, the Rotterdam Study and the Monozygotic twins study (n=12,361). The genetic risk profile explained 3.9% of the total variance in sex- and age-adjusted total cholesterol, 4.8% in HDL, 3.4% in LDL and 3.0% in TG.

The risk scores were also significantly associated with increased intima-media thickness and incidence of CHD. The amount of lipid variance explained by the score approaches that explained by body mass index. (252) This suggests that lifestyle factors could be more important determinants of dyslipidemia than genetic factors; or possibly certain lifestyle and environmental factors precipitate manifestation of the characteristics of genes.

Dietary pattern and physical activity have been found to influence lipid levels. Saturated fat intake is related to increased LDL levels (254, 255) whereas mono- and polyunsaturated fatty acids are related to a decrease in total cholesterol and LDL levels but increased HDL level. (256, 257) Intake of dietary fibre is inversely associated with total cholesterol, LDL, and triglyceride levels. (254, 255, 258) Drawing from this evidence, a diet comprising the right quality and quantity of essential fatty acids and dietary fibre (soluble fibre) is potentially an effective non-pharmacological therapy for dyslipidemia.

Physical activity is another lifestyle behaviour associated with lipid profile. In the Women's Health Study, a prospective observational cohort study which recruited 27,000 healthy women with an average age of 58 years, increased physical activity was associated with decreased total cholesterol and LDL levels and increased HDL levels. (107) Similar relationships between physical activity and total cholesterol and HDL levels were observed in the NHANES study which included more than 3,600 healthy men and women with an average age of 53 years in the analysis. (259) In a cross-sectional study involving 51 women and 19 men aged 60 years and above (mean age for men 69 years; women 74 years), non-vigorous habitual physical activity (such as lawn bowls or light callisthenics that do not lead to heavy breathing) was found to have a beneficial effects on HDL levels. (111) The benefit of regular physical activity on the lipid profile continues to be observed in the elderly population. (109) This evidence from observational studies in younger old adults may be inferred to people of advanced age.

Combining dietary changes with exercise intervention may possibly have a synergistic impact on the lipid profile. A group of 25 participants (mean age 64±9 years for men and 58±14 years for women) with known coronary artery disease (>50% stenosis in one or more coronary arteries) underwent a three-month treatment programme consisting of a multiple intervention: diet containing 10% fat and 75% carbohydrate, exercise prescription (20 minutes/day, 4 day/week at 60-70% of maximum heart rate), and psychological stress management. After three months of the treatment

programme, there was a significant reduction in total cholesterol of 8%, and LDL particles became significantly less oxidisable (i.e. LDL contained 27% more α-tocopherol and 17% more β-carotene per particle). (260) Would the multiple non-pharmacological interventions be appropriate for the very old? It is likely that these interventions need to be tailored according to the health status of those in advanced age.

In summary, prevalence of dyslipidemia increased up to the sixth and seventh decade of life, as mirrored in total cholesterol levels which increased with age up to 65 years old. (24-27) After that, total cholesterol, LDL, and HDL levels begin to decline; as does the prevalence of dyslipidemia. (24-27, 261) In view of this, the association between lipid profile and CVD could possibly change with advancing age. This was observed in the Reykjavik Study. The hazard ratio per mmol/L increase of total cholesterol for MI at age 40 was 1.39; decreasing to 1.17 at age 70. (246) In a meta-analysis of 61 prospective studies, the hazard ratio for ischemic heart disease (IHD) mortality in both genders at ages 40-49, 60-69, and 70-89 years for each 1 mmol/L decrease of total cholesterol was 0.44 (95% CI 0.42-0.48), 0.66 (0.65-0.68), and 0.83 (0.81-0.85). (262) In other words, the reduced risk of IHD mortality per mmol/L decrease of cholesterol lessened with age. It seems that cholesterol lowering in older adults has nominal magnitude in reducing the risk of CVD. This raises the question: whether intervention for dyslipidemia, both pharmacotherapy (statin) and lifestyle intervention, proven effective in younger adults (263, 264) has the same efficacy in those of advanced age?

Dyslipidemia is a common phenomenon worldwide and its relationship with CVD is established. Randomised controlled trials of both pharmacologic and non-pharmacologic interventions have shown some promising results. Nonetheless, meta-analyses of these randomised controlled trials focus on younger old adults; none or only a small percentage of the participants in clinical trials are people of advanced age. (265-269) The interconnectedness of changes in bodily functions suggests the relationship between lipid profile and CVD is more complex in advanced age, and probably different from younger elderly adults. Therefore, it is important to understand these relationships in those of advanced age. Perhaps interventions for dyslipidemia in those of advanced age need to be adapted to the individual's health condition.

2.6 Inflammatory markers

Beyond the conventional risk factors, inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), fibrinogen, and erythrocyte sedimentation rate (ESR), have drawn much attention in the research of cardiovascular disease. The inflammatory process is a fundamental pathology for atherosclerosis. Russell Ross (1999) states that atherosclerosis is an inflammatory disease. (18) Intrinsically, the immune function deteriorates with ageing, sometimes termed as immunosenescence. (153) Age-related deterioration of the immune function includes increased number of inflammatory cells, concomitantly with attenuated cytotoxic function of cells, altered capacity of proinflammatory cytokine production and prolonged proinflammatory activity. (270) Ageing is associated with a dysregulated acute phase response.

The acute phase response is composed of local events and systemic activation of the inflammation cascade. It constitutes a complex molecular network and cellular interactions to eliminate foreign substances, to aid tissue repair and to facilitate a return to physiological homeostasis. (270) Following the detection of foreign substances, an inflammatory response is incited; triggering the release of local cytokines[17] TNF-α and IL-1ß at the inflamed site by macrophages to promote wound repair. TNF-α and IL-1ß induce a second wave of cytokines, including IL-6 and chemokines[18]. This second wave of cytokines leads to growth factor stimulation and recruitment of macrophages and platelets. (272) During this acute phase response, acute phase proteins such as CRP, fibrinogen, and serum amyloid A (SAA) are synthesised in the liver. Besides stimulation by IL-6, production of CRP is also stimulated independently by TNF-α and IL-1ß. (270) The goal of this inflammation cascade is homeostasis.

In the artery wall, a similar homeostatic process takes place. Prolonged exposure of the endothelial cells of the artery wall to conventional CV risk factors leads to injury of the endothelium. Following the injury, the innate immune response is activated. The atheroprotective mechanism is exhibited through the homeostatic process. When this compensatory response fails, the homeostatic properties of the endothelial cells change, and this alteration is linked with various proinflammatory chemoattractants, causing the arterial intima to undergo inflammatory change. (18, 19) (Section 2.7 page 57)

[17] Cytokines are chemicals secreted by a specific cell in response to a specific stimulus, and altering the behaviour of other cells. (271)

[18] Chemokines are cytokines that cause chemotaxis and regulate the influx of leukocytes to the infected site (271)

The inflammatory process is the initial reactive response of the immune function. Hence immune cells were believed to be the main source of proinflammatory cytokines. (270) However, adipose tissue has been found to be a secretary organ, producing proinflammatory cytokines. (239) It is thought that up to 30% of circulating IL-6 emerges from adipose tissue. (154, 221) The release of cytokines from adipose tissue may have relevance to the morbidity and mortality of those in advanced age. This is because a shift in body composition is observed, i.e. a higher fat ratio with ageing. (234) Not only the increased adipose tissue per se, but redistribution of body fat from the peripheral to the abdominal region seen with ageing, is more strongly associated with increased systemic inflammation. (239) Visceral adipose tissue has been found to be a key promoter of low-grade chronic inflammation. (240, 241) Individuals with abdominal obesity have higher circulating CRP, IL-6, TNF-α, PAI-1 (plasminogen activator inhibitor-1), angiotensinogen, increased platelet-activating eicosanoids, and increased numbers of activated platelets compared to BMI-matched people with increased subcutaneous fat deposition. (221, 239, 273, 274) Therefore, central adiposity-induced proinflammatory mediators play an important role in the pathophysiology of atherosclerosis. (Figure 2-2)

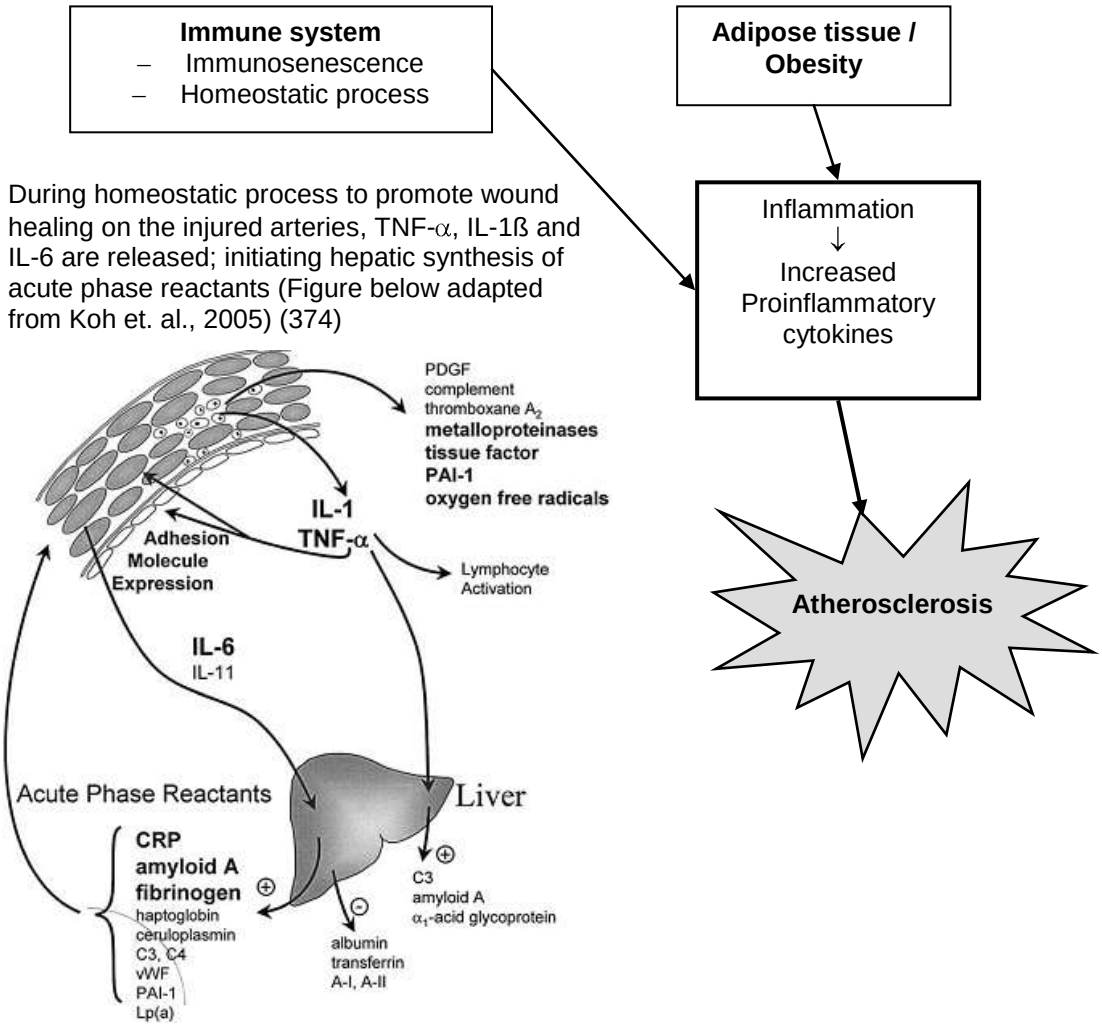


Figure 2-2: Main sources of proinflammatory cytokines

As the processes within the inflammatory cascade are inter-related, plasma levels of inflammatory markers are often correlated. Nevertheless, they have separate effects with different clinical impacts. This section will review the role of CRP, IL-6, TNF-α, fibrinogen, and ESR in association with CVD risk factors, predictive values of CV events, CVD and all-cause mortality and, lastly, intervention for elevated inflammatory markers.

2.6.1 C-reactive protein

C-reactive protein (CRP) is a systemic acute phase protein belonging to the pentraxin protein family. (275) It is mainly produced by hepatocytes in response to proinflammatory cytokines such as IL-6 and TNF-α. (276) Smooth muscle cells and adipocytes are also a source of CRP. (275, 277) Since these inflammatory markers are tightly linked, CRP is therefore correlated with IL-6, TNF-α, and fibrinogen. (270, 278) However, CRP has a specific role in the inflammatory cascade,

as do other inflammatory markers. In the inflamed vasculature, CPR induces monocyte recruitment into the arterial wall by up-regulation of an adhesion receptor on the intimal endothelial cells. CRP enhances uptake of LDL by endothelial macrophages. CRP binds to oxidised LDLs and is opsonised by macrophages, leading to foam cell formation. CRP binding to immunoglobulin receptors of the immune cells triggers the production of cytokines and complement related to inflammation, thus further exacerbating the inflammatory response and causing instability of the plaque. (89, 279) The role of CRP on early atherogenesis was demonstrated when CRP was found to accumulate in the intracellular environment of macrophages and co-localise with the terminal complement complex near areas of extracellular lipid deposition. (279, 280) The multi-functional roles of CRP in relation to inflammation are the reason why this analyte is one of the most studied emerging cardiovascular risk factors.

As non-specific biomarkers of inflammation, CRP has robust characteristics of an analyte. It has a long plasma half-life of about 19 hours, no significant seasonal and diurnal variation, is not affected by dietary intake (275, 281) and is not significantly affected by the freezing and thawing cycle. (88) Additionally, assays for CRP are widely available; reproducibility analysis showed satisfactory inter-assay precision; and availability of standards for proper assay calibration. (281) These important features, from the clinical perspective, provide an added advantage for wider use of CRP as an emerging cardiovascular risk factor.

In an apparently healthy person, CRP levels are elevated in those with subclinical disease (282) many years prior to manifestation of myocardial infarction (MI) or stroke (283). Carotid intima-medial thickness (CIMT) is one of the two measures of subclinical atherosclerosis (the other is coronary artery calcification). CRP levels are linearly correlated with CIMT. (284) Carotid intima-medial thickness is mentioned in Section 2.8 (page 58). Peripheral arterial disease (PAD) is a common manifestation of atherosclerosis. In a nested case-control study of 280 (140 controls and 140 cases) healthy men (mean age of 58 years old), increased CRP level were associated with a nearly three-fold increase in the risk of future arterial disease (adjusted analysis of highest vs. lowest quartile, relative risk (95% CI) 2.8 (1.3–5.9), p=0.01). (285) Moreover, the severity of PAD, measured by the ankle-brachial pressure index (ABPI), is correlated with CRP levels (277); and the occurrence of cardiovascular complications in patients with PAD during a 2-year follow-up was proportionate to CRP levels. (277)

In the Northern Manhattan Study, with more than 2,200 participants with a mean age of 69 years, the CRP level ≥3mg/L was associated with increased risk of MI [adjusted hazard ratio (95% CI) 1.70 (1.04–2.77)]. (286) In the Cardiovascular Health Study, women older than 65 years (mean age 73 years) with a higher CRP level have a 1.6-fold increased risk of coronary heart disease (CHD) incidence compared to those in the lowest quartile. There were no significant associations in men. (282) In the Three-City Study with participants' average age of 74 years at baseline, the hazard ratio of CHD increased from 1.69 for the CRP level 1.0 to 2.9 mg/L to 2.32 for the CRP level 3.0 to 10.0mg/L. This significantly greater risk of CHD with higher CRP levels remains after adjustment for other CV risk factors and presence of carotid plaques and intima-medial thickness. (287) Similar positive relationships were observed between CRP levels and incidence of heart failure (HF). In a Swedish study following nearly 4,700 participants with ages ranging between 54 and 60 years old, compared to those with a CPR level < 1mg/L, participants with CPR ≥3mg/L had twice the risk of having HF over 13 years after adjustment for age, sex and conventional CV risk factors. (288) In a subgroup of the older population in the Framingham Heart Study (mean age of 79 years), a CRP level of ≥5mg/mL was associated with a 2.8-fold increased risk of CHF. (35) The Framingham Heart Study excluded institutionalised individuals and included mainly white individuals, hence, this finding cannot be generalised to elderly from different ethnic groups with different physical function. The Rotterdam Study and the Cardiovascular Health Study showed elevated CRP levels are among the leading predictors of CHF in elderly persons aged between 65 and 100 years old. (33, 34) In adults aged 85 years and above, the Leiden 85+ study found participants in the top tertile of CPR levels had twice the risk of stroke compared with the first and second tertile. (289) The cumulative risk of mortality from stroke increased with CRP levels over a 2.6-year follow-up duration (289), corresponding to up to a 10-fold increased risk in participants with the highest CRP levels over a 5-year follow-up duration. (36)

The relationship between the CRP level and its predictive value of CV events remains inconsistent. The Northern Manhattan Study showed that CRP level was associated with MI but not with stroke. (286) In the Health, Aging and Body Composition (Health ABC) study, CRP was a significant predictor of CHF incidence but not for stroke. (290) The Rotterdam Study reported that the CRP level was not an independent predictor of MI. (291) Results of these studies suggest CRP is a sensitive but nonspecific marker of systemic inflammation. (286) Additionally, there is a sex-

specific difference in the CRP level and its association with CV events. The relationship between the CRP level and the risk of MI was stronger in women than in men (282); whereas the relationship between the CRP level and CHF was stronger in men than in women. (33) Furthermore, the association between the CRP level and CVD is likely to be dependent on the baseline cardiovascular profile and inter-relationships between CV risk factors. A meta-analysis of 37 published articles from 24 cohorts reported that the CRP level is independently related to coronary heart disease (CHD), with a risk ratio of 1.58 for high versus low CRP levels. (292)

Epidemiological studies show that CRP levels are linearly associated with CVD risk. Nonetheless, the evidence remains inconclusive. These results may be masked by the interactions with other CV risk factors such as gender. Despite a few exceptions, a meta-analysis shows that CRP is related to CHD irrespective of other conventional CV risk factors. (292) It is not clear whether the relationship between CRP and CVD is stronger or weaker with ageing. In both the Leiden 85+ study and the ilSIRENTE study, with participants aged above 85 years, higher CRP values were associated with higher risk of all-cause mortality (293) and stroke (36), The relationship between CRP and CVD in advanced age remains to be established.

2.6.2 Interleukin-6

Interleukin-6 (IL-6) was initially known as hepatocyte-stimulating factor and was discovered by Ritchie and Fuller in 1983 and given the name by Prupart *et al.* in 1987. (294) In this short span of time, this protein has drawn plenty of research interest due to its pleiotropic action, i.e. it is both a pro- and anti-inflammatory cytokine. Hence, IL-6 plays an important role in the acute-phase inflammatory response. This 26kDa protein, with a reasonably long half-life of four hours (295) is produced in response to infection and several other cytokines including TNF-α. (296) IL-6 is produced by a variety of cells including adipose tissues (154, 221), particularly visceral adipose tissue. (297) However, during systemic inflammation, it is mainly synthesised by endothelial cells, smooth muscle cells, fibroblasts, and macrophages. (298) Its role in the inflammatory cascade includes promoting inflammation through activation of T-cells, differentiation of B cells and induction of acute phase reactants by hepatocytes. (299) IL-6 promotes atherogenesis through several pathways: induces production of CRP and fibrinogen, increases endothelial cell adhesiveness, activates tissue factor and von Willebrand factor production, decreases anticoagulant levels, and increases production of thrombogenic platelets. (300) Furthermore, IL-6 regulates the secretion of

fatty acids and lipoprotein from the liver. (31) In short, IL-6 influences the atherosclerotic process by enhancing coagulation, thrombosis (278), and influencing plasma lipid levels. (31)

In view of the participation of IL-6 in every pathway toward atherosclerosis, measuring its concentration accurately would provide important information in a CVD risk prediction model. It has been determined that IL-6 concentrations are stable in serum and EDTA-plasma samples for up to 1 hour at room temperature, 6 hours at 4°C, 24 hours at -20°C, and 24 hours at -70°C. (301, 302) Additionally, IL-6 levels were not affected by repeated freeze-thaw treatment. (302) In a group of 200 post-MI patients followed up for an average of 7.3 months and with at least 6 blood samples, IL-6 demonstrates a good repeatability (intraclass correlation coefficient, R_i value 0.66) and the precision of the assay (ELISA) was good. (303) These features suggest that measurement of IL-6 levels is feasible in the research setting and could be a valuable biomarker for CVD. Nevertheless, a standard procedure for collection and treatment of blood samples would ensure inter-assay variations are kept to a minimum. (302)

In healthy young individuals, IL-6 is tightly regulated, hence it is not normally detected in this population unless one is experiencing trauma, infection or stress. (304) However, Erchler & Keller (2000) reported that circulating IL-6 increases in the serum of older people, notably after menopause and andropause, without overt illness or inflammation. (298) In the Framingham Heart Study, IL-6 was detected in the elderly (average age of 79 years) living independently and free of hepatic and renal disease. (304) In the Vitality 90+ study, nonagenarians had significantly higher IL-6 levels than the control group (i.e. middle-aged clinically healthy subjects living in the same community in Finland) (4.39±5.25 vs. 1.88±1.98pg/mL), independent of the presence of diabetes, coronary heart disease and use of lipid-lowering medications. (31) In short, IL-6 levels are detectable in healthy elderly individuals.

In older adults with known or suspected coronary artery disease (CAD), IL-6 levels are associated with atherosclerosis in carotid arteries. (278) Among those with clinically manifest CVD, IL-6 levels are significantly higher than in their counterparts without CVD. (278, 296) In healthy individuals, IL-6 levels are proportionate to the risk of CVD. In more than 400 apparently healthy middle-aged men followed up for 6 years, those in the highest quartile of IL-6 levels (>2.28 pg/mL) had a 2.3 times higher risk of developing first MI than those in the lowest quartile (<1.04pg/mL).

(296) This significant relationship between IL-6 levels and risk of future MI was independent of baseline differences in conventional CV risk factors. (296) In an older population with mean age 78 years without MI at baseline, followed up for an average of 5.2 years, an increase of every standard deviation of IL-6 level (=0.64pg/mL) was associated with a 36% increased risk of CHF. (35) These studies suggest an association between IL-6 and the progression of CVD. The IL-6 level was found to be inversely correlated with left ventricle ejection fraction (LVEF) and is elevated in adults (average age of 62 years) with asymptomatic LV systolic dysfunction (LVEF<55% and absence of the clinical syndrome of CHF). (305) In patients with unstable coronary artery disease (CAD), an IL-6 level ≥5pg/mL was associated with a 3.5-fold increased risk of all-cause mortality at 12 months compared to those with an IL-6 level <5pg/mL. (295) In older women with a history of CVD, those with the highest tertile of IL-6 had more than a four-fold risk of mortality than women in the lowest tertile after adjustment for chronic diseases and disease severity measures (ankle-branchial index, forced expiratory volume, and exercise tolerance). (306)

Studies have shown that IL-6 is an inflammatory marker that has a consistent linear relationship with CVD. This is attributable for its role in the inflammatory cascade as a key player in the regulation of the acute phase response. It seems likely that IL-6 is involved in the pathophysiology of CVD. Moreover, it continues to be a reliable predictor of mortality among older adults, whether or not they are afflicted with CVD. With this vital role within the inflammation system and a relatively long half-life (2-4 hours) (307), IL-6 is emerging as a novel biomarker that could add significant value for risk prediction of CVD in those of advanced age.

2.6.3 Tumour necrosis factor-alpha

Tumour necrosis factor-alpha (TNF-α) is a pleiotropic cytokine that has a central role in the inflammatory cascade. It induces and suppresses a wide variety of genes including those encoding the production of cytokines and adhesions molecules. (308) TNF-α is mainly produced from the activated macrophages at the local inflammatory site but other cells such as lymphocytes, fibroblasts, neutrophils, smooth muscle and mast cells also produce TNF-α. (270, 308) Its presence activates endothelial cells to express adhesion molecules as well as proinflammatory cytokines and chemokines receptors. (309) Meanwhile, it promotes synthesis and release of a variety of inflammatory cytokines (IL-6) and chemokines (IL-8 and macrophage inflammatory

protein). (270, 309, 310) These processes promote further recruitment of activated leukocytes to an inflammatory lesion, hence sustaining the proinflammatory state within the lesion. Additionally, TNF-α promotes oxidative stress and directly impairs nitric oxide bioavailability. (309) This contributes to endothelial dysfunction, arterial stiffness and increased carotid intima-medial thickness. (309) In short, TNF-α has a pivotal role during both initiation and amplification of inflammatory reactions. (309)

With the critical role TNF-α has in the inflammatory cascade, it is no surprise that TNF-α protein in plasma is one of the strongest risk factors as well as disease markers among the oldest old. (270) TNF-α concentrations are stable in serum and EDTA-plasma samples for up to 6 to 8 hours at 4°C (301, 302); and it remains stable when stored for 24 hours at -20°C, and 24 hours at -70°C. (301, 302) However, TNF-α concentrations are sensitive to freeze-thaw treatment. TNF-α level increases with every consecutive freeze-thaw cycle and it becomes significantly higher after three cycles. (302) With proper treatment and storage, measurement of TNF-α has a moderate repeatability (intra-class correlation coefficient, R_i value 0.57) plus a high degree of statistical correlation ($p \leq 0.001$) between visits. (311) Additionally, commercial assays are available for measurements of TNF-α. These characteristics make it possible for TNF-α to be measured and studied in the research setting. Combining the role and characteristics of TNF-α, determination of TNF-α concentrations would yield valuable information on cardiovascular health particularly in those of advancing age.

TNF-α is produced by activated macrophages during infection and acute injury, and is a key regulator in inflammation lesion. (270, 308) In a clinical study of 96 healthy 50-year-old men, TNF-α levels were associated with CIMT (a measure of early atherosclerosis). (312) The influence of TNF-α on the atherosclerotic process may be associated with several established risk indicators such as systolic and diastolic blood pressure, lipid profile and LDL particle size. (312) There is limited evidence on the association between TNF-α and atherosclerosis. Nonetheless, existing clinical study in healthy adults supports the role of TNF-α early in the atherosclerotic process.

Besides production of TNF-α at the inflammation site, a recent intriguing observation is that cardiomyocytes are capable of producing TNF-α in response to cardiac injury. (313) In 47 patients

with clinically significant aortic stenosis (AS) or mitral regurgitation (MR) with mild symptoms (New York Heart Association functional class I or II), patients had significantly higher TNF-α levels than healthy age- and sex-matched controls. (314) In the multiple regression analysis adjusting for age and sex, the presence of AS [OR (95%) 1.4 (1.13–1.85)] and MR [OR (95% CI) 1.2 (1.03–1.55)] predicted higher TNF-α levels. This finding indicates that hemodynamic pressure and volume overload stimulates the production of cytokine. Nevertheless, it is unknown if TNF-α levels normalised after surgical correction of pressure or volume overload, (314)

The role of TNF-α in the inflammation response may be an explanation for the positive relationship observed between TNF-α level and coronary events in population studies. In younger elderly patients (mean age 60±9 years, n=544) with MI, elevated TNF-α levels after MI (blood samples were taken at least three months post MI, an average of 8.9 months) were associated with recurrent coronary events, i.e. TNF-α levels above the 95th percentile were associated with a 2.5 fold increase risk of recurrent coronary events, independent of conventional CV risk factors. (315) In the Framingham Heart Study with 732 older adults (mean age 78 years) free of prior CHD and CHF, followed up for an average of 5.2 years, every standard deviation increment in log TNF-α was associated with a 46% increased risk of CHF, independent of conventional CV risk factors plus valve disease, atrial fibrillation, presence of CVD and ECG-LVH. (35) A similar trend was observed in the Health ABC study which recruited 2,610 healthy older adults aged between 70–79 years (median 74 years) and followed up for 9.4 years (median). In the Health ABC study, the TNF-α level was associated with heart failure (HF) risk; for every increment of $\log_2$ TNF-α, the hazard ratio (95% CI) for incident HF risk was 1.46 (1.17–1.84) (p=0.001), independent of baseline characteristics and baseline subclinical atherosclerosis. (316) The independent relationships observed in these studies add evidence that TNF-α is probably involved in the pathophysiology of coronary heart disease.

In addition to increased risk of coronary events, the TNF-α level is associated with the deterioration of NYHA (New York Heart Association) functional class. Among patients with clinically significant aortic stenosis (AS) or mitral regurgitation (MR) with mild symptom (NYHA functional class I or II), TNF-α levels were higher in patients in NYHA class II than patients in NYHA class I. (314) In patients with HF, TNF-α levels were associated with NYHA functional class. (317, 318)

Furthermore, increased TNF-α levels were associated with increased mortality risk in HF patients. In a population-based study in Olmsted County in the U.S.A, 486 patients (mean age 76.7±13 years) with HF were enrolled in the study over a 32-month period. (319) The Kaplan-Meier analysis showed risk of mortality in patients with HF increased from the lowest to the highest TNF-α quartile; and in the adjusted model (adjustment for age, gender, ejection fraction, and comorbidities), the hazard ratio (95% CI) for mortality was 1.88 (1.09-3.25) in the highest versus the lowest TNF-α quartile, p=0.028. (319) These studies indicate that increased TNF-α levels are associated with severity of heart failure. On the other hand, the association between TNF-α levels and heart failure may be due to reverse causality. Patients with heart failure have poor tissue perfusion which may increase inflammatory mediators. It has been reported that cardiomyocytes are capable of producing TNF-α in response to cardiac injury. (313) Therefore, TNF-α level may be a marker and a risk factor for heart failure.

In short, TNF-α is a key regulator in the inflammatory cascade. Although it was previously linked to rheumatological diseases, its role in CVD is emerging, as it has been discovered that the heart produces TNF-α. In younger elderly adults, TNF-α levels predict recurrent coronary events. (315) In older adults, TNF-α levels predict coronary events in healthy individuals. (35, 316) Moreover, TNF-α is related to deterioration of cardiovascular health (314, 318) and eventually CVD-related mortality. (319) Therefore, TNF-α is a promising biomarker for CVD risk in those of advanced age, as more than half of individuals aged 85+ are affected by CVD. (3)

2.6.4 Fibrinogen

Fibrinogen is a large glycoprotein (340kDa) that has an important role in both the coagulation and inflammatory cascades. As a haemostatic factor, it plays a role in platelet aggregation and is the precursor to fibrin. (320, 321) Therefore, a small increase in fibrinogen levels will have an impact on plasma viscosity. (320-322) Fibrinogen is produced in the liver during the acute phase response. (272, 320) Hence, fibrinogen is considered a 'downstream' marker in the inflammation process, regulated by cytokines (such as TNF-α and IL-6). (323) The dual roles explain why its usability is extended from haemorrhagic risk to CVD risk. Plasma fibrinogen has a long half-life of 3-4 days (324), providing a broader window period for a measurable level. Several fibrinogen assays are available for assessment of fibrinogen levels. (322) The commonly used assay is the

Clauss method but the Framingham Heart study found fibrinogen levels obtained from the immunoprecipitation test showed a stronger association with CVD than the former method. (325) Nevertheless, fibrinogen results from both methods showed a similar association with CVD risk. (326) Standard guidelines are available for each of the fibrinogen assays, ensuring repeatability of the chosen method. (281, 322) These features are one of the reasons fibrinogen is the most studied inflammatory/ coagulation marker relating to CVD risk.

Fibrinogen, an acute phase reactant, is measurable in prolonged subclinical inflammatory response. In healthy middle-aged adults (without clinically overt atherosclerotic diseases), fibrinogen levels were linearly associated with CIMT, independent of conventional CV risk factors, CRP levels, and von Willebrand factor (marker of endothelial damage). (30) Similar associations were observed in healthy older adults. In the Inflammation in the Carotid Arteries Risk for Atherosclerosis Study (ICARAS) of more than 1,200 participants (median age 69 years, range 60 to 76 years) without symptoms from carotid artery disease 12 months prior to the study enrolment, baseline fibrinogen levels were associated with progression of carotid atherosclerosis[19]; each 1 mg/dL increment of the fibrinogen level was associated with increased risk of disease progression [adjusted hazard ratio (95% CI) 1.003 (1.001–1.005), p=0.019]. (327) Fibrinogen levels also predict peripheral arterial disease (PAD) in healthy men. (285) In a subgroup of the Physician's Health Study, men free of vascular disease at baseline (mean age 58 years old) with elevated fibrinogen levels had twice the risk of developing future arterial disease than those with a low fibrinogen level (adjusted analysis of highest vs. lowest quartile, relative risk (95% CI) 2.2 (1.1–4.7), p=0.02]. (285) These epidemiological studies agreed that fibrinogen plays a key role in the preliminary phase and the advanced stages of atherosclerosis.

The role of fibrinogen is also associated with clinical CVD. In the Framingham Offspring Study with 2,632 participants (mean age 55±10 years), participants with CVD had significantly higher fibrinogen levels than those without CVD. (326) A similar trend was observed in older adults, that is those with CVD had higher fibrinogen levels than those without CVD. (34, 278) In the meta-analysis of 31 prospective studies, with 154,211 participants free from CVD at baseline (mean age 54 years), a long-term increase of 1 g/L of the plasma fibrinogen level is associated with approximately a two-fold increased risk of CVD outcomes (CHD, stroke, and other vascular

[19] The ICARAS study defined progression of carotid atherosclerosis as the degree of stenosis in the internal carotid arteries.

mortality). (321, 328) In a population-based study of more than 6000 men (mean age 46 years) followed up over a mean duration of 22 years, it was observed that fibrinogen levels (along with several other inflammatory markers) were elevated many years before the incidence of HF, and those with high fibrinogen levels (top quartile) had 1.8-fold increased risk of HF than those with a low level of fibrinogen (bottom quartile) after adjustment for other CV risk factors. (329) These studies showed a consistent relationship between fibrinogen levels and the risk of CVD.

The role of fibrinogen in pre-clinical and clinical CVD is well researched, and it was found to be an important CV risk factor. (321, 330) This is probably due to the apparent way fibrinogen affects the CV system through both the coagulation mechanism (which is related to blood viscosity) and the inflammation process. It has been shown that the active role and interactions between viscosity, haemostasis, and the inflammation process are associated with atherosclerotic heart disease. (331) Take note that all these epidemiological studies and meta-analyses included younger adults with a mean age range between 46 and 69 years. (278, 285, 321, 326-329), with the exception of the Cardiovascular Health Study (34) which recruited adults aged 65 and above (mean age 73 years). With almost the entire elderly population having atherosclerosis in their blood vessels (332), possibly fibrinogen (both a haemostatic factor and an acute phase reactant) may be a reliable biomarker to assess progression of atherosclerotic disease (327) in older adults.

2.6.5 Erythrocyte sedimentation rate

Erythrocyte sedimentation rate (ESR) is a measure of the tendency of the red blood cells to aggregate. (333) Increased aggregation of the red blood cells increases blood viscosity, which is associated with an increased risk of coronary heart disease (CHD). (334) Concentration of acute phase protein is one of the determinants of ESR. Increased concentration of acute phase protein (which occurs during inflammation) increases ESR. (333, 335) Although ESR is closely related to acute phase protein (fibrinogen), ESR may still provide substantial additional information on fibrinogen to CVD risk. (336) This is because, in healthy adults, less than 25% of the variance of ESR is explained by differences in fibrinogen levels. (337) In patients with rheumatoid arthritis, ESR is uses to monitor disease activity. (338) In apparently healthy adults, compared to CRP, ESR responds more slowly to the onset of the inflammatory process but the elevated ESR persists longer than CRP, and is more sensitive to age-related changes. (339) This suggests that ESR could be a consistent marker of a prolonged inflammatory state in older adults. (339) Measurement of

ESR is guided by the International Council for Standardization in Haematology. (335) The Westergren method, which is more commonly used than the Wintrobe or Fåhraes method, is a standardised, accurate, universally available and inexpensive measurement of ESR. (333) From a clinical perspective, a reliable and cost-effective measure is among the important features of a potential screening/diagnostic biomarker. In the last two decades, the relationship between ESR and CV risk has been explored.

Erythrocyte sedimentation rate is increased during inflammation. In more than 2000 apparently healthy Norwegian men aged between 40 and 60 years, men with a high ESR had a higher coronary heart disease (CHD) risk than men with low ESR. (336) During the 23-year follow-up, controlling for other conventional CV risk factors, ESR was a strong predictor of CHD mortality. (336) The study found men who had an ESR ≥15mm/h with angina pectoris or with silent ischemia had a marked increase risk of CHD mortality. (336) Similarly, a linear association was observed between ESR and the risk of heart failure. In the Uppsala Longitudinal Study of Adult Men (ULSAM) which recruited 50-year-old men free from heart failure, myocardial infarction and valvular disease at baseline, during the 30-year follow-up, men with ESR ≥11mm/h had a 46% increased risk of heart failure than those with ESR ≤6mm/h after adjustment for conventional risk factors. (340) Both studies found ESR was a significant predictor of CHD and CHD mortality in healthy middle-aged men over time. (336, 340)

In middle-aged adults with probable ischemic heart disease (IHD), ESR is also likely to predict cardiac mortality. In a hospital-based, retrospective observational cohort study with 1726 patients (mean age 55 years) who underwent coronary angiography, ESR was independently associated with coronary stenosis. (333) Over a median follow-up period of 7.7 years, the risks of cardiac mortality for men and women with high ESR (>18 and >23mm/h, respectively) was 72% higher than those in the lower three quartiles, after adjusting for age and sex. (333) The significant predictive value of a high ESR for cardiac mortality persists after further adjustment for the presence of previous MI and unstable angina [odds ratio (confidence interval): 1.67 (1.12–2.49)]. (333) The study also showed an ESR greater than 18mm/h in men carried a similar negative prognosis for cardiac mortality (as with the presence of previous MI). (333) In an age-matched case-control study, men (aged between 40 and 60 years) with angiographically proven ischemic heart disease (IHD) had higher ESR levels than their counterparts without known history of IHD. (341) Findings

from these studies convincingly indicated that the ESR level is independently associated with coronary arthrosclerosis and is a strong predictor of cardiac mortality among patients with IHD.

Understanding of the relationship between ESR and CVD is in progress. To date, studies examining this relationship have been conducted in middle-aged adults, mostly middle-aged men. The predictive value of ESR for CVD risk in older adults should be explored. This is because ESR is one of the major components of blood viscosity which is associated with increased risk of CHD. (334) ESR is sensitive to the effect of multiple acute phase proteins. It indicates the level of rapid response acute phase protein (CRP) and slower response acute phase protein (fibrinogen). This broad spectrum of sensitivity enables and is suitable for monitoring chronic inflammatory processes. (342) Exploring the predictive value of ESR is feasible because measurement of ESR is inexpensive and is guided by a standardised method.

2.6.6 Intervention influencing inflammatory markers

Elevated levels of inflammatory markers are associated with the occurrence of new onset of CV events and are strong predictors of recurrent CV events. There appears to be a dose-dependent relationship between levels of inflammatory markers and the risk of CVD. In prospective cohort studies, participants who had elevated levels of all three inflammatory markers (CRP, IL-6 and TNF-α) had two- to four-fold increased risk for CHD and HF compared to those with one or two elevated markers. (35, 290, 316) Therefore, strategies to reduce inflammatory markers may reduce CVD risk.

Intervention strategies for management of elevated level of inflammatory markers are in the exploratory phase; to date, the strategies are related to management of conventional CV risk factors. Much of this evidence is from observational studies, which can only show inference.

Cigarette smoking is associated with an increase in TNF-α and fibrinogen levels. (321, 326, 343) Therefore, smoking cessation may reverse the amount of circulating cytokines (e.g. TNF-α and fibrinogen levels) and acute phase protein (CRP) in the blood stream. (321, 326, 344) However, there is no evidence for this.

A diet rich in fruit, vegetables and olive oil was found to be independently associated with significant decreased levels of CRP, IL-6, and fibrinogen (257, 345, 346), and a marginal decreased

for TNF-α level. (346) Conversely, a diet rich in pasta, meat, eggs, and sweets is associated with increased levels of inflammatory markers. (257, 345) The effect of dietary fibre on inflammatory markers is inconclusive. Some reported dietary fibre was associated with lower concentrations of CRP (347) and IL-6 levels (345), others found no association between dietary intake of whole grains with concentration of CRP, IL-6 or fibrinogen. (348) In the Cardiovascular Health Study (CHS), intake of vitamin C, beta-carotene and vitamin E was inversely associated with IL-6. (349) These observational studies were mostly conducted in middle-aged adults except the CHS which recruited participants over 65 years. In an experimental study, a diet rich in monounsaturated fatty acids (olive oil) resulted in lower release of IL-6 from adipocytes compared to a diet rich in saturated fat. (350) Therefore, dietary pattern may regulate the production of inflammatory markers. In a randomised controlled trial, adults (mean age 44 years) with CRP $\geq$ 1.0mg/L assigned to receive vitamin C (1000mg/day) for two months had a significant reduction of CRP levels compared to those randomised to placebo or vitamin E (800IU/day). (351) The effect of vitamin supplements for reducing inflammatory markers requires further investigation, particularly in adults of advanced age. This research area is yet to be explored.

Physical activity is found to be related to concentration of inflammatory markers. (106) In the NHANES study, physical activity was inversely associated with CRP and fibrinogen levels. (259) In the ATTICA health and nutrition survey (province of ATTICA, Greece), compared to sedentary individuals, those who are highly active have lower levels of IL-6 (32%), CRP (29%), TNF-α (20%), and fibrinogen (11%). (352) Significant differences were also observed between moderately physically active and sedentary individuals. (352) Among individuals with metabolic syndrome, physical activity was associated with a reduction in inflammatory markers. (353) Similar inverse associations between physical activity and inflammatory markers were observed in adults over 65 years old. (349, 354, 355) In the Cardiovascular Health Study, healthy adults with the highest levels of physical activity have lower CRP (23%) and fibrinogen (4%) levels than the lowest physical activity group. (355) In the InCHIANTI Study (participants' mean age 75 years), compared to inactive adults, moderate-high physical activity was independently inversely associated with CRP, IL-6, fibrinogen, and ESR. (349) These studies led to a consensus that physical activity levels are inversely associated with inflammatory markers. Among patients with coronary artery disease (mean age 62 years), in a subgroup of patients with high inflammatory markers, 24 months of

regular exercise reduced CRP levels by 41% and IL-6 by 18%. (123) This trial suggests physical activity intervention is effective for reduction of elevated inflammatory markers. The impact of physical activity on inflammatory markers levels in adults of advanced age remains to be explored.

Therapeutic interventions for treatment of elevated levels of inflammatory markers have not been proven. To date, statins appear to reduce CRP levels in individuals free of CVD (356) and among patients with coronary artery disease. (276, 278, 356) The reduction of CRP with statin is greater for those with higher CRP levels than those with lower CRP levels. (276) Generally, studies with pravastatin, lovastatin, cerivastatin, simvastatin, atorvastatin, and rosuvastatin have all demonstrated that median CRP concentration reduces by 15% to 40% as early as six weeks after initial treatment. (276) Fenofibrate was found to reduce inflammatory markers. In patients with type 2 diabetes who had hyperlipidemia, a 12-week treatment with fenofibrate (200mg/day) significantly reduced CRP (36%), fibrinogen (18%) and ESR (48%) levels. (357) Other pharmacological intervention found to affect CRP levels includes anti-diabetic agents (not insulin), anti-oestrogen therapy, β-adrenoreceptor antagonists, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, and calcium channel antagonists. (182, 344, 358) These pharmacotherapies, however, cannot be attributed to lowering CRP levels because they are used for management of the pertinent disease conditions. In addition, changes in CRP levels with these pharmacotherapies were inconsistent, as some studies reported no effect on CRP levels. (358)

Corticosteroid and non-steroidal anti-inflammatory drugs (NSAIDs) are used to treat chronic inflammatory disease such as rheumatoid arthritis and osteoarthritis. These medications are known to alleviate inflammation. Among the list of anti-inflammatory drugs, aspirin (a member of the NSAIDs) at low dose was found to be effective for primary and secondary prevention of CVD. (359-361) The role of other corticosteroids and NSAIDs for CVD prevention was studied and the outcomes have been discouraging. An observational study with 181,400 non-aspirin NSAIDs users and 181,400 controls (532,634 person-years of follow-up) found naproxen or other non-aspirin NSAIDs confers no protective effect on the risk of coronary heart disease in adults aged 50-84 years (mean age 64 years). (362) Rofecoxib[20] (cyclooxygenese-2 inhibitors, a new class of NSAIDs) was found to increase the risk of MI in patients 65 years and above (mean age 82 years, n=54,475). (363) A similar result was observed in a population study with more than 113,900 older

[20] In 2004, rofecoxib (commonly known as Vioxx) was taken off market due to increase risk of myocardial infarction and stroke associated with long-term, high dosage used.

adults (mean age 75 years) without a history of MI. Individuals exposed to rofecoxib in the past 12 months had an increased risk of MI compared with those who had not used an NSAID within the same time frame [RR (95%CI) 1.24 (1.05-1.46)[21]]; celecoxib was not associated with an elevated risk of acute MI, It is uncertain if non-aspirin NSAIDs has a cardioprotective role.

The anti-platelet and anti-thrombotic properties of aspirin (364, 365) are likely to be the mechanism by which aspirin prevents CVD. Beyond the anti-platelet and anti-thrombotic properties, aspirin may have an anti-inflammatory action. (344) Experimental studies show that aspirin inhibits the activation of nuclear factor-κβ (which is a transcription factor that holds a central role in the vascular inflammation process) (366) and reverses CRP-induced thrombosis. (367) The clinical effectiveness of aspirin for reduction of inflammatory markers remains a topic for research. In a randomised double-blind cross-over trial, 40 patients (mean age 55 years) with stable angina and normal cardiac function were treated with 300mg aspirin daily. At the end of the three-week treatment, there was a significant reduction in CRP (29%) and IL-6 (37%) levels; CRP and IL-6 levels were similar to the baseline values at the end of the placebo phase. (368) In patients with type 2 diabetes without cardiovascular disease, use of aspirin resulted in a modest reduction of CRP and IL-6 levels. (369) Aspirin therapy for elevated inflammatory markers requires further investigation.

In recent years, anti-TNF agents e.g. infliximab, adalimumab, and etanercept are used to treat rheumatoid arthritis (RA). Anti-TNF agents have been shown to effectively control RA disease activity, improve physical function and attenuate radiological progression in patients with RA. (309) Rheumatoid arthritis is associated with increased mortality, which is primarily attributed to accelerated coronary artery and cerebrovascular atherosclerosis. Patients with RA had a CV event a decade earlier than the general population. (370) In RA patients, TNF-α blocker was associated with a lower risk of CV events and morbidity. (370) Infliximab and standard anti-TNF therapy (methotrexate and prenisone) improved arterial flow-mediated diameter, and significantly reduced ESR and CRP levels in RA patients. (371, 372) The efficacy of these treatments for low-grade inflammation aiming to ameliorate CVD risk remains to be proven.

[21] Cox proportional hazards regression models were adjusted for age at index (continuous variable); sex, hypertension, coronary artery disease, cerebrovascular disease, peripheral vascular disease, congestive heart failure, diabetes, respiratory illness, gastrointestinal ulcer disease, thyroid disorders, depression/psychiatric illness, and cancer in the year preceding cohort entry; use of concomitant therapy, including antilipemic agents, anticoagulants, and low-dose aspirin in the year preceding cohort entry; health care utilization, including hospitalizations, outpatient visits to any physician, and outpatient cardiologist visits, in the year preceding the index date; and number of different drugs taken, chronic disease score, and Charlson index score in the year preceding the index date.

In summary, intervention strategies for chronic low-grade inflammation are yet to be tested. Several studies observed that a combination of therapy produces a synergistic effect in lowering inflammatory markers. (373, 374) Since the inflammation process is likely to be the underlying mechanism for CVD, a pharmacologic intervention which could potentially intercept the inflammatory pathway(s) may be effective in preventing clinical CVD. Perhaps there are lessons to be learnt from treatment of rheumatoid arthritis with TNF-α blocker. No doubt, the concept of treating chronic low-grade inflammation is far from sight. Prospective studies are still needed to: first, establish contribution of inflammatory markers for assessment of CVD risk; second, to examine the relationships between reductions in inflammatory markers and outcomes of CV events. Future studies should seek to include people of advanced age.

2.7 Atherogenesis: the role of immune and inflammatory response

With the advent of the cell biology era, we now have a better grasp on the pathogenesis of atherosclerosis. In the traditional view, atherosclerosis is a blend of lipid deposits on the surface of arteries expanded to a degree that restricts blood flow to the tissues, and subsequently leads to cardiovascular disease (CVD). Advancement in cell biology supplanted this simplistic concept. It revealed to us the involvement of the immune and inflammatory response in the development of atherosclerosis.

Prolonged exposure to conventional CV risk factors, e.g. hyperlipidemia, smoking, hypertension, hyperglycaemia and obesity, contribute to endothelial injury and activation of the immune system. (19) The injured endothelium causes vascular inflammation and initiates a fibroproliferative response. (375) Simultaneously, the host defence system responds to what it perceives as foreign intruders, such as modified lipoprotein, in two approaches. Firstly, there is the uptake of the toxic blood lipids by monocytes. And secondly, pattern-recognition receptors (such as macrophage scavenger receptors and T cell receptors) that recognise the foreign substance structures activate a complex intracellular signalling cascade that produces proinflammatory cytokines and other inflammatory mediators. (376) These are the central mechanisms of both the innate and adaptive immune response. Monocytes that engulf the 'toxic' blood lipids attach to the arterial endothelium. This is facilitated by vascular cell adhesion molecule-1 (VCAM-1), which was induced by oxidised lipids through a pathway mediated by nuclear factor-κB, interleukin (IL)-1β and

tumour necrosis factor (TNF)-α. Once adhered to the arterial endothelium, monocytes migrate through the endothelial lining and enter the intima layer of the vessel wall. This process is assisted by monocyte chemoattractant protein-1 (MCP-1). Within the intima, monocytes mature into macrophages. The lipid-laden macrophages, i.e. foam cells, infiltrate the vessel wall and at the same time they multiply and release several growth factors and cytokines, thus amplifying and sustaining proinflammatory signals. Foam cells lead to the formation of obstructive atherosclerotic plaques. (19, 376, 377) In short, atherosclerotic lesions progress at the site of arterial inflammation, which is most likely impelled by established conventional risk factors.

In summary, extrinsic factors, including but not limited to CV risk factors, act synergistically in altering the highly organised arterial structure and function. Advancement in medical science has established the role of inflammation in the initiation and development of atherosclerosis. Additionally, it was observed that atheromatous plaques developed within the arterial wall, rather than on the arterial walls. Intima-media thickness (IMT), i.e. the distance between the lumen-intima interface and the media-adventitia interface, has been identified as a marker of pre-clinical atherosclerosis. The European Vascular Aging study demonstrated the association between IMT and plaques formation. (20) The study showed the prevalence of plaque and its severity increased from the lowest to the highest quintile of IMT in both sexes. Therefore, IMT has been studied exhaustively in the past two decades to explore its risk factors, association with CVD, and cardiovascular and all-cause mortality. (378-380) In addition, IMT has been used in randomised controlled trials to assess effectiveness of pharmacological treatments (blood pressure-lowering and lipid-lowering medications) on its progression over time. (381)

2.8 Carotid intima-media thickness

Atherosclerosis is the most important underlying cause of the manifestation of cardiovascular disease (CVD). Carotid intima-media-thickness (CIMT), a measurement of the thickness of the carotid artery walls, is an indicator of the total atherosclerotic burden. (21, 382, 383) This measurement technique was preferred in epidemiological studies over cardiac imaging because it is non-invasive and the equipment is widely available. (381, 384) Even though the examination techniques vary, for example which arterial segment to examine, should measurement of the B-mode images be made on the near or far walls, and whether to use one clearest image or several

images (381, 384), reproducibility of CIMT measurements were adequate (385) and the measurement errors have reduced over time from 25-40% to 10-20%. (386) The variation in examination techniques echoes the relatively early stage of CIMT measurement in the medical research setting. The reproducibility of the technique now allows further exploration of whether CIMT truly predicts major coronary heart disease (CHD) events. (384)

Risk factors for carotid wall thickening closely resemble risk factors for cardiovascular disease (CVD) in every age group. (387, 388) In the young (20–34 years) and middle-aged adults (33-42 years), LDL cholesterol was the key predictor of greater common CIMT. (388) As research progressed, the association between age and CIMT was established. In middle-aged men and women (45–64 years), the Atherosclerosis Risk in Communities (ARIC) study reported that CIMT increased by 0.01mm for each year. (389) Similar findings were observed in the Cardiovascular Health Study with participants aged 65 years and above. (390) Men have greater carotid artery wall thickness than in women at every age. (389, 390) Blood pressure is another major predictor of common carotid artery thickening, both in the middle-aged (391) and those 65 years and above. (390) Other CV risk factors that consistently exhibit significant relationships with CIMT include smoking status, diabetes, and increased body weight. (148, 389, 390) These studies provide contemporaneous measures of the association between conventional CV risk factors and CIMT. A time-integrated measure of associations would allow further comprehension. The Hoorn Study is the latest longitudinal population-based cohort study to provide insight into this issue. The study followed 581 Dutch participants between the ages of 50 and 74 at baseline for 10 years. They found persons with increased CIMT had unfavourable risk factor profiles throughout the preceding decade. A multivariate linear mixed model demonstrated that baseline total cholesterol, HbA1c and, to a lesser extent, systolic blood pressure were independently associated with CIMT status. (150) Results await from another prospective, multicentre, longitudinal observational study involving five European countries with a similar focus (the IMPROVE study), will extend the findings of the Hoorn Study. There was an interesting revelation from the baseline data of the IMPROVE study. Latitude, north-to-south gradient, was independently associated with CIMT (392). Although reasons for this finding remain unclear, the IMPROVE study underscores the fact that novel risk factors may play a role in carotid wall thickening not explained by the conventional risk factors.

Inflammatory markers have been associated with CIMT. In a case-control study with 100 study participants aged 55 years and below, white cell count, fibrinogen and CRP increased across CIMT quartiles irrespective of the presence of carotid artery stenosis or occlusion. (393) A cross-sectional study of 519 participants aged between 28 and 71 years showed that the fibrinogen level was positively correlated to CIMT after controlling for age, sex and CV risk factors. (30) In the Cardiovascular Health Study, there was a significant linear correlation between CRP level and CIMT; the geometric mean of CRP was 1.58, 1.85 and 2.20mg/L across the increasing tertiles of CIMT. (284) An extensive review by Baldassarre *et al*. on the association between CIMT and soluble markers concluded that CRP and fibrinogen are unequivocally related to CIMT. (320) To summarise, both conventional and emerging cardiovascular risk factors contribute to carotid wall thickening. CIMT, a novel and emerging risk factor itself, has been found to predict future clinical cardiovascular events. (379)

Evidence for the predictive value of CIMT in predicting CV events are consistent. In a prospective study of 4,700 Swedish participants aged between 54–60 years old, the participants were followed up for 13 years. Participants with CIMT in the highest quartile at baseline had twice the relative risk of having heart failure (HF) [hazard ratio (HR):2.1; confidence interval (CI): 1.0 to 4.6] compared to the lowest quartile (CIMT $\geq$0.88 vs. $\leq$0.67mm for men; $\geq$0.82 vs. $\leq$0.65mm for women) after controlling for age, sex and conventional CV risk factors. The risk increased substantially in participants with high CIMT and CRP$\geq$3mg/L [HR (95% CI): 3.7 (1.9–7.3)] adjusted for age, sex and conventional CV risk factors. (288) In the Atherosclerosis Risk in Communities (ARIC) Study, 5,552 men and 7,289 women aged between 45-64 years and free of coronary heart disease (CHD) were recruited and followed up for 5.2 years. Men and women with the top CIMT tertile had 2.0 and 3.8 times the incidence of CHD respectively, compared to participants in the lowest CIMT tertile after controlling for age, ethnicity and other CHD risk factors. (383) In the cross-sectional analysis of the Cardiovascular Health Study which recruited nearly 6000 participants aged 65 years and above, an increase of one standard deviation in CIMT (0.22mm) was associated with a 9% increased risk of coronary disease. (390) In the prospective analysis, where 4,476 participants without history of CVD at baseline were followed for 6.2 years, an increase of one standard deviation (0.20mm) in CIMT was associated with a 24% increased risk of myocardial infarction (MI) and a 28% increase in the risk of stroke after adjustment of age, sex and other CV risk factors. (394) The Multi-Ethnic Study of Atherosclerosis (MESA), with nearly 6,700 participants

aged between 45 and 84 years free of symptomatic CVD at baseline, showed that over the 3.9-year follow-up, participants in the highest quartile of CITM (≥0.97mm) had 2.3 times the risk of a CVD event compared to those in the lowest CIMT quartile (CIMT ≤0.74mm) after adjustment for age, sex and ethnicity. (395)

Up to this point, studies on the association of CIMT with CVD in different age groups have been broadly presented. There are many more studies which support the findings that increased CIMT is related to CVD. A table in a review article by Alain Simon *et al.* (2010) summarises the evidence (TABLE 2-4). The two apparent observations from the table are, firstly, heterogeneity of studies, particularly study outcomes. It was found that CIMT provide a better prediction for stroke than for CHD. Moreover, CIMT had a closer prediction of CHD and stroke in women than in men. (380) This leads to a second observation, i.e. study participants. Although these studies included the general population, participants from most of these studies had a mean age younger than 85 years. To date, only the Newcastle 85+ study has obtained images of the carotid arteries measured in older adults 85 years and above awaiting published findings. What would be the relationship between CIMT and CVD in the special population of those in advanced age with CV risk factors, e.g. hypertension, diabetes, and dyslipidemia, who have a higher incidence of CAD? On the other hand, this group would be more likely to have received intensive treatment for their existing risk factors. To what extent would such intervention affect the predictive value of CIMT on the prognosis of CVD?

TABLE 2-4: Risk of MI, Stroke, and CVD associated with CIMT measured in the common carotid artery in main prospective studies in the general population
(adapted from Simon, Megnien and Chironi, 2010 (380))

Study	Event	Follow-up, years	Sex / Age range, year	CCA measure	Absolute Risk, %/yr (Positive Test Result for CIMT)	Relative Risk (95% CI) [Hazard Ratio for CIMT]
KIHD (396)	MI	1.0	Both / 42–60	Maximum	2.2 (>1mm)	2.2 (0.7– 6.7) [CIMT ≥1 vs. <1 mm]*
ROT (397)	MI	2.7	Both / ≥55	Mean	0.7 (>0.91mm and 80th P)	1.4 (1.2–1.8) [per 0.16 mm CIMT, 1 SD]†
CHS (394)	MI	6.2	Both / ≥65	Maximum	1.6 (>1.18mm and 5th quintile)	3.2 (2.0–5.1) [5th vs. 1st CIMT quintile] †
MDCS (398)	MI	7.0	Both / 46–68	Mean	NA	2.1 (1.2–3.4) [3rd vs. 1st CIMT tertile] †
CAPS (398)	MI	4.2	Both / 19–90	Mean	2.1 (>0.79mm and 4th quartile)	2.2 (1.9–4.0) [4th vs. 1st CIMT quartile] †
ROT (397)	Stroke	2.7	Both / ≥55	Mean	0.8 (>0.91mm and 80th P)	1.4 (1.3–1.8) [per 0.16-mm CIMT, 1 SD]
CHS (394)	Stroke	6.2	Both / ≥65	Maximum	1.8 (>1.18mm and 5th quintile)	2.8 (1.8–4.2) [5th vs. 1st CIMT quintile] †
CAPS (398)	Stroke	4.2	Both / 19–90	Mean	1.1 (>0.79mm and 4th quartile)	2.3 (0.9–6.3) [4th vs. 1st CIMT quartile] †
MDCS (399)	Stroke	7.0	Both / 46–68	Mean	0.4 (>0.81mm)	3.0 (1.6–5.7) [3rd vs. 1st CIMT tertile] †
Kitamura *et al.* (400)	Stroke	4.5	Men / 60–74	Maximum	1.3 (>1.07mm and 4th quartile)	3.5 (1.3–9.5) [4th vs. 1st CIMT quartile]
MESA (395)	CVD	5.3	Both / 45–84	Maximum	1.8 (>0.97mm and 4th quartile)	2.3 (1.4–3.8) [4th vs. 1st CIMT quartile]‡
CAPS (398)	CVD	4.2	Both / 19–90	Mean	3.2 (>0.79mm and 4th quartile)	2.3 (1.4–3.8) [4th vs. 1st CIMT quartile] †

Abbreviations: **CAPS:** Carotid Atherosclerosis Progression study: **CCA:** common carotid artery: **CHS:** Cardiovascular Health Study; **CI:** confidence interval; **CIMT:** carotid intima-media thickness; **CVD:** cardiovascular disease; **KIHD:** Kuopio Ischemic Heart Disease study; **MDCS:** Malmo Diet and Cancer Study: **MESA:** Multi-Ethnic Study of Atherosclerosis; **MI:** myocardial infarction; **NA:** not available; **P:** percentile; **ROT:** Rotterdam Study; **vs.:** versus
* Non-adjusted
† Age and sex adjusted
‡ Age adjusted

The associations between CIMT and CVD in special groups were explored in smaller studies. In a study comprising 279 patients ages between 31 and 82 years with hypertension and clinical symptoms of coronary artery disease (CAD), patients with increased CIMT had a 38% higher risk of all-cause mortality after controlling for age, sex, and other CV risk factors; and only 78% of those with high CIMT (above the median of 1.13mm) survived at 60 months versus 99% of patients with low CIMT (CIMT$\leq$1.13mm). (401) A multicentre prospective study recruited 900 high risk patients (i.e. patients with more than one CV risk factor or with established atherosclerosis) aged 40 years and above. Patients in the highest CIMT tertile (>1.18mm) had a 5.5 times greater risk of a CVD event than patients in the lowest tertile (CIMT<0.90mm) after adjustment for age and sex over 2.6 years of follow-up. And each increase of one standard deviation (=0.46mm) of CIMT was associated with a 34% increased risk of a CVD event. The prognostic value of CIMT for CVD risk was even greater in a subgroup of 574 patients without CVD history. In this group, those in the highest CIMT tertile (>1.10mm) had 12.1 times greater risk of a CVD event than patients in the lowest CIMT tertile (<0.83mm). In addition, per increase of one standard deviation of CIMT there was an associated 57% increase in the risk of a CVD event. (402) These studies suggest the value of CIMT as a predictor for CVD in special groups is similar to that observed in large epidemiological studies in the general population.

Clinical trials have demonstrated the effect of pharmacological intervention on CIMT. The European Lacidipine Study on Atherosclerosis (ELSA) is a randomised intervention study where 2334 hypertensive patients were assigned to receive either lacidipine-based or atenolol based antihypertensive treatment. (403) The ELSA study found that the group receiving calcium antagonist lacidipine delayed IMT progression compared with the β-blocker atenolol, but IMT changes induced by these pharmacology agents did not have a predictive role for CVD and CVD-related death. Besides pharmacotherapy, a randomised, double-blind, controlled trial evaluating the effect of vitamin on IMT in patients at risk of cerebral ischemic (i.e. those with CIMT values ≥ 1mm) found that daily supplementation of 2.5mg folic acid, 25mg Vitamin B_6 and 0.5mg Vitamin B_{12} for one year reduced CIMT significantly (p=0.034), in contrast to the placebo group where CIMT increased. (404) It is unknown if vitamin supplementation-induced CIMT reduction would translate into positive change in the risk of CVD.

In summary, CIMT is an established surrogate marker of atherosclerosis. As most of the cardiovascular diseases originate from atherosclerosis, risk factors for CIMT and CVD are similar. Numerous studies, as presented earlier, showed that increased CIMT is proportionate to CVD risk and CVD-related death. Findings from studies of the general population and in patients with established CV risk factors seem to suggest that the latter group, even when receiving active treatment, has higher CIMT than the 'healthy' population. To draw a firm conclusion from this observation, an age-, sex-, and race- match study sample is needed for comparison. Older adults, particularly those in very old age, who generally have established CV risk factors, should not be excluded from studies exploring the relationship between CIMT and CVD. This is because some CV risk factors change with increasing age, for example, BMI, total cholesterol and blood pressure decreases in the very old age. (22, 23, 150) Thus, the impact of the CV risk profile observed in the younger elderly may be different in those of advanced age. Atherosclerotic changes occur throughout the life-time and are a cumulative measure of cardiovascular risk for an individual. CIMT, a variable determined non-invasively, is a well accepted indicator for manifestation of clinical CVD.

2.9 Brain natriuretic peptide

Brain natriuretic peptide (BNP) belongs to the natriuretic peptide family and is mostly synthesised and released primarily by the cardiac ventricles in response to myocardial stretch and wall tension. (405) BNP is synthesised as a prehormone comprising 108 amino acids. Upon release into the circulation, it is cleaved in equal proportions into the biologically active 32-amino acid BNP and the biologically inactive 76-amino acid N-terminal pro-BNP (NT-proBNP). (406) In healthy adults, age and sex are the key determinants of natriuretic peptide levels. (407-409) In comparison to men, women had higher natriuretic peptides levels and the level increased with age. (407, 410-412)

Measurement of BNP assists in discerning congestive heart failure (CHF) from other diagnoses in patients with symptoms of dyspnoea. (410, 413, 414) In emergency departments setting, BNP (32 amino acid) alone, at a level of 94pg/ml, has an accuracy of 91% (area under the curve, AUC = 0.97) for diagnosing CHF (413), and when combined with clinical, ECG, and chest X-ray information, the accuracy is 97%. (414) In similar setting, NT-proBNP alone, at a level of 450pg/ml

for adults less than 50 years old and 900pg/ml for adults 50 years and above, has an accuracy of 83% and 87% respectively (AUC = 0.94) (415) for diagnosing CHF. (415) In the primary care setting, provision of NT-proBNP results with GP clinical assessment improved the diagnostic accuracy for CHF from 49% to 70% (AUC = 0.85). (416) By and large, BNP and NT-proBNP are robust biomarkers for a diagnosis of heart failure. Comparison studies showed there were subtle differences in the diagnostic performance of BNP and NT-proBNP, in relation to patients' clinical characteristics, in patients with symptomatic heart failure. (417, 418)

The prognostic performance of BNP and NT-proBNP has also been evaluated. In patients with CHF, BNP levels predict worsening of heart failure (HF), future hospitalisation, and exercise capacity. (419, 420) Similarly, in patients with CHF, levels of NT-proBNP were associated with increased risk for HF events and all-cause mortality. (421) In patients (mean age 63 years) with suspected coronary artery disease, BNP predicted HF admission and death, independent of conventional risk factors, use of β-blockers, ACE inhibitors, angiotensin receptor blockers, statins, ejection fraction, and LV end-diastolic pressure. (422) In patients (mean age 70 years) with symptoms of breathlessness and/or oedema, NT-proBNP predicts hospitalisation. (423) It was also found that in the general population, elevated NT-proBNP concentrations is a strong predictor of cardiac morbidity and all-cause mortality. (424, 425) In apparently healthy community dwelling adults (mean age 77 years), a 1-SD increase in log NT-proBNP was associated with 39% increase in the risk of mortality of any cause. (425) The prognostic performance of BNP and NT-proBNP did not differ materially. (417, 418)

Although the prognostic performance between BNP and NT-proBNP were mainly found to be similar (417, 418), NT-proBNP had a slightly better predictive value for asymptomatic structural or functional cardiac abnormalities (410, 418, 426), particularly among high-risk adults (men age 50 years and above, or with hypertension) (410) than BNP. This is likely due to the wider reference range of NT-proBNP enabling detection of the slightest elevation of NT-proBNP levels in adults with subclinical cardiac abnormalities. (406, 410) The wide reference range of NT-proBNP is attributed to a longer half-life of NT-proBNP than BNP (120 minutes versus 20 minutes), i.e. a higher circulating level of NT-proBNP (approximately six times higher) than BNP values. (406) Besides cardiac ventricles, in-vitro studies report that BNP is directly released from cardiomyocytes in response to myocardial ischemia. (427) Thus, it has been proposed that natriuretic peptide levels

are associated with pre-clinical ventricular impairment and pre-clinical CVD. (427) In the Cardiovascular Health Study, older adults with elevated NT-proBNP levels has substantial risk for developing atrial fibrillation; a 1-SD increase in log peptide value was associated with 50% increase in the risk of developing atrial fibrillation. (428) The opportunity of NT-proBNP as a screening test for LV dysfunction and CV risk prediction is being explored. (410, 424, 429)

Collectively, studies showed BNP and NT-proBNP are robust cardiac markers for diagnosing heart failure and assessing a prognosis in patients with established heart failure or cardiac dysfunction. Studies showed that the diagnostic and predictive values of BNP and NT-proBNP were also acceptable in older adults with and without clinical CVD. Between BNP and NT-proBNP, the latter has a better predictive value for subclinical abnormalities. Further research is needed to determine the prognostic performance of natriuretic peptide for LV dysfunction in the general population, particularly in those living to advanced age.

2.10 Left ventricular structure and function

The aged heart is inherently associated with aged cardiomyocytes. Ageing of the cardiomyocytes is attributable to both intrinsic (e.g. genetic material and increased oxidative stress) and extrinsic (e.g. environmental) factors, and the interaction of these two factors regulates the pace of ageing of the cardiomyocytes. (430) Altered gene expression leads to defective activation, contraction and relaxation of myocytes. Telomeres, which cap and protect the end of the chromosome from deterioration, have been found to be related to left ventricular (LV) function, cardiovascular disease and mortality. (431, 432) Older adults with shorter telomeres have up to a three-fold increased risk of incident myocardial infarction and stroke. (433) Extrinsic factors such as cigarette smoking causes oxidative stress which down-regulates genes important for oxidant defence and affects the ability of a cell to repair DNA damage caused by oxidants. (430) Oxidative damage and cell necrosis promote repair and inflammation. In turn, inflammation causes oxidative stress and damage, creating a vicious cycle that accelerates the cardiomyocyte ageing process.

Aged cardiomyocytes have decreased mitochondrial function, decreased contractile function and increased susceptibility to apoptosis and necrosis. (152) Cardiomyocytes are low-proliferative cells (146, 415) Therefore, the remaining cells are enlarged to cope with the increased mechanical burden. This leads to increased heart mass and altered heart structure. (152, 430) In short, the

cardiomyocytes undergo a dynamic compensatory mechanism prior to the phenotypic manifestation of cardiovascular changes, both structurally and functionally. (152, 430)

Increase heart mass is associated with conventional CV risk factors. In a longitudinal study tracking more than 4,200 Framingham study participants[22] over a 16-year period, increased LV mass was associated with age, and this relationship was compounded by the presence of conventional CV risk factors, particularly higher blood pressure, higher BMI, smoking and diabetes mellitus. (434) Individuals with a higher CV risk factor burden had higher baseline LV mass, and they had a greater increase of LV mass over time compared to participants with a lower CV risk factor burden. Additionally, the study found a sex-related difference in the evolution of LV mass with age; women have a steeper increase in LV mass compared to men. Briefly, age is the common denominator in altered heart structure and function, and the presence of CV risk factors accelerates the process. The augmentation of LV mass with age is sex-specific.

Increased LV mass and divergence of structure from its original state is independently associated with CVD. In the Cardiovascular Health Study with more than 2,000 participants aged 76±5 years, each gram/meter$^{2.7}$ increase in LV mass was related to a 3% increase in risk of incident heart failure (HF), independent of the prevalence of myocardial infarction and CV risk factors. (435) A population-based case-controlled study[23] found that LV hypertrophy was associated with a 2.5-fold increase in risk of stroke after adjustment for other stroke risk factors. (436) Not only is enlarged LV mass associated with CVD, abnormal LV remodelling also carries an incremental risk of CVD. Three abnormal LV remodelling patterns are identified: concentric hypertrophy (increased mass and relative wall thickness), eccentric hypertrophy (increased mass but normal relative wall thickness), and concentric remodelling (normal mass but increased relative wall thickness). (437, 438) Concentric hypertrophy and concentric remodelling are observed in patients with diastolic heart failure, whereas eccentric hypertrophy is usually present in patients with depressed ejection fraction. (437) With regard to stroke risk, patients with concentric hypertrophy had the highest stroke risk (odds ratio 3.5, 95% CI 2.0–6.2), followed by eccentric hypertrophy and concentric remodelling. (436)

[22] The Framingham study with 4,217 participants with mean age at baseline 45(10) years

[23] A sample drawn from the Northern Manhattan Stroke Study with 394 cases (first ischemic stroke) and 413 control with mean age 68 (12) years.

Abnormality of the LV mass and LV structure disrupts the LV function. The mechanism leading to LV dysfunction is attributed to changes of the cardiomyocytes. Hypertrophied cardiomyocytes and alterations of the extracellular collagen network cause an inability of the myofibrils to relax completely; hence stiffness of the ventricle. (430, 439) Additionally, myocardial infarction results in replacement of myocytes with the fibrous scar tissues which can adversely impact LV function. (440) The stiff ventricle implies myofibrils are unable to rapidly or completely return to their resting length, leading to slow ventricular filling. Failure of the ventricle to relax adequately results in longer isovolumetric relaxation time, increased LV filling pressure, and left atrial enlargement. (441, 442) At the same time, the stiff ventricle has attenuated contraction strength, therefore is unable to eject blood into the high pressure aorta. Failure of the ventricle to contract efficiently leads to reduced ejection fraction and increased end-diastolic volume. (439, 443, 444) The hallmark of the aged heart is prolonged myocardial relaxation. (332)

In the general population, the prevalence of LV diastolic and systolic dysfunction increased with age. The prevalence of diastolic dysfunction was between 6.9% and 7.5% in 40-54-year-old and increased to 33% and 39% in adults above 70 years. For systolic dysfunction the prevalence increased from between 0.3% and 0.8% in 45-54-year-old to between 3.6% and 4.4% in adults above 75 years. (442, 445, 446) These studies suggest a higher prevalence of LV diastolic dysfunction than LV systolic dysfunction in the general population, and abnormalities of diastolic function rise more steeply with increasing decades of life. This observation was confirmed in the MONICA Augsburg study with 1,274 participants from the community aged between 25 and 75 years old. (441) Similarly, a retrospective cohort study of 1,160 older adults 65 years and above, free of CVD found 56% of the participants had mildly abnormal diastolic function, 23% moderately abnormal and 4% severely abnormal LV diastolic function (mitral E/A>1.5 or deceleration time $\leq$240ms), compared to 4% of the participants who had LV systolic dysfunction (ejection fraction <50%). (447) In the Newcastle 85+ study with adults average age of 85 years, 57% of the 89 study participants with an echocardiogram had evidence of at least mild diastolic dysfunction compared to 14% who had systolic dysfunction (ejection fraction <50%). (432) In brief, LV function declines with age.

The prevalence of LV dysfunction is likely to differ between men and women. Independent of age, the prevalence of LV systolic dysfunction was higher in men than in women. (34, 443, 446,

448) Nevertheless, the difference in the prevalence of LV diastolic dysfunction between the sexes was less definite. In the Flemish Study on Environment, Genes, and Health Outcomes, the prevalence of LV diastolic dysfunction was higher in women (442); in the MONICA Augsburg study, the prevalence was higher in men (441); and in the Olmsted County population study the prevalence of LV diastolic dysfunction was similar in both sexes. (446) The Flemish Study on Environment, Genes, and Health Outcomes and the MONICA Augsburg study had study participants of a similar age group, mean 51±14 years. The Olmsted County study sample was slightly older with participants' mean age being 63±11 years. In short, there was a distinct sex difference for LV systolic dysfunction but the relationship between the sex of the individual and LV diastolic dysfunction is less conclusive. Future studies determining the prevalence of LV dysfunction among individuals in their eighth or ninth decades of life will add evidence to the relationship between the sex of the individual and LV diastolic function.

The notion of LV function declining with age corresponds to the increasing prevalence of CHF with age. Left ventricular (LV) dysfunction is the main cause of CHF. LV dysfunction is often due to underlying coronary artery disease (and, frequently, prior myocardial infarction). LV systolic dysfunction is more commonly observed in patients with CHF. LV diastolic dysfunction, on the other hand, is frequently present in individuals without recognised symptoms. (445) In two population-based studies (The Echocardiographic Heart of England Screening study and the population study of Olmsted County) with participants' mean (± standard deviation) ages ranging between 61 and 63(±11) years, 41% to 45% of participants with CHF had LV systolic dysfunction (ejection fraction <40%). (445, 446) In the Rotterdam study with participants' mean age being 69±9 years, the proportion of LV systolic dysfunction (fractional shortening ≤25%) in those with CHF reduced to 29%. (443) The proportion of LV systolic dysfunction among CHF patients continues to decline in an even older population. In the Cardiovascular Health Study with participants' mean age being 77±5 years, 20% of participants with CHF had moderate to severely reduced systolic function. (449) Additionally, ninth-tenths of CHF incidence in community-based elderly people (mean age 73±5 years) was preceded by intact systolic LV function. (34) These results suggest CHF in the middle-aged is commonly preceded by LV systolic dysfunction, whereas in older individuals, LV diastolic dysfunction is probably a more common cause of CHF than LV systolic dysfunction. This phenomenon, heart failure with preserved systolic function, is more prevalent in elderly women who frequently have a prior history of hypertension. (439, 450)

Doppler echocardiography is a robust assessment for preclinical cardiac abnormalities, which include increased LV mass, abnormal LV remodelling, and LV dysfunction. Deterioration of cardiac function established by Doppler echocardiography is an independent predictor of all-cause mortality in the general population. (446, 451) Combining clinical risk factors and echocardiographic variables (LV ejection fraction<50%, evidence of any diastolic dysfunction, LA volume/body surface area $\geq$32ml/m^2, and LV mass/height of $\geq$120g/m) enhanced risk stratification which can better predict first cardiovascular events in older adults. (447)

2.11 Concluding remarks

The population is ageing and the oldest elderly (i.e. 85 years plus) are the fastest growing segment of the population. In the year 2004, 1.3% of the population in New Zealand was aged 85+ and consumed 10% of Vote Health Expenditure on health and disability support services. This figure is projected to increase to approximately 15% by 2021 when 2.3% of the population will be 85+. (5) Although death rates from coronary heart disease in New Zealand have improved since the 1960s (452), cardiovascular disease affects more than 45% of those reaching advanced old age and accounts for 53% of deaths among the oldest elderly. (3)

The existing literature sufficiently indicates lifestyle behaviour is likely to be the precursor of various cardiovascular risk factors. Over-nutrition and a sedentary lifestyle are closely related to obesity, increased insulin resistance, type 2 diabetes, hypertension, and dyslipidemia. While CV risk factors associated with lifestyle behaviour are modifiable, the non-modifiable risk factors, i.e. age, sex, and genetic factors, have no lesser contribution to CVD risk. Collectively, interactions of these risk factors determine the risk of a first cardiovascular (CV) event in middle-aged adults. The relationship between CV risk factors and CVD risk alters in the sixth and seventh decade of life.

After the seventh decade of life, the relationship between conventional CV risk factors and CVD risk and mortality is altered. The linear relationships between CVD risk and systolic blood pressure (SBP), BMI and total cholesterol levels (TC) became inverse. Higher SBP, BMI and TC, which have an adverse effect on CV health in middle age and younger-old adults, were found to be protective against an increase in mortality risk in people of advanced age. (214, 236, 237, 453) Regardless, more than 50% of deaths in people of advanced age are attributed to CVD. In the Health in Men Study (HIMS), a prospective cohort study of more than 4,300 men with an average age of 75 years,

conventional vascular risk factors (diabetes, cholesterol and blood pressure) were not independently associated with incident stroke/MI. (454) This finding suggests that new, emerging CV risk factors may have replaced conventional CV risk factors in advanced age. In the HIMS study, the variables that are independently associated with incident stroke/MI are age, DBP ≤70mmHg, CRP≥3mg/L, homocysteine≥15μmol/L, WHR≥1, and a fair or poor self-rated health. (454) Perhaps certain CV risk factors emerge to have a greater effect on CVD risk in advanced age.

In the last decade, extensive research explored the relationship between the inflammatory process and atherogenesis. Through biological cell research, we have extended our understanding of atherosclerotic lesions. Constant exposure to conventional CV risk factors, e.g. smoking, hyperlipidemia, hypertension, hyperglycaemia and obesity leads to endothelial injury, thus activating the immune system. (19) This response aims for tissue reparation and to facilitate a return to physiological homeostasis. Unabated inflammatory processes in the injured artery will result in an advanced lesion leading to atherogenesis. (18) Physical disruption of the atherosclerotic plaque is a common aetiology for coronary arterial thrombi that cause fatal acute myocardial infarction. (89) Inflammatory markers (CRP, IL-6, TNF-α, fibrinogen, and ESR) are elevated during chronic inflammation. Epidemiological studies provide good evidence that inflammatory markers are associated with an increased risk of CVD in middle-aged adults. The utility of CRP in CVD risk assessment remains an open topic (455, 456) The relationship between inflammatory markers and CVD observed in the younger population seems to persist into advanced age but this is yet to be established.

CIMT, a measure of sub-clinical atherosclerosis, is a novel risk factor which indicates the total atherosclerotic burden. (21) CIMT is closely linked to conventional CV risk factors and inflammatory markers. In the general population, CIMT is found to increase by 0.01mm per annum. (389, 390) Epidemiological studies have consistently shown that CIMT predicts CV events. (379) In adults aged 65 years and above, a 0.20mm higher CIMT was associated with a 9% increased risk of coronary disease, a 24% increased risk of myocardial infarction, and a 28% increased risk of stroke. (390, 394) A recent review article showed that the predictive value of CIMT is possibly sex- and CV outcome-specific. (380) More investigations are needed to establish the relationship between CIMT and CVD risk in advanced age, who has a higher incidence of coronary artery disease and stroke.

Left ventricular (LV) mass and function changes with ageing. Epidemiological studies show a linear relationship between age and increasing LV mass and declining LV function. In older adults (mean age 76 years), each gram/meter$^{2.7}$ increase in LV mass was related to a 3% increase in the risk of incident heart failure (435) and LV hypertrophy was associated with a 2.5-fold increased risk of stroke. (436) LV dysfunction is common among older people. (442, 445, 446) In the general population, LV diastolic dysfunction (ranges between 21% and 27%) is more common than LV systolic dysfunction (range between 2% and 6%), and diastolic dysfunction is more likely with increasing age. (442, 445, 446) Compared to LV systolic dysfunction, LV diastolic dysfunction is frequently present in individuals without recognised symptoms. (445) In population-based studies, it seems heart failure in middle-aged adults is commonly preceded by LV systolic dysfunction, whilst in older adults LV diastolic dysfunction is probably a more common cause of heart failure. Studies unanimously indicated that LV diastolic dysfunction is common in the younger elderly adults. In people of advanced age, the Newcastle 85+ Study reported that 57% of those living to advanced age had evidence of at least mild diastolic dysfunction. (432) Population-based studies are needed to establish the prevalence of LV diastolic dysfunction in the advanced-age population. Prospective studies will inform the prognosis to guide the management of LV diastolic dysfunction in those living to advanced age.

In summary, the inter-relationships between CV risk factors are complex and likely to evolve in a cyclical way. Lifestyle plays an important role in CV health. The mechanism underpinning the relationship between lifestyle behaviours and CVD risk are CV risk factors and an unfavourable inflammatory profile (30, 107, 160). (Figure 2-3, page 74) The synergistic impact of CV risk factors on the arterial structure and function initiate the atherosclerosis process. The pathophysiological pathways leading to inflammation and, subsequently, atherosclerosis were showed in Figure 2-1 (page 20). Atherosclerosis is the result of a chronic effort to eradicate local inflammatory triggers (e.g. cholesterol deposits and smoking) and to repair the damaged vascular wall (resulting from mechanical stress). Over time, these protective responses turn into a harmful, self-perpetuating process inside the arterial wall. (457) Atherosclerotic lesions release pro-inflammatory markers, thus amplifying and sustaining pro-inflammatory signals and creating a vicious cycle. Atherosclerotic lesions progress to atherosclerotic plaques. Meanwhile, excessive repair to a damaged vascular wall leads to diminished function of the vascular wall. (18) Vasculopathy is a precursor for the ischemic conditions of the heart. Consequently, remodelling of the heart structure

is triggered to preserve cardiac hemodynamic. The remodelling process cause changes to the heart structure and may lead to LV dysfunction which usually precedes heart failure. Alternatively, vasculopathy in the cerebrovascular system leads to transient ischemic stroke and full-blown stroke. Clinically manifest CVD usually requires hospitalisation and is related to disability. (7, 8, 11, 42, 160) (Figure 2-3) Those who survive the disease may have disability or restricted physical function, limiting the activities of daily living of the affected individual. (458) Therefore, they are likely to be at risk of undernutrition. Prolonged exposure to the risk of undernutrition leads to malnourishment which may contribute to further deterioration of cardiovascular health. Low levels of vitamin antioxidants (vitamin B_6, B_{12}, C and D) were associated with increased CVD risk. (18, 84-98) Without timely and effective intervention (both lifestyle and pharmacological intervention), the existing CVD condition will deteriorate further leading to worsening of physical function (459), thus entering a downward spiral of declining CV health. (Figure 2-3)

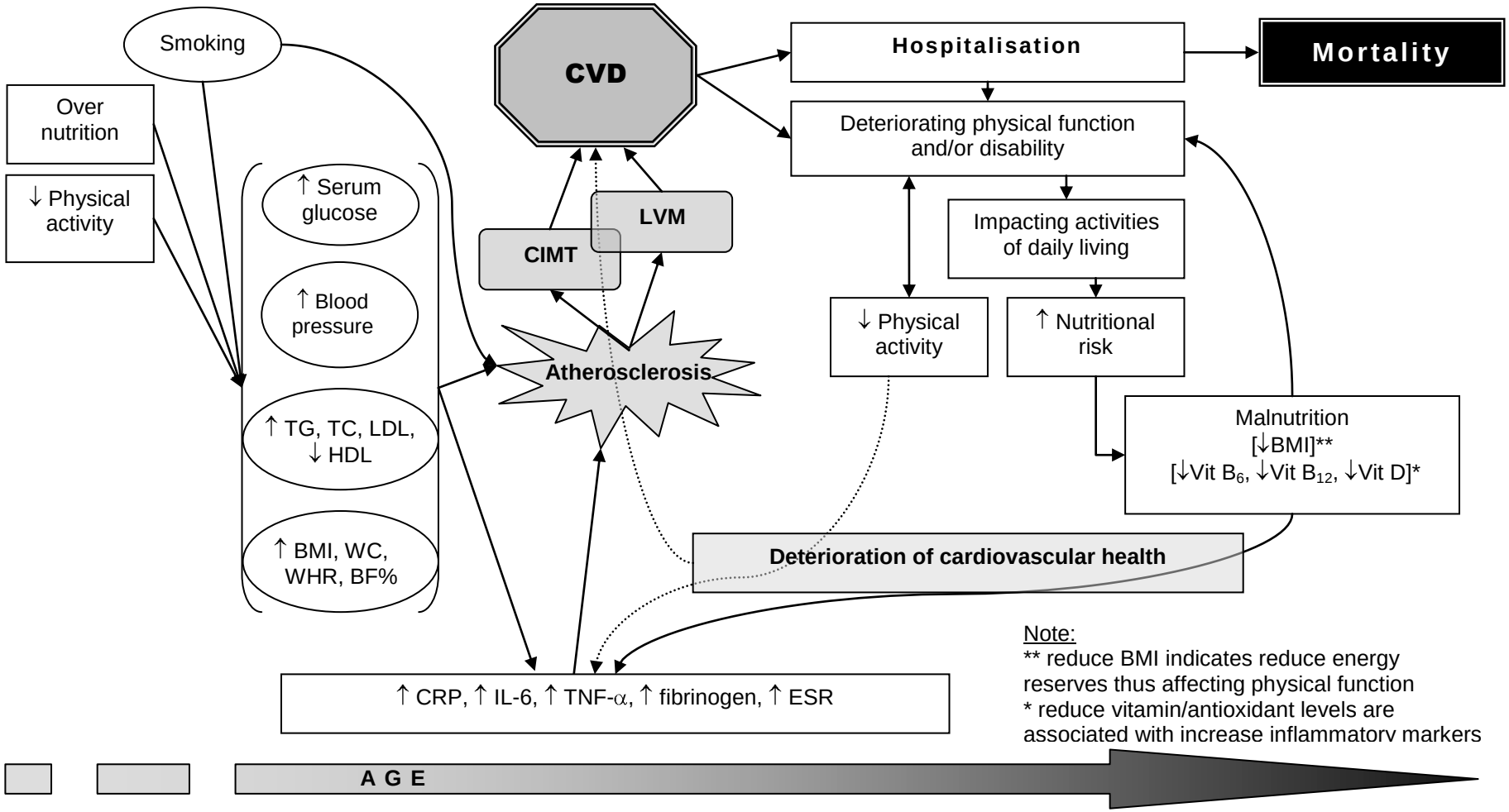


Figure 2-3: The pathways of CVD, its consequences and impact on cardiovascular health
Abbreviations: **BF%:** percentage of body fat; **BMI:** body mass index; **CIMT:** carotid intima-media thickness; **CRP:** C-reactive protein; **CVD:** clinically manifest cardiovascular disease; **ESR:** erythrocyte sedimentation rate; **HDL:** high-density lipoprotein; **IL-6:** Interleukin-6; **LDL:** low-density lipoprotein; **LVM:** left ventricular mass; **TC:** total cholesterol; **TG:** triglyceride; **TNF-α:** tumour necrosis factor-alpha; **WC:** waist circumference; **vit:** vitamin: **WHR:** waist-to-hip ratio

2.12 Rationale for the study

Epidemiological studies have so far provided insights, although limited information, about CV risk factors and CVD in adults of advanced age. The relationship between conventional CV risk factors and CVD may alter in the seventh and eighth decade of life. Conventional risk factors seem to have a non-linear relationship with CVD risk in those of advanced age. Firstly, older adults in the mid-seventies (6) are more likely to have isolated systolic hypertension, which is associated with increased heart failure risk. (213) But among those 85 years and older, CHF patients with increased systolic blood pressure have a better chance of survival than those with normal systolic blood pressure. (214) So, is systolic hypertension a CV risk or protective factor in adults of advanced age? Secondly, BMI increases up to 65 years old and then gradually decreases in the seventh decade. (460) The association between BMI and CVD increases up to 75 years and seems to diminish thereafter. (243, 461, 462) Among hospitalised patients above 80 years old, low BMI was an important predictor of all-cause and CVD mortality. (238) Is BMI a protective factor for CV health in those living to advanced age? Thirdly, LDL reduction is proportional to the magnitude of CV risk reduction in octogenarians (463), but the risk of fatal heart failure and all-cause mortality decreases with a higher LDL level (a J-shape relationship), and a high total cholesterol level has been linked to longevity in the oldest elderly. (293, 464, 465) Is total and LDL cholesterol a risk or protective factor for CV health in adults of advanced age? These studies underline the fact that the relationship between conventional CV risk factors and CVD risk may differ in people of advanced age.

Presuming conventional risk factors in the middle-aged has lead to premature mortality, those living to advanced age may have either different CV risk factors or different pathways to CVD. Inflammatory markers increase with age. (31, 32, 343, 466) The relationship between inflammatory markers and the risk of CVD observed in younger people continues in a similar manner even into very old age. (33, 36, 293, 467) For this reason, increased levels of inflammatory markers could be an important CV risk factor in those of advanced age. This research area merits further investigation.

Concerning vascular and cardiac structure and function, there are very few studies involving those in advanced age. Almost all population-based studies examining carotid intima-media

thickness (288, 383, 390, 395), LV mass and function, and their relationship with increased CVD risk (34, 435, 436, 441-443, 445, 446, 449) have the participants' average age at younger than 85 years old. This research gap calls for studies to investigate vascular and cardiac structure and function in those of advanced age.

In brief, information on CV health in those of advanced age is scarce. As the population is ageing, the inter-relationship between CV risk factors (both conventional and emerging risk factors), LV structure and function and CVD in adults of advanced age warrants further research. This is because understanding of the current CV health profile and its risk factors will assist in development of intervention strategies to prevent deterioration of CV health for those in advanced age. Furthermore, insights gained will inform and assist preparation for sustainable health care services to accommodate the growing size of the advanced age population.

This thesis aims to determine the cardiovascular health profile and its risk factors in advanced age. Findings from this research will extend existing evidence on CV risk factors and the CVD risk of the ageing population. The next chapter will stipulate the study aims for this thesis, followed by the study design and methods to attain the study aims.

CHAPTER THREE: METHODS

This PhD thesis was part of a larger study funded by the Health Research Council (HRC) of New Zealand: Living to advanced age – feasibility for a cohort study. The feasibility study aimed to establish the feasibility of a longitudinal cohort study in those of advanced age. The main aim of the proposed cohort study was to identify predictors of successful advanced ageing. The feasibility study developed a comprehensive evaluation of people in advanced age, identifying relevant enquiry domains and measurement tools to conduct a broad assessment of health, social, cultural, economic, and environmental status. The feasibility study established the appropriate consultation methods to successfully recruit older people.

The objectives of this thesis are separate from the objectives of the HRC feasibility study and while the processes overlapped, the cardiological enquiry belongs to the thesis. The candidate contributed all the cardiovascular and cardiological aspects of the feasibility project, including relevant sections of the questionnaire, conducted the ECG and physical assessments, contributed to conducting the comprehensive interviews, analysed the CIMT values from the carotid images obtained by the ultrasonographer, designed and conducted the data management and analysis, completed the interpretations and wrote the thesis.

This chapter will state the aims of the thesis followed by detailed description of the study design and methods engaged to address these aims.

3.1 Aims

Since the Framingham Heart Study which began enrolment in 1948, risk factors have been identified for the development of cardiovascular disease (CVD). Age, male sex, family history of CVD, cigarette smoking, hypertension, diabetes, dyslipidemia and obesity – known as conventional cardiovascular risk factors, are closely related to an increased risk of CVD. In the last decade, atherosclerosis, the underlying cause of CVD, has been identified as an inflammatory disease. (18) Hence, inflammatory markers have been included in the list of potential cardiovascular risk factors. Conventional risk factors and inflammatory markers are influenced by lifestyle factors, which in turn may mediate structural changes of the vessels and ventricles. These risk factors have been studied in depth in people of middle and early old age. There are some people who reach advanced old age

without clinical manifestation of CVD and those who do reach old age have outlived the chronic diseases such as diabetes that cause mortality in younger old-age.

This thesis aims to assess the cardiovascular health and examine the relationships between cardiovascular risk factors and presence of clinically manifest CVD in people of advanced age. Cardiovascular risk factors examined were nutritional risk, physical activity, conventional cardiovascular risk factors, nutritional biomarkers, inflammatory markers, carotid intima-media thickness (CIMT), left ventricular mass (LVM), and N-terminal pro-brain natriuretic peptide (NT-proBNP). The main outcome measure was clinically manifest CVD and the secondary outcome measures were CIMT and LVM (TABLE 3-1).

Specific aims for study of cardiovascular health in people of advanced age:

1. To examine the associations between lifestyle factors with conventional cardiovascular risk factors, nutritional biomarkers, and inflammatory markers.
2. To examine the associations between CIMT and LVM with lifestyle factors, conventional cardiovascular risk factors, nutritional biomarkers, and inflammatory markers.
3. To examine the associations between clinically manifest CVD with lifestyle factors, conventional cardiovascular risk factors, nutritional biomarkers, and inflammatory markers controlling for CIMT and LVM.

TABLE 3-1: Variables examined in this study

Cardiovascular risk factors				Outcome
Lifestyle factors: ▪ Nutritional risk ▪ Physical activity	**Conventional cardiovascular risk factors:** ▪ Smoking ▪ Fasting glucose ▪ Blood pressure ▪ BMI ▪ WC ▪ WHR ▪ BF% ▪ TC ▪ TG ▪ HDL ▪ LDL ▪ TC-HDL ratio	**Nutritional biomarkers:** ▪ PLP (Vit B_6) ▪ Cobalamin (Vit B_{12}) ▪ 25-OH D (Vit D)	CIMT	**Primary:** ▪ CVD
		Inflammatory markers: ▪ CRP ▪ IL-6 ▪ TNF-α ▪ Fibrinogen ▪ ESR	▪ LVM ▪ NT-proBNP	**Secondary:** ▪ CIMT ▪ LVM

Abbreviations: **25-OH D:** 25-hydroxyvitamin D; **BF%:** percentage of body fat; **BMI:** body mass index; **CIMT:** carotid intima-media thickness; **CRP:** C-reactive protein; **CVD:** clinically manifest cardiovascular disease; **ESR:** erythrocyte sedimentation rate; **HDL:** high-density lipoprotein; **IL-6:** Interleukin-6; **LDL:** low-density lipoprotein; **LVM:** left ventricular mass; **NT-proBNP:** N-terminal pro-brain natriuretic peptide; **PLP:** pyridoxal 5' phosphate; **TC:** total cholesterol; **TG:** triglyceride; **TNF-α:** tumour necrosis factor-alpha; **WC:** waist circumference; **WHR:** waist-to-hip ratio

3.2 Study design and recruitment

A cross-sectional study design was used to identify the status and relationships between cardiovascular risk factors and outcome measures. Study participants were identified and recruitment was carried out in three areas in the North Island: Rotorua, Whakatane and Opotiki. The recruitment in Rotorua was completed through Rotorua General Practice Group (RGPG)[24] and Korowai Aroha Health Centre, a local Māori Health Service. Participants from Whakatane and Opotiki were recruited through the Eastern Bay of Plenty District Health Board (EBOPDHB), Māori Health Services, Whakatane, and Whakatohea Iwi Social and Health Services, Opotiki.

A purposive sampling was carried out with recruitment completed using two methods: 1) direct mailing of study information and invitation letters through local general practitioners with a follow-up telephone contact by the practice nurse, and 2) personal approach through a personal contact of local health services personnel or a study interviewer. These methods were chosen because direct mailing from a trusted source (the general practice) is likely to generate the highest recruitment rate of age-eligible individuals (468), and local consultation with health and cultural organisations indicated that personal contact was the more appropriate approach to invite older Māori to participate in the study. Participants enrolled in the study were contacted and interviewed by one of

[24] RGPG is an independent practitioners group working in a Primary Health Organisation

seven interviewers in the respective study area, and completed a series of study visits as depicted in the following flow chart (Figure 3-1).

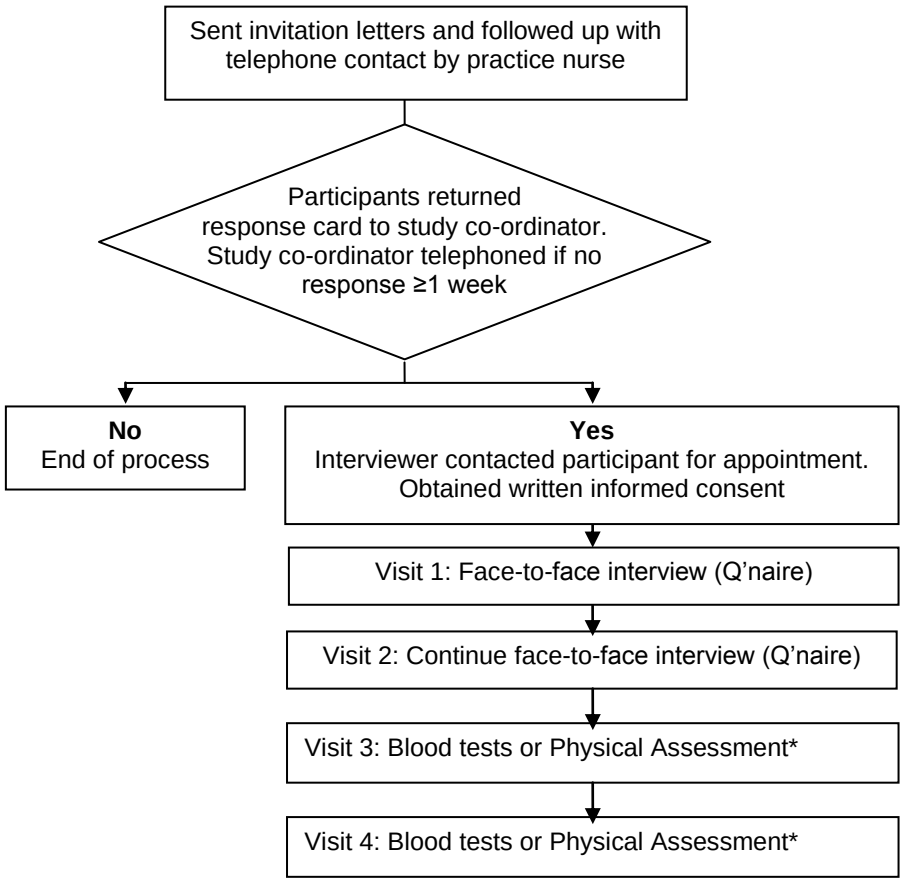


Figure 3-1: Flow chart of study visits
* Physical Assessment included: Measurement of height, weight, waist and hip circumference, blood pressure, ultrasound imaging: measures of right carotid artery and echocardiography, ECG, bioimpedance analysis.

3.3 Data collection

As shown in Figure 3-1, the study consists of three phases: study questionnaire, physical assessments, and a fasting blood test. The questionnaire was administered through face-to-face interviews conducted either at the participants' residence or the local health care centre. Six interviewers were identified from Rotorua, Whakatane and Opotiki, plus an interviewer from Auckland to administer the standardised questionnaire. All interviewers completed a one-day standardised interviewers' training session with briefing on study objectives and procedures, familiarisation with the questionnaire, and administration of the questionnaire. Physical assessments were performed by the research team from Auckland at local health centres. For participants having difficulties getting to the health centre, either due to physical condition or logistical issues, physical assessments were completed at the participants' residences by the same

research team. Similarly, blood samples were collected either at a local laboratory or by a trained phlebotomist going to the participants' homes if they had physical difficulties or requested this.

Three central laboratories were involved in analysis of blood samples: Diagnostic Rotorua, LabPlus and Canterbury Health Laboratories (CHLab). Each of these laboratories conducted a specified list of blood analysis, as shown in Figure 3-2. All three laboratories were accredited by International Accreditation New Zealand and were briefed on the study purpose and timeline. Figure 3-2 illustrates the logistics of collected blood samples from study areas to central laboratories.

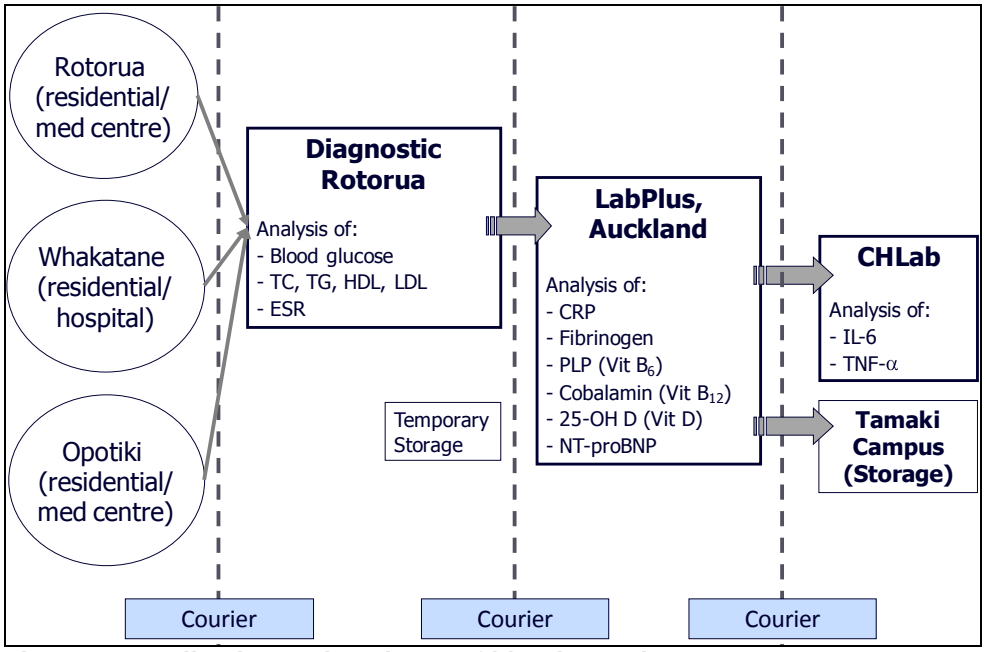


Figure 3-2: Collection and analyses of blood samples
Abbreviations: **25-OH D:** 25-hydroxyvitamin D; **CRP:** C-reactive protein; **ESR:** erythrocyte sedimentation rate; **HDL:** high-density lipoprotein; **IL-6:** Interleukin-6; **LDL:** low-density lipoprotein; **NT-proBNP:** N-terminal pro-brain natriuretic peptide; **PLP:** pyridoxal 5' phosphate; **TC:** total cholesterol; **TG:** triglyceride; **TNF-α:** tumour necrosis factor-alpha

3.4 Study sample

The study population were Māori 75-79 years and all ethnic groups who turned 85 years old during the data collection period, i.e. January to August 2008. This group represents the top percentile of the New Zealand population. (42) Eligible older persons were all those who understood and were able to communicate in English or in te reo Māori, were able to provide written informed consent, or had a family member/whānau with whom to discuss the study for a proxy consent.

A younger age group for Māori participants was selected because Māori have a higher mortality, attributable to circulatory diseases at earlier ages. (42) For example, the mean age of stroke for Māori has been reported as 55 years compared to 73 years in New Zealand Europeans. (469) Cardiovascular risk factors are higher for Māori than non-Māori independent of age group. Within the population of those aged 65+ years, there were more Māori who are overweight or obese, smoked tobacco, less likely to consume the recommended servings of fruit and vegetables per day, and less likely to participate in regular physical activity, compared to non-Māori. (470) Life expectancy for Māori men is 69 years, and for women 73 years; a disparity of 8.2 years and 8.8 years compared with non-Māori men (77 years) and women (82 years) respectively. (471) The top percentile for Māori thus differs from that for non-Māori and the selection criteria recognised this.

The study included a representative sample of Māori participants in the study as this conforms to Article 3 of the Treaty of Waitangi which grants Māori equal access to health care resources.

3.5 Sample size calculation

It is estimated that at least 30% of participants will have had CV events allowing comparison between those with and those without clinically manifest CVD. A sample size of 115 participants will have 80% power at the 0.05 level of significance to detect a difference in CRP of 1.2mg/L in those with and those without clinically manifest CVD. This is based on a meta-analysis by Danesh *et al.* (472) comparing the lowest one third to the highest one third with a standard deviation of the log CRP of 0.33 and a difference in the logged scores of 0.21. The same sample size will have 80% power at the 0.05 level of significance to detect a difference in fibrinogen of 1.0 g/dL with standard deviation of 0.1g/dL in those with and those without clinically manifest CVD. Elizabeth Robinson (biostatistician) assisted with the sample size estimate.

The power calculation for selected major CV risk factors (systolic blood pressure, HDL and CRP) was determined using the standard deviation available from the study sample.

3.6 Ethics Committee

The study obtained approval from the Multi-Region Ethics Committee, Ministry of Health New Zealand in June 2007 (MEC/06/10/135). (Appendix A, Figure A-1 page 291)

3.7 Study timeline

The study began recruitment in Opotiki in January 2008. The first physical assessment session was in Rotorua in early March, and blood samples were first collected and analysed in Rotorua at the end of March. (Figure 3-3) Physical assessments were done at least once a month and the last session was completed by the end of July 2008. Blood samples were collected up until August. The last participant completed the face-to-face interview, physical assessment, and blood test in August 2008.

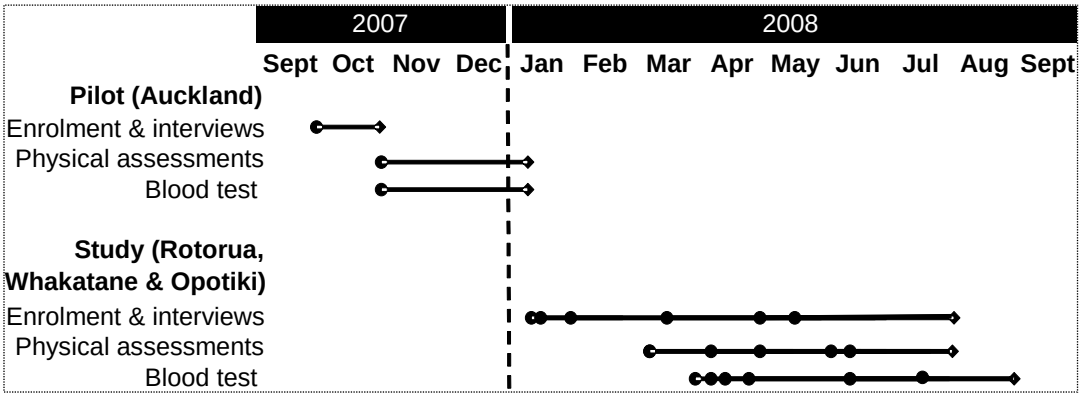


Figure 3-3: Timeline for study recruitment and completion

3.8 Study measures

Information collected included demographic data, medical history, use of medications including hormone replacement therapy (for female participants), nutritional supplements and herbal products, alcohol consumption, cigarette smoking status, nutritional risk, and physical activity. These were obtained through face-to-face interviews guided by a standardised questionnaire administered by trained interviewers. Interviews were carried out at the participants' home or health/medical centres based on the participants' preference.

Physical and health assessments performed included blood pressure, anthropometry measurements, percentage of body fat, biomarkers, electrocardiogram, carotid intima-media thickness, and left ventricular mass. Participants were given the option of whether to have physical and health assessments done at the local health care centre or at home. All assessments were performed by trained study personnel.

The following will describe specific variables most pertinent to this thesis in the following order: cardiovascular risk factors and outcome measures.

3.8.1 Cardiovascular risk factors ascertained through standardised questionnaires

Nutritional risk

Nutritional risk was assessed using the validated questionnaire – SCREEN II (Seniors in the Community: Risk Evaluation for Eating and Nutrition, version II). SCREEN II is a 14-item questionnaire which consists of items pertaining to the three attributes of nutritional risk which provide information on weight change, food intake (consumption of vegetables/fruit, meat/meat alternative, milk/milk products, and fluid intake) and risk factors for food intake (meal frequency, diet restriction, appetite, chewing and swallowing difficulties, meal replacement, eating alone, meal preparation, and shopping difficulties). (473) SCREEN II has been identified as a sufficiently suitable and reliable tool to identify nutritional risk for this study because it has been validated in community–living seniors. Additionally, SCREEN II requires minimal training and had demonstrated high agreement between self- and interviewer– administration of the questionnaire. (473) Detailed assessment of nutrient and energy intake was beyond the scope of the study. We considered food frequency questionnaires and food intake diaries and, after discussions with the group involved in the Newcastle 85+ study (personal communication with Prof Ashley Adamson), deemed food frequency assessment to be constrained by time in interviewing and diaries to be too great a participant burden.

Physical activity

Physical activity levels were identified with a face-to-face interview using a validated questionnaire for the elderly – Physical Activity Scale for the Elderly (PASE). PASE is a brief questionnaire consisting of ten main questions which identify leisure, household and work–related activity, and duration of each activity over a one-week period. Leisure activities were recorded in both frequency and duration. Frequency is categorised as never, seldom (1-2 days/week), sometimes (3-4 days/week), and often (5-7 days/week). Duration is categorised as less than 1 hour, between 1 and 2 hours, 2-4 hours, or more than 4 hours. Household activities were recorded as yes/no. Work–related activities were recorded in total hours per week. Scoring method: The total PASE score was computed by multiplying the duration of each activity (hours/week) or participation (yes/no) by the empirically derived item weights and summing over all activities. (117) PASE has been selected to determine physical activity in this study because its validity and

reliability as a measure of physical activity in adults aged 65 years and over has been established and the scale has been found suitable for use in epidemiological studies. (117, 474)

Cigarette smoking

Cigarette smoking status was identified by self-report on interviewer administered standardised questionnaire. Additionally, the age at which participants started and stopped smoking and numbers of cigarettes smoked were determined in order to report a pack year history of smoking.

3.8.2 Cardiovascular risk factors ascertained through physical assessments

Blood pressure

Systolic and diastolic blood pressures were recorded after the participant had been seated for at least five minutes, using a digital blood pressure monitor (Microlife BP A100). A participant with an irregular pulse rate or atrial fibrillation had the blood pressure measured with a manual sphygmomanometer. The average of three measurements was used for analysis.

Anthropometry measurements

Height was measured with participants standing bare foot, and measurement recorded to the nearest 0.1cm using a portable stadiometer. Duplicate measures were obtained, and if the difference between the first two measurements was more than 0.5cm, a third measurement was completed. For participants who were not able to stand, or with significant kyphosis or vertebral collapse, height was estimated with the demispan. Demispan is the measure from the midline of a participant's sternal notch to the web between their middle and ring fingers of the horizontally outstretched arm with the wrist in neutral rotation. This was measured using a stainless steel tape. Height in centimetres was then calculated with the following formula. When stature could not be measured, the measure was not completed.

Female: (1.35 x demispan in cm) + 60.1

Male: (1.40 x demispan in cm) + 57.8

Body weight was measured with the Tanita digital scale (Inner Scan Body Composition Monitor, BC-541, Tanita Corporation, Japan) to the nearest 0.1kg. The participant was requested

to stand on the scale, wearing light clothing. For those who were unable to stand on the scale, measurements were based on the participant's or carer's recollection of the last weight reading or the last recorded measure from the place of residence.

Body Mass Index (BMI) is weight in kilograms divided by height in metres squared. As BMI classification for older adults is yet to be established, the current World Health Organisation (WHO) classification was used. According to the WHO classification, a person is considered underweight when BMI is less than 18.5kg/m^2; normal range 18.5 to less than 25kg/m^2; overweight 25 to less than 30 kg/m^2; and obese is 30kg/m^2 and above. (218)

Waist circumference (WC) is the measure of distance around the abdomen. A non-stretchable tape was placed evenly mid-way between the lowest rib and the iliac crest with participants standing and breathing normally. **Hip circumference** is the measure of maximum circumference over the buttocks. Measurements of both waist and hip circumference were taken twice to the nearest 1.0cm and the average value was recorded. **Waist-to-hip ratio (WHR)** is waist circumference in centimetres divided by hip circumference in centimetres.

According to the WHO classification, the cut-off point for healthy waist circumference for men is <94cm and for women <80cm; values above this cut-off are termed as increased waist circumference. The cut-off point for healthy waist-to-hip ratio for men is $\leq$1.0 and for women $\leq$0.85; values above this cut-off are termed as high waist-to-hip ratio. (218)

Percentage of body fat

Percentage of body fat is a measure of body composition. Body composition was estimated from bioimpedance analyses using the *Tanita* Inner Scan Body Composition Monitor, BC-541, Tanita Corporation, Japan. Participants were requested to maintain a normal fluid balance and abstain from vigorous exercise and ingestion of alcohol and caffeine for at least 12 hours prior to assessment. Percentage of body fat was computed: fat mass (kg) $\div$ total body weight (kg) $\times$ 100.

Biomarkers

Blood samples were collected in the morning by venepuncture after an overnight fast of at least 8 hours, whenever possible, and the participant seated for at least 15 minutes. Blood drawn was

conducted by a phlebotomist or nurse trained in geriatric venepuncture. After collection, aliquots from local laboratories were sent to three central laboratories for determination of serum concentration of glucose, total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), pyridoxal 5' phosphate (PLP), cobalamin, 25-hydroxyvitamin D (25-OH D), high sensitive C-reactive protein (CRP), interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), fibrinogen, erythrocytes sedimentation rate (ESR), and N-terminal pro-brain natriuretic peptide (NT-proBNP). (Figure 3-2, page 81) Three central laboratories were used to run the specified tests to ensure the same analytical methods were applied to all samples. The total amount of blood sample required from each study participant was 31ml, which included the extra 5ml serum aliquot stored below -20°C for future analysis. The laboratory analysis method for each of the biomarkers are showed Appendix A (TABLE A-1, page 293).

- Interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α)

Analyses for IL-6 and TNF-α were performed by the Canterbury Health Laboratories. Sixty eight (77%) of the study participants had their serum analysed for IL-6 and TNF-α concentrations between June and October 2008. The majority of the results for both IL-6 (91%) and TNF-α (96%) were reported with a cut-off value of <1.6pg/mL and <7.8pg/mL, respectively. Due to the lack of sensitivity of the assay in detecting lower concentration of these two cytokines, the standard curve[25] for IL-6 and TNF-α was extended from an 8-point to a 10-point standard curve. The remaining participants' serum samples, 20 of them, were therefore measured with the extended 10-point standard curve in January 2009. With the 10-point standard curve, IL-6 concentrations as low as 0.2pg/mL and 1.0pg/mL for TNF-α, were able to be reported. The new lower level for IL-6 and TNF-α was the lowest possible detection limit without affecting the precision of the results. With extra funding made available, a decision was made to reanalyse stored serum samples of all 68 participants who had the blood analysis done in 2008. However, 13 participants did not have enough serum samples to re-run the test. The IL-6 and TNF-α re-test with the extended standard curve was completed in April 2009. The inter- and intra-assay coefficient of variation for IL-6 was 2.9% and 3.9%. The inter- and intra-assay coefficient of variation for TNF-α was 3.8% and 20.0%. Although the Canterbury Health Laboratories aims for intra-assay variability between 10-15%, the high intra-assay variability for TNF-α was within the acceptable limit. (Personal communication with

[25] Standard curve is the plotting of assay data that is used to determine the concentration of a substance

Dr. Myfanwy Spellerberg) This high intra-assay coefficient of variation for TNF-α was due to two different lot numbers with two different quality control (QC) values. The head of the immunology department who ran the test did not consider that such variability would affect the results.

With the new standard curve, the proportion of IL-6 results with an absolute value increased from 9% to 73%. The remaining 27% (n=20) of IL-6 results was reported as <0.2pg/mL. As for TNF-α, the proportion of results with an absolute value did not increase with the better detection standard curve. In other words, the majority of the participants with an initial TNF-α result of <7.8pg/mL (96%) also had results reported as <1.0pg/mL (88%) in the re-test.

There are at least two methods in dealing with biomarkers outside the detectable concentration. The first method is to retain the lowest reported value for statistical analyses and the other method is to perform a random imputation. (Personal communication with Steven Vender Hoorn) This study choose to perform a random data imputation for the 20 participants who had IL-6 results reported as <0.2pg/mL. The random imputation was done with a value between 0.1 and 0.2. The lower limit of 0.1 was selected based on several research articles reporting the detection limit for IL-6 as 0.1pg/mL (240, 290, 354); another reported the detection limit was 0.6pg/mL (31). The analysis method used in those studies was similar to this study, i.e. ELISA, but assay kits were from a different company. The imputation was done so that the variable could remain a continuous variable and the dataset would have a better power for univariate and multivariate analysis. This inaccuracy in 27% of the IL-6 values being spurious (imputed) is a limitation of the analyses but was considered to be acceptable as all the imputed values were in the lowest tertile of values and the continuous measure allowed greater discrimination in analyses which would have been valid at least for the upper two-thirds of values.

Electrocardiogram (ECG)

Electrocardiogram was done using Welch Allyn CardioPerfect Workstation PC ECG System. It was performed on the participant in the supine position with a standard ECG protocol. To minimise variation, all examinations were carried out using the same machine.

Carotid intima-media thickness (CIMT)

Images of the CIMT were digitally acquired with non-invasive B-mode ultrasounography, Sonosite MicroMaxx, with a 7·5-MHz linear-array transducer by research-trained sonographers. To minimise variation, all examinations were carried out using the same machine. Ultrasound imaging was performed on the participant in the supine position. The right common carotid artery (CCA), 5–10mm proximal to the carotid bulb, was used for measurements of intima-media thickness (IMT). The sonographer scanned longitudinally for all interfaces of the near and far walls of the distal CCA to obtain high image quality. In all cases, an average of three beats was used. The CCA was imaged because it had less variability in measurement compared to the internal carotid artery. (387) The actual measurements of CIMT of the far wall were performed off-line at the Department of Medicine by the candidate using an automated computerised edge-tracking method–SonoCalc ™IMT, Sonosite version 3.0.0.1. However, when the interfaces on the images were less clear, the automated edge detection programme was overridden by manual tracings. CIMT was measured at sites free of any discrete plaques and was defined as the distance between the lumen-intima interface and the media-adventitia interface. A random sample of ten CIMT images was visually re-assessed and verified by the experienced trainer cum researcher in CIMT. A quantitative assessment between raters was not completed.

Left ventricular mass (LVM)

A portable echocardiography device, Sonosite MicroMaxx, was used to evaluate cardiac size, structure and function in all consented participants. All images were digitally obtained according to a standardised protocol by trained research sonographers, with the participant in the supine position. Transthoracic echocardiography images were acquired in standard planes according to the American Society of Echocardiography (ASE) guidelines, including M-mode, 2D and Doppler techniques, and measured off-line (Digiview, Digisonics, Houston, Texas) without knowledge of the participants' clinical details.

Measurements recorded and analysed: *Left ventricular (LV) size and hypertrophy:* Measurements of LV wall thickness and diameter were obtained at end-diastole and LV dimension at end-systole. LV mass and fractional shortening were calculated. *Pulsed wave Doppler and tissue Doppler:* Mitral valve inflow pulsed wave Doppler (PWD) was recorded between the leaflet tips; tissue Doppler imaging (TDI) recordings were obtained from the medial aspect of the mitral annulus

in the apical 4-chamber view. All Doppler signals were acquired using a 5mm sample volume, optimized, and recorded at 100mm/s sweep speed.

LV mass was calculated according to the ASE using the cube-function formula: LV mass = 0.8 $\times$ {1.04 [(LVID + PWT + SWT)^3] – (LVID)^3} + 0.6g. (149) Due to the correlation between LVM and body size, LVM was corrected by indexing to height to the power of 2.7 ($Ht^{2.7}$). This adjustment is a sensitive and specific method in indentifying left ventricular hypertrophy. (475)
[*Abbreviations:* LVID: internal diameter of the left ventricle; PWT: posterior wall thickness; SWT: septal wall thickness]

Left ventricular (LV) function was assessed with echocardiographic parameters. **Left ventricular diastolic function** was assessed with ratio of mitral E velocity to mitral annular E velocity (E/E') and left atrial (LA) area. E/E' value is a measure of left ventricular (LV) filling pressure. A value of E/E'<8 suggests normal filling pressure and >15 suggests an elevated LV filling pressure; E/E' between 8 and 15 are intermediate values. (476) Left atria (LA) area reflects atrial function and may be enlarged when the pump function of the atrium is impaired due to atrial fibrillation and increased LV filling pressure. Enlarged LA area is defined as LA area $\geq$20cm^2 for both men and women. LA area between 20 and 30cm^2 were mildly enlarged, LA area between 30 and 40cm^2 were moderately enlarged, and LA area $\geq$40cm^2 were considered severely enlarged. (444) **Left ventricular systolic function** was assessed with fractional shortening (FS) and a visual assessment of LV systolic function. Fractional shortening was derived from formula *[(LV end-diastolic diameter – LV end-systolic diameter)/LV end-diastolic diameter] x 100*. Abnormal FS value is defined as FS<25% for men and 27% for women (TABLE 3-2). (444) A fractional shortening value of less than or equal to 25% corresponds to an LV ejection fraction of 42.5%. (443, 477) LV systolic function was assessed by an experienced cardiologist (R.N.D) based on the objective assessment of fractional shortening value and clinical interpretation of LV regional wall motion, LV size and visual interpretation of LV ejection fraction. LV systolic function was reported as normal, mild, moderate or severe. Presence of **valve disease**, defined as moderate or greater regurgitation, or stenosis of mitral, tricuspid or aortic valves, was also established using standard clinical interpretation of 2D and Doppler echocardiographic data (R.N.D).

TABLE 3-2: Reference values and partition values of left ventricular fractional shortening (%) for men and women

	Men	Women
Reference range	25 – 43	27 – 45
Mildly abnormal	20 – 24	22 – 26
Moderately abnormal	15 – 19	17 – 21
Severely abnormal	≤14	≤16

(Adapted from reference 444)

3.8.3 Outcome Measures

Primary outcome: Clinically manifest cardiovascular disease (CVD)

Clinically manifest cardiovascular disease (CVD) was established by self-report through face-to-face interviews and from review of hospitalisation records from the New Zealand Health Information System (NZHIS). NZHIS is a group within in the Ministry of Health New Zealand responsible for the collection and dissemination of health-related information. Self-reported CVD in the elderly was found to have good agreement with the medical records. (478)

The study defined clinically manifest CVD as: 1) *previous cardiovascular events*: myocardial infarction (MI), stroke, coronary artery bypass grafting (CABG), peripheral artery bypass grafting (PABG), congestive heart failure (CHF), percutaneous coronary intervention (PCI), or hospital admission due to CVD; 2) *symptomatic CVD*: angina or intermittent claudication (IC). (Figure 3-4) Hospitalisation records from NZHIS were supplied in the 9th version of the International Classification of Disease (ICD-9) for CVD related events and symptoms. ICD-9 codes were identified and matched to the above definition for clinically manifest CVD. ICD-9 codes are listed in TABLE 3-3 (page 92).

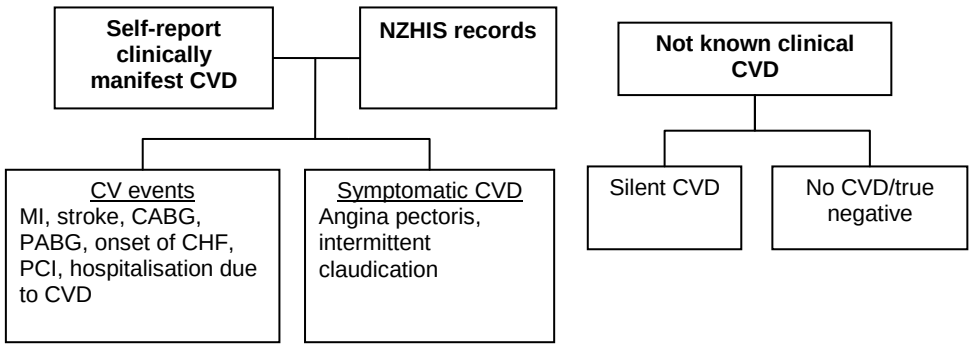


Figure 3-4: Ascertainment of clinically manifest CVD
Abbreviations: **CV**: cardiovascular; **CVD**: cardiovascular disease; **MI**: myocardial infarction; **CABG**: coronary artery bypass grafting; **CHF**: congestive heart failure; **PABG**: peripheral artery bypass grafting; **PCI**: percutaneous coronary intervention

TABLE 3-3: ICD 9 codes for clinically manifest CVD defined in the study

	ICD-9	Clinically manifest CVD	Atherosclerotic CVD	Coronary heart disease
Diagnoses and conditions				
Hypertensive heart disease				
- Unspecified hypertensive heart disease	402.9	✓	✓	✓
Acute myocardial infarction				
- Acute myocardial infarction of other anterior wall initial episode of care	410.11	✓	✓	✓
- Acute myocardial infarction of inferolateral wall	410.12	✓	✓	✓
- Acute myocardial infarction of inferolateral wall initial episode of care	410.21	✓	✓	✓
- Acute myocardial infarction of other inferior wall episode of care unspecified	410.41	✓	✓	✓
- Subendocardial infarction initial episode of care	410.71	✓	✓	✓
- Acute myocardial infarction of unspecified site initial episode of care	410.91	✓	✓	✓
Other acute and subacute forms of ischemic heart disease				
- Intermediate coronary syndrome	411.1	✓	✓	✓
Old MI	412	✓	✓	✓
Angina pectoris				
- Prinzmetal angina	413.10	✓	✓	✓
- Other and unspecified angina pectoris	413.90	✓	✓	✓
Other forms of chronic ischemic heart disease				
- Of unspecified type of vessel, native or graft	414.00	✓	✓	✓
- Of native coronary artery	414.01	✓	✓	✓
- Other specified forms of chronic ischemic heart disease	414.80	✓	✓	✓
- Chronic ischemic heart disease, unspecified	414.90	✓	✓	✓
Cardiac dysrhythmias				
- Cardiac arrest	427.5	✓		✓
Heart Failure				
Congestive heart failure, unspecified	428.0	✓		✓
Left heart failure	428.1	✓		✓
Heart failure, unspecified	428.9	✓		✓
Ill-defined descriptions and complications of heart disease				
- Cardiomegaly (cardiac: dilatation, hypertrophy; ventricular dilatation)	429.3	✓		✓
Occlusion and stenosis of precerebral arteries				
- Occlusion and stenosis of carotid artery without cerebral infarction	433.10	✓	✓	
- Occlusion and stenosis of multiple and bilateral precerebral arteries without cerebral infarction	433.30	✓	✓	

TABLE 3-3 continued

	ICD-9	Clinically manifest CVD	Atherosclerotic CVD	Coronary heart disease
Occlusion of cerebral arteries				
- Cerebral artery occlusion, unspecified	434.91	✓	✓	
Transient cerebral ischemia				
- Vertebrobasilar artery syndrome	435.3	✓	✓	
- Other specified transient cerebral ischemia	435.8	✓	✓	
- Unspecified transient cerebral ischemia	435.9	✓	✓	
Acute, but ill-defined, cerebrovascular disease	436	✓	✓	
Other and ill-defined cerebrovascular disease				
Other generalized ischemic cerebrovascular disease	437.1	✓	✓	
Late effects of cerebrovascular disease				
Unspecified late effects of cerebrovascular disease	438.9	✓	✓	
Atherosclerosis				
- Atherosclerosis of native arteries of the extremities unspecified	440.20	✓	✓	
- Atherosclerosis of native arteries of the extremities with intermittent claudication	440.21	✓	✓	
- Generalized and unspecified atherosclerosis	440.9	✓	✓	✓
Aortic aneurysm and dissection				
- Abdominal aneurysm without mention of rupture	441.4	✓		✓
Other peripheral vascular disease				
- Peripheral vascular disease, unspecified	443.9	✓	✓	
Operation/procedures related to the heart or vessels				
Operations on valves and septa of heart				
- Other replacement of aortic valve	35.22	✓		✓
Operations on vessels of heart				
- Single vessel percutaneous transluminal coronary angioplasty [ptca] or coronary atherectomy without mention of thrombolytic agent	36.01	✓	✓	✓
- Single vessel percutaneous transluminal coronary angioplasty [ptca] or coronary atherectomy with mention of thrombolytic agent	36.02	✓	✓	✓
- Insertion of non-drug-eluting coronary artery stent(s)	36.06	✓	✓	✓
- (Aorta) coronary bypass of three coronary arteries	36.13	✓	✓	✓
- Single internal mammary-coronary artery bypass	36.15	✓	✓	✓

TABLE 3-3 continued

	ICD-9	Clinically manifest CVD	Atherosclerotic CVD	Coronary heart disease
Other operations on heart and pericardium				
- Left heart cardiac catheterization	37.22	✓		✓
- Initial insertion of transvenous lead [electrode] into ventricle	37.71	✓		✓
- Initial insertion of transvenous leads [electrodes] into atrium and ventricle	37.72	✓		✓
- Insertion of temporary transvenous pacemaker system	37.78	✓		✓
- Initial insertion of single-chamber device, not specified as rate responsive	37.81	✓		✓
- Initial insertion of single-chamber device, rate responsive	37.82	✓		✓
- Initial insertion of dual-chamber device	37.83	✓		✓
Incision, excision, and occlusion of vessels				
- Endarterectomy, other vessels of head and neck	38.12	✓	✓	
- Intravascular spectroscopy	38.23	✓	✓	
- Resection of vessel with replacement, aorta	38.44	✓	✓	✓

The definition of clinically manifest CVD was further subcategorised to atherosclerotic CVD and heart disease (TABLE 3-3). This was done to allow examination with secondary outcomes, i.e. carotid intima-media thickness and left ventricular mass (Figure 3-5). Carotid intima-media thickness (CIMT) is a measure of subclinical atherosclerosis. Therefore, association between CIMT and CVD was narrowed to atherosclerotic CVD. Left ventricular mass (LVM) is a measure of the cardiac structure and enlarged LVM can be attributable to atherosclerotic CVD. Hence, the associations between LVM and heart disease and between LVM and CVD were examined.

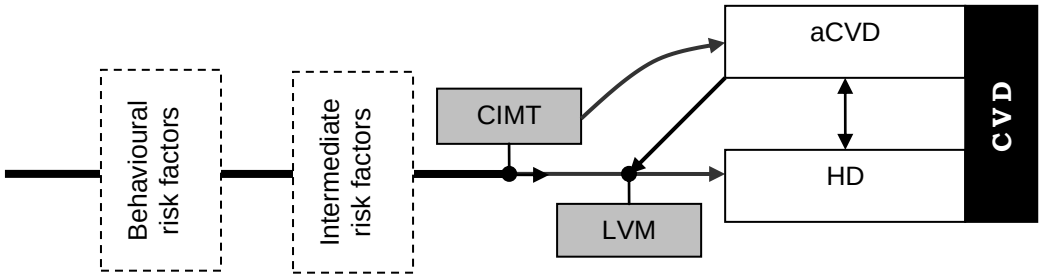


Figure 3-5: A simplified schematic diagram of the hypothetical pathophysiological pathway leading to clinically manifest CVD
Abbreviations: **aCVD**: atherosclerotic cardiovascular disease; **CIMT**: carotid intima-media thickness; **CVD**: cardiovascular disease **HD**: heart disease; **LVM**: left ventricular mass

Secondary outcomes: Carotid intima-media thickness and left ventricular mass

The common carotid intima-media thickness (CITM) was imaged and measured according to the procedures outlined in Section 3.8.2, page 89. In the general population, CIMT for women aged 45, 55 and 65 years old ranges between 0.53-0.58, 0.62-0.69, and 0.69-0.74mm, respectively. CIMT for men of similar age groups ranges between 0.57-0.61, 0.66-0.72 and 0.76-0.85mm, respectively. Overall, the Atherosclerosis Risk in Communities (ARIC) study found CIMT increased by 0.01mm for each year. (389) In older adults, 65 years and above, with no history of CVD, the average CIMT was 0.99mm. (390) According to the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC), a normal intima-media thickness (IMT) is less than 0.9mm, increased IMT is between 0.9 and 1.5mm, and more than 1.5mm is considered asymptomatic carotid plaque. (479) This reference range from the ESH/ESC was derived from a population with a limited number of people in advanced age. Since CIMT increased linearly with age, it has been proposed that CIMT value greater than or equal to the 75th percentile is a better indication of early atherosclerosis and increased risk of CVD because it takes into account the ages

for both men and women. (480) This study defined abnormal CIMT as a value above the 75th percentile of all values.

The left ventricular mass (LVM) was obtained according to the procedures outlined in Section 3.8.2, page 89. A LVM of ≥48gm$^{-2.7}$ for men and ≥44gm$^{-2.7}$ for women is considered as left ventricular hypertrophy (LVH). (444)

3.9 Ascertainment of diabetes, hypertension and dyslipidemia

Diabetes mellitus was defined as self-reported diabetes from the questionnaire, records of glucose-lowering medications identified from the medication table in the questionnaire, fasting serum glucose ≥7.0mmol/L (481), or hospitalisation records from the New Zealand Health Information System (NZHIS) with International Classification of Diseases, Ninth Revision (ICD-9) code 250 [0-8]. According to the World Health Organisation (WHO) Anatomical Therapeutic Chemical (ATC) (http://www.whocc.no/atcddd/), medications for diabetes were identified as code A10.

Hypertension was defined as self-reported hypertension from the questionnaire, records of prescribed medications indicated for hypertension as reported by the participant in the medication table in the questionnaire, an average of three sitting blood pressure measurements on the day of the physical assessment with a systolic/diastolic blood pressure ≥140/90mmHg, isolated systolic hypertension (SBP≥140mmHg, DBP<90mmHg) (203), or hospitalisation records from NZHIS with hypertension (ICD-9 401.90). Hypertension was coded as a secondary diagnosis in the NZHIS database. Isolated systolic hypertension was included as one of the criteria for hypertension because it accounts for 65% of hypertension in the elderly and is associated with increased risk of heart failure. (212, 213)

Dyslipidemia was defined as receiving treatment with lipid-lowering agents identified from the medication table in the questionnaire (WHO-ATC code C10), hospitalisation records from NZHIS with hyperlipidemia (ICD-9 code 272.0, 272.4, 272.9), or abnormal fasting serum lipids according to the New Zealand Heart Foundation recommendation (469), i.e. total cholesterol (TC) ≥4.0mmol/L, triglyceride (TG) ≥1.7mmol/L, high-density lipoprotein (HDL) ≤1.0mmol/L, low-density lipoprotein (LDL) ≥2.5mmol/L, and TC/HDL ratio ≥4.5mmol/L.

3.10 Medication coding

Self-reported medications were collected through the interview process by direct observation of the medications in the participants' homes, or having them bring all medications into the interview site. All medications were recorded as prescribed by review of the bottles, and were classified according to the World Health Organisation (WHO) Anatomical Therapeutic Chemical (ATC) Classification System. The ATC Index 2009 is available at http://www.whocc.no/atcddd/ free of charge (accessed from February to April 2009). The name of the drug substance, typically the International Nonproprietary Names (INN), was used to search for the ATC code. For medications and nutrition/mineral supplements where only trade names are provided, the INN name was identified using either one or combination of the following methods: MIMS Jul-Dec 08 Issue 9; Medsafe website (http://www.medsafe.govt.nz/index.asp) (accessed from February to April 2009); or Google search. Each INN was matched to the full ATC code[26]. Traditional herbal products were not coded.

3.11 Data Management and Statistical Analysis

3.11.1 Data Management

All consenting participants were allocated a personal identifier which consists of a site number, an interviewer's code and a sequential enrolment number. Data were obtained through questionnaires and physical assessment reports, hereafter referred to as case report forms (CRF), and entered into the Access database using single data entry method. Data cleaning was performed and any data queries generated during the process were rectified by first going back to the CRF to verify the consistency of records on the CRF and data entered. If queries remain unresolved after the consistency checked, for example if data on the CRF did not correspond to the available answers/options on the questionnaire, the project manager contacted the interviewers to verify the written answers on the CRF. Corrections on the CRFs were initialled and dated by the interviewers or the project manager. Data analyses commenced in January 2009.

[26] ATC code is made up of 5 different levels. The first level indicates the organ or system the chemical act upon; second level indicates the pharmacological/therapeutic main group; third and fourth level indicates the chemical/pharmacological/therapeutic subgroups; and the fifth level indicates the chemical substance. (http://www.whocc.no/atcddd/)

3.11.2 Statistical Analysis

Statistical analyses were completed for a single group of people of advanced age, i.e. analyses were not completed for Māori and non- Māori separately, owing to the sample size.

Descriptive statistics were used for socio-demographic data and all study variables. The distribution of the data for each of the continuous variables was examined with histogram and box-plots. Normality of the distribution was verified by the Shapiro-Wilk test. Variables with a skewed distribution were presented as median (interquartile range, IQR); variables with a normal distribution, the mean (standard deviation, SD) was presented. Chi-squared tests were used to determine the relationship between categorical variables. When the expected frequency in a cross-tabulation table is less than 2 or if more than 20% of the expected frequencies are less than 5, Fisher's exact test was used. (482) Independent t-test tests were used to determine the differences between participants with and without clinically manifest CVD for normally distributed data; for variables with skewed distribution, the Mann-Whitney U test was used. Pearson's or Spearman's correlation was used to determine the correlation between study variables. Regression models were constructed to determine the association between the outcome variable and variables of interest adjusting for sex, age-ethnicity, smoking status, and pertinent pharmacotherapy. Sex, age-ethnicity and smoking status were included in the models as they are the major risk factors for CVD. As some pharmacotherapy has an effect on certain study variables, pertinent medication was added to the covariate list (as binary data) to control for its effect on the variable of interest. (TABLE 3-4)

TABLE 3-4: Medications that have an effect on a particular study variable

Study variable	Medication affecting study variables
Serum glucose	glucose-lowering medication
Blood pressure	blood pressure-lowering medications
Hypercholesterolemia	lipid-lowering medication
Inflammatory markers	statin and aspirin (368, 373)
CIMT	blood pressure and lipid-lowering medications (378, 381)
NT-proBNP and LVM	pharmacotherapy for heart failure (483, 484)

Abbreviations: **CIMT:** carotid intima-medial thickness; **LVM:** left ventricular mass; **NT-proBNP:** N-terminal pro-brain natriuretic peptide

Variables were examined in blocks according to lifestyle factors (Chapter Six), conventional CV risk factors and inflammatory markers (Chapter Seven), and CIMT and LVM (Chapter Eight). A

multiple logistic regression model was developed to examine the independence of risk factors most relevant to manifestation of clinical CVD (the primary outcome) in those of advanced age (Chapter Nine). The criteria for inclusion of risk factors that possibly modify the relationship between variable of interest and CVD in the regression model were p value ≤0.2 and a ratio of outcome events to independent variables of 10:1. (485, 486)

Linear regression models were constructed to determine the association between CIMT and LVM (the secondary outcome) with CV risk factors (Chapter Eight). In constructing linear regression models to examine the association between CIMT and variables of interest, the entry criterion of $p \leq 0.2$ was used. For linear regression models examining the association between LVM and variables of interest, the entry criterion of $p < 0.1$ was used. The different p values used as the entry criterion is to ensure that the number of variable entered to the model was within the recommended cases-to-independent variables ratio, i.e. between 20:1 (the ideal ratio) and 5:1 (the lowest possible ratio). (487)

This study acknowledges the potential presence of Type I error from multiple comparisons. However, a decision was made not to adjust for multiple comparisons because associations identified from this cross-sectional study can be examined more rigorously in a cohort study.

Data were analysed using SPSS version 15.0.

All analyses were completed by the candidate, with advice from Elizabeth Robinson (biostatistician) and Steven Vender Hoorn (biostatistician).

TABLE 3-5: Planned multivariate regression models to determine the associations between primary and secondary outcomes with cardiovascular risk factors

		Independent variables
Primary outcome: **Clinically manifest CVD** Logistic regression modelling	Categorical variables:	Sex, age-ethnic group, smoking status, TNF-α
	Continuous variables:	SCREEN II score, PASE, serum glucose, SBP, DBP, TC, TG, HDL, LDL, TC-HDL ratio, BMI, WC, WHR, BF%, CRP, IL-6, fibrinogen, ESR, PLP, cobalamin, 25-OH D, CIMT, and LVM
Secondary outcomes: **1) CIMT** Linear regression modelling	Categorical variables:	Sex, age-ethnic group, smoking status, TNF-α
	Continuous variables:	SCREEN II score, PASE, serum glucose, SBP, DBP, TC, TG, HDL, LDL, TC-HDL ratio, BMI, WC, WHR, BF%, CRP, IL-6, fibrinogen, ESR, PLP, cobalamin, and 25-OH D
2) LVM Linear regression modelling	Categorical variables:	Sex, age-ethnic group, smoking status, TNF-α
	Continuous variables:	SCREEN II score, PASE, serum glucose, SBP, DBP, TC, TG, HDL, LDL, TC-HDL ratio, BMI, WC, WHR, BF%, CRP, IL-6, fibrinogen, ESR, PLP, cobalamin, 25-OH D, CIMT, and NT-proBNP

Abbreviations: **25-OH D**: 25-hydroxyvitamin D (Vitamin D); **BF%**: body fat percentage; **BMI:** body mass index; **CIMT:** carotid intima-media thickness; **CRP:** C-reactive protein; **CVD:** clinically manifest cardiovascular disease; **DBP**: diastolic blood pressure; **ESR:** erythrocyte sedimentation rate; **HDL:** high-density lipoprotein; **IL-6:** Interleukin-6; **LDL:** low-density lipoprotein; **LVM:** left ventricular mass; **NT-proBNP:** N-terminal pro-brain natriuretic peptide; **PASE**: Physical Activity Scale for the Elderly; **PLP:** pyridoxal 5' phosphate (Vitamin B_6); **SBP**: systolic blood pressure; **SCREEN II**: Seniors in the Community: Risk evaluation for eating and nutrition, Version II; **TC:** total cholesterol; **TG:** triglyceride; **TNF-α:** tumour necrosis factor-alpha; **WC:** waist circumference; **WHR:** waist-to-hip ratio

CHAPTER FOUR: PILOT STUDY

The research project of this thesis is part of a larger study funded by the Health Research Council (HRC) of New Zealand: Living to advanced age – feasibility for a cohort study. This chapter describes a small pilot study conducted as part of preparations prior to the initiation of the HRC funded study. The candidate completed the pilot study as part of the thesis, as a way of testing the feasibility of the cardiovascular questions and physical assessments in those of advanced age, particularly the echocardiogram and CIMT measurements.

Aims

The aim of the pilot study was to identify the feasibility of conducting a cross-sectional study investigating cardiovascular health in advanced age. This includes the recruitment procedures, acceptability and order of the questionnaire, duration of the questionnaire and processes entailed in the physical assessment, blood sample collection and analysis e.g. logistical matters, and the image quality of hand-held echocardiograms in those of advanced age.

Study participants

To achieve these aims, a small group of potential study participants living in Auckland was identified. Those who fulfilled the pre-defined selection criteria were contacted. The selection criteria were: anyone who turned 85 years old during the recruitment period, being able to understand and communicate in English, and being able to provide written informed consent (or consent able to be obtained from a family member if the identified elderly individual was unable to, due to physical or mental disability). Elderly individuals with permanent severe hearing or visual impairment that was not remediable were excluded from the study. A sample of ten was sought to represent those with more advanced disabilities as well as those who were very independent and able. A sample of ten participants was thought to be enough to try out the processes and give a range of responses on the questionnaire and physical assessments, and to be able to represent acceptability to those in advanced age.

Recruitment strategies

Identified elderly individuals were approached through two methods: direct mailing of study information and invitation letters through local general practitioners and a personal approach through a personal contact of the candidate. Recruitment began in September 2007, and the last participant recruited completed the physical assessment in mid-January 2008.

Data collection

- Questionnaire

Questions pertaining to demographic information were mostly adapted from the 2006 New Zealand Census questionnaire. Questions pertaining to the ascertainment of cardiovascular disease (CVD) and its risk factors were adapted from the Cardiovascular Health Study (488) and The Assessment and Management of Cardiovascular Risk, New Zealand Guideline Group, 2003 (469). Face-to-face interviews were conducted in the participants' residences. All measures outlined in Chapter Three were included.

- Physical assessments

Upon completion of the interviewer-administered questionnaire and on a scheduled date, study participants were taken to the Auckland City Hospital for physical assessments. The assessments included: measures of height, weight, blood pressure, ECG, bioimpedance analysis using a bioimpedance analyser, echocardiography and imaging of the common carotid artery using a portable echocardiogram. Sequences of the assessments were carefully structured. The reasons were, firstly, to minimize movement for the study participants, e.g. getting in and out of the bed and moving from room to room, and secondly to ensure the research protocols for each assessment were able to be adhered to. This was done with future participants in mind, who potentially would have different levels of physical function.

- Blood samples

Fasting blood samples were collected for analysis of serum glucose and lipids (total cholesterol, triglycerides, and high-density lipoprotein). In addition to these standard biomarkers of cardiovascular risk factors, blood samples were also analysed for serum concentration of pyridoxal

5’ phosphate (PLP), cobalamin, vitamin C, 25-hydroxyvitamin D (25-OH D), and five inflammatory markers: high-sensitivity C-reactive protein (CRP), interleukin (IL)-6, tumour necrosis factor-alpha (TNF-α), fibrinogen, and erythrocyte sedimentation rate (ESR). IL-6 and TNF-α are among the recent biomarkers found to be related to CVD and to be predictors of cardiovascular events. (457, 489) Because assays for IL-6 and TNF-α are not widely available in New Zealand, arrangements were made with Canterbury Health Laboratories in Christchurch for the test analysis. The rest of the blood analyses were performed in LabPlus, the medical laboratory of Auckland City Hospital.

Findings and modifications for the study

The pilot phase was undertaken in fourteen weeks and recruited nine of the sixteen elderly individuals invited to participate; response rate was 56%. Their ages ranged between 83 and 87 years old. Two participants were not 85 years old; one was recruited through the GP and the other from a personal contact. The circumstances were considered and it was decided to enrol them. As for the negative response, it was from personal and/or family member refusals (n=7). Between the two recruitment strategies, i.e. direct mailing and personal approach, the latter strategy produced a higher response rate (n=6, 75%) compared to direct mailing (n=3, 38%). These strategies were found feasible in identifying potential participants. Even though direct mailing resulted in a lower response rate, previous experience with a similar study population suggested that this technique generates the most contacts with age-eligible individuals. (468) Hence, both strategies were combined to improve the response rate for the study i.e. letters of invitation with study information were posted from local general practitioners with the practice nurse following up by telephone contact to explain the study.

Generally, participants did not find the questions difficult to answer. However, recollection of their parents’ age of death seemed to be challenging, but they usually had a reliable written record of the information. There was ambiguity in providing the cause of death for participants’ parents. This was mainly due to the participant not being told of the specific cause or because they had been too young to remember. Questions pertaining to medical history and cardiovascular diseases were well accepted. Therefore, no changes were required for these questions and they were used in the main study.

Participants did not have problems undergoing the comprehensive physical assessments. The duration required was between one-and-a-half and two hours. To date, this is the first study in New Zealand to perform echocardiographic measurements using a portable echocardiogram among those of advanced age. Images from the portable echocardiogram were assessed by the cardiologist (R.N.D) and their quality was found to be satisfactory. Thus, echocardiographic measurements with the portable echocardiogram were feasible for the main study. The bioimpedance analyser used for the pilot study was not available for use in the main study. Therefore, a Tanita Inner Scan Body Composition Monitor (Model BC-541) was purchased for measurement of body composition in the main study. Although this is not the most accurate measurement for body composition, accessibility to more sophisticated measures such as dual energy X-ray absorptiometry (DEXA) or a computed tomography (CT) scan was a logistical challenge.

A fasting blood sample was obtained in eight of the nine enrolled study participants. The one man, who did not fast, forgot – that is, it was not due to physical health problems but forgetfulness. This showed that a reminder is needed nearer to the blood draw. All of the blood sample analyses were able to be carried out. During the planning stage for the study, it was found that the process of ensuring stability of vitamin C concentration in the serum specimen was arduous, i.e. deliveries of serum samples in EDTA tubes had to be sent on ice to the laboratory for deproteinisation within 30 minutes of collection. With such intricacy, analysis for this biomarker was found to be impossible for study sites outside Auckland city. This is because, firstly, study participants lived too far from a laboratory with the facility to analyse serum vitamin C, and secondly some participants will have blood samples taken in their home. Hence, this test was not included in the study. After a comprehensive discussion with laboratory personnel, the funds available for analysis of vitamin C were used for measurement of N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration.

Conclusion

All findings, processes and challenges encountered during the pilot phase were reviewed. Recruitment strategy was refined to enhance the response rate. Bioimpedance analysis was done using the Tanita Inner Scan Body Composition monitor. Analysis of serum vitamin C was not done in the study and was replaced with analysis of NT-proBNP concentration. All other areas, i.e.

participants' inclusion criteria, questionnaires, physical assessments, and blood analysis remained the same.

CHAPTER FIVE: RESPONSE AND COMPLETION RATE, DEMOGRAPHIC, AND MEDICAL HISTORY

This chapter presents the recruitment and completion rate, demographic, and medical history information from the cross-sectional study investigating the cardiovascular health of those reaching advanced age in New Zealand. The latter section will discuss the recruitment process, the response and completion rate, and the key findings of the medical history and pharmacotherapy in this study sample.

5.1 Results

5.1.1 Recruitment and completion rate

A total of 186 eligible older adults were invited to participate in the study (Figure 5-1). Of these, 112 agreed and consented to the study; the response rate was 60% (Figure 5-2). Reasons for those who declined include: refused personally or their family members refused on their behalf (n=65), died before enrolment (n=4), did not respond at all or were not contactable (n=4), and one was excluded by the study co-ordinator because of ill-health.

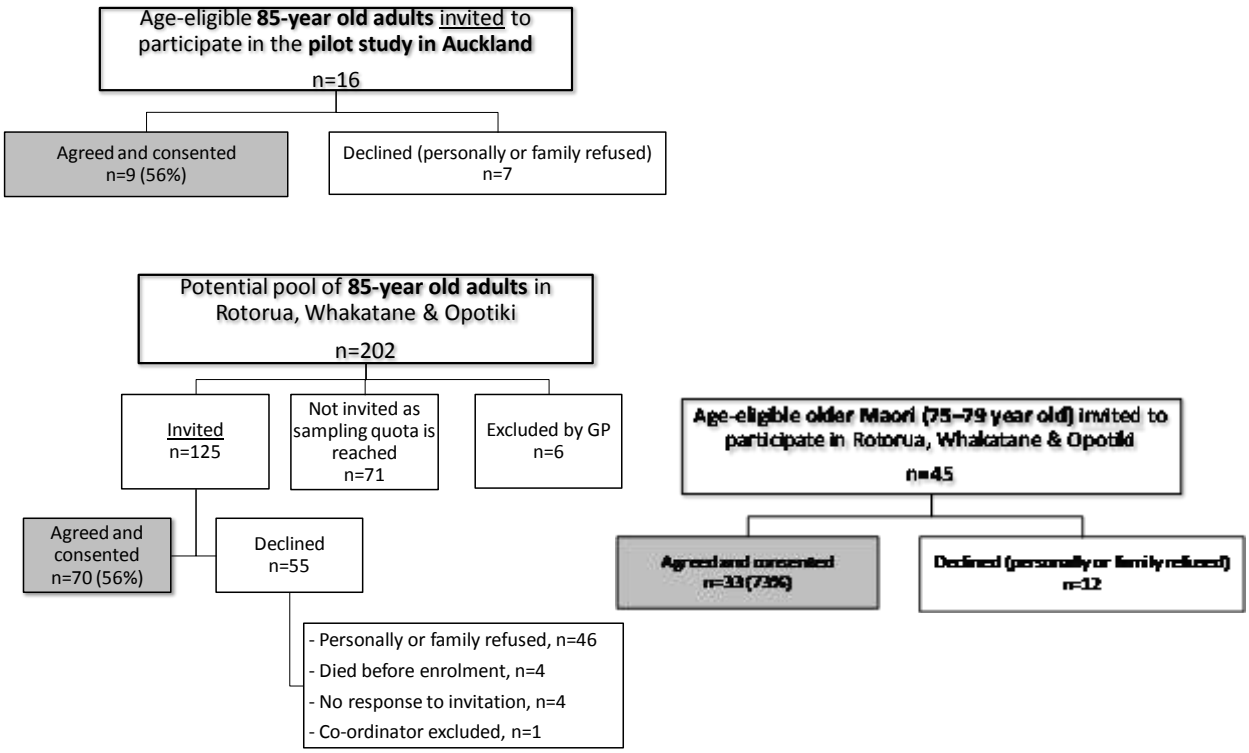


Figure 5-1: Sampling procedures

During the study period, four participants withdrew consent. One hundred and eight participants completed the questionnaire; one died after completing the questionnaire (Figure 5-2). Of these 108 questionnaires, five (5%) interviews were conducted with proxy interviewees because they had a Mini Mental Status Examination (MMSE) score of less than 23, a cut-off score indicating significant cognitive impairment. One hundred and three participants underwent physical assessments. Of these 103 physical assessments, 17 (16%) participants had assessments completed in their homes and the rest had the assessment completed at the local health centre. Physical assessments completed at home required a longer time compared to physical assessments completed at the local health centres (2 hours versus 1.5 hours). The reasons for having physical assessments done at the participants' residences included: one's preference (n = 7); health conditions (n = 7); and timing/logistics complexity (n = 3). The same assessments completed in the health centre were carried out at the participants' homes. The main reason a part of the assessment was not completed was either the participant was wheel-chair bound (weight and bioimpedance measurements not possible) or availability of specialist staff constrained completion (echocardiogram and CIMT imaging). Ninety participants agreed to give blood samples for analysis. The main reasons for refusal were: the participant felt they were too frail to give more blood in addition to their routine blood investigations completed during usual care (n=11), five Māori participants (from the same study area) believed blood is sacred, one withdrew halfway through the physical assessment, and one died.

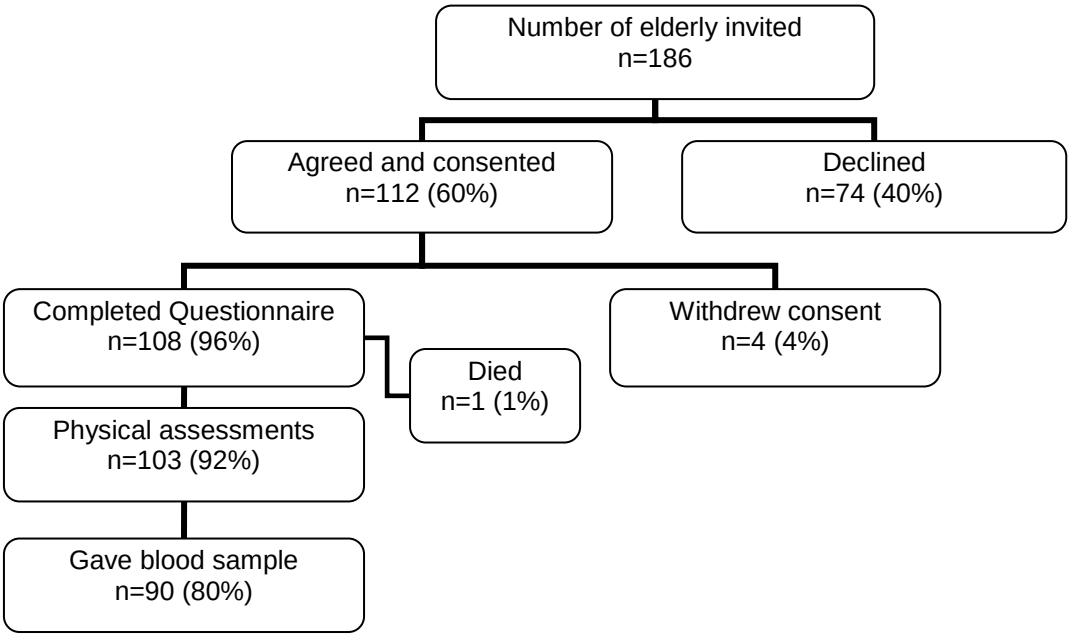


Figure 5-2: Response and completion rate

Note: Of these 108 participants, three were outside the age i.e. 71, 83 and 87 years old, respectively. Considering the small number in this group, they were included in the study.

5.1.2 Demographic characteristics

Of the 108 participants in this study, 33 were Māori and 75 were non-Māori. There were more women than men in this study sample (56% vs. 44%) and more than three-quarters of the sample were widows or widowers. Nearly half (46%) of them live alone and the rest live with someone (54%). The majority of the study participants lived in a private residence (86%), followed by living in a retirement village (6%), rest home/private hospital (4%), and the remaining participants lived either in *marae* (*iwi* based housing) or other settings (4%). Three-quarters of the participants had completed secondary education. The main income for the majority of the study participants was New Zealand superannuation (88%), followed by income from investment (8%), other financial support (3%), and superannuation from other sources (1%). Most of them were comfortable with their current financial situation (86%), eleven percent had just enough to get along, and three percent reported they could not make ends meet. Eleven (10%) participants were still engaged in paid work - eight men and three women. As per the study selection criteria, Māori participants were significantly younger then the non-Māori (76.6±1.8 vs. 85.2±0.6; $p<0.001$).

5.1.3 Medical history

In this study, only a small proportion of the participants were current smokers. More than one-third (37%) of the sample reported never drink alcoholic beverages; 38% had alcohol at least twice a week and the remaining participants had alcohol at least monthly. Twenty-two (20%) participants have diabetes mellitus, 91 (84%) have hypertension and 92 (85%) had dyslipidemia. Smoking status and prevalence of diabetes, hypertension and dyslipidemia in this sample will be presented in a detailed manner in the Chapter Seven7 (Cardiovascular Risk Factors). Nearly one-third (29%) of the participants had a family history of cardiovascular disease (CVD).

Clinically manifest CVD was established by self-report through face-to-face interviews and ascertained by hospitalisation records from the New Zealand Health Information System (NZHIS), Ministry of Health New Zealand. Two-thirds (n=72) of the study participants had clinically manifest CVD. More than half (n=39, 54%) of the participants with CVD had the status established by face-to-face interviews and hospitalisation records, 25 (35%) participants self-reported CVD and the CVD status of eight participants (11%) was ascertained from the hospital records (i.e. participants

probably were unaware of having had CVD) (Figure 5-3). Most of self-reported CVD cases (n=16, 64%) were symptomatic CVD such as angina, transient ischemic attack and intermittent claudication. For the 25 participants with only self-reported CVD (i.e. no hospital record of CVD), these were verified with the GP medical records using a one-page questionnaire. Fifteen (60%) completed questionnaires were returned and ten (40%) were not. Of the 15 completed questionnaire from the GPs, 10 (67%) confirmed the self-reported CVD; five (33%) did not. Equal proportions of men and women had CVD (73% vs. 62%), p=0.218. Similarly, equal proportions of Māori and non-Māori participants had CVD (70% vs. 65%), p=0.658.

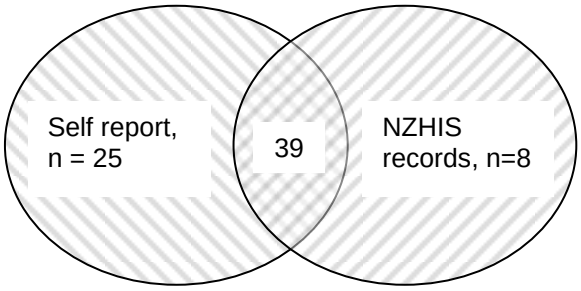


Figure 5-3: Proportion of clinically manifest CVD ascertained through self-report and hospitalisation records.
Abbreviations: **NZHIS**: New Zealand Health Information System

The most common clinical symptoms or events observed in participants with CVD was angina pectoris (44%), followed by myocardial infarction (40%), and ischemic heart disease (IHD) (28%; n=20/72). (Figure 5-4) Ischemic heart disease was ascertained from hospitalisation records. In Figure 5-4, IHD was grouped under category *"other heart or circulatory problems"*, presented in the bar chart.

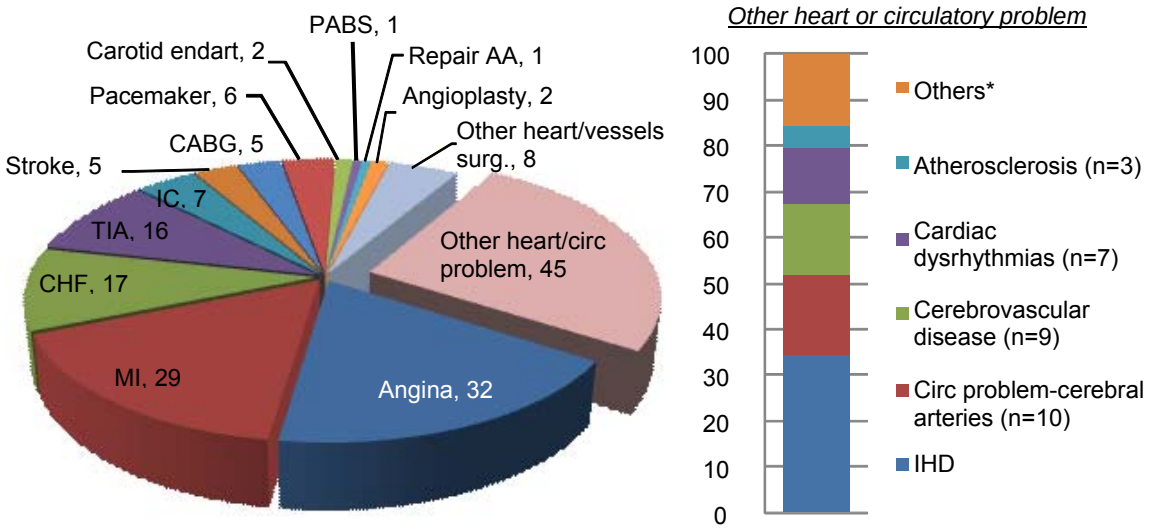


Figure 5-4: Pie chart shows the cardiovascular diseases from face-to-face interviews and hospitalisation records. Bar chart specified the "*other heart or circulatory problems*"
Abbreviations: **AA**: aortic aneurysm; **CABG**: coronary artery bypass surgery; **Carotid endart**: carotid endarterectomy; **CHF**: congestive heart failure; **circ**: circulatory; **IC**: intermittent claudication; **IHD**: ischemic heart disease; **MI**: myocardial infarction; **TIA**: transient ischemic attack; **PABS**: peripheral artery bypass surgery; **surg**: surgery;
*Others include cardiomegaly (n=1), aortic aneurysm (n=1), unspecified peripheral vascular disease (n=1) and personal history of other vascular diseases (n=6)

5.1.4 Electrocardiogram

All 103 participants who agreed to physical assessments had an electrocardiogram (ECG) done. All but two ECGs (n=101, 98%) were read by a general practitioner (N.K.) and verified by an experienced cardiologist (R.N.D.). Parameters identified from the ECG were: left ventricular hypertrophy (LVH), old myocardial infarction (MI), current ischemia, atrial fibrillation (AF) and bundle branch block (BBB). The remaining two ECGs were not evaluated due to crossed-lead. Fifty-four participants (53%) had a normal ECG and 47 (47%) had an abnormal ECG. The breakdowns of abnormalities found on the ECG are show in TABLE 5-1.

TABLE 5-1: Abnormalities ascertained from the 47 abnormal ECG

Number of abnormalities on the ECG	Type of abnormalities on the ECG
1 abnormality, n=43	BBB, n=16
	LVH, n=10
	AF, n=8
	Old MI, n=6
	Partial BBB, n=1
	First degree heart block, n=1
	Paced, n=1
2 abnormalities, n=3	LVH + AF, n=2
	Old MI + AF, n=1
3 abnormalities, n=1	LVH & old MI + AF, n=1

Abbreviations: **AF**: atrial fibrillation; **BBB**: bundle branch block; **ECG**: electrocardiogram; **LVH**: left ventricular hypertrophy; **MI**: myocardial infarction

Bundle branch block was the most commonly-found abnormality on the ECG (34%) and 'current ischemia' was not found on the ECG. When comparing the occurrence of AF from the ECG and self-reported from the questionnaire, there was more self-reported AF compared to the occurrence ascertained from the ECG (Figure 5-5). This is likely due to effective treatment; 13 participants were on either beta-blockers (n=7), felodipine (n=2), verapamil (n=1), amidarone (n=1), digoxin (n=1) or warfarin (n=1), and four participants had a pacemaker (n=4).

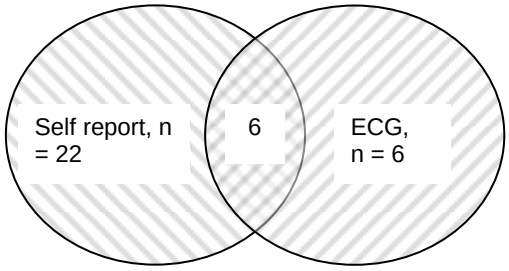


Figure 5-5 Reporting source of atrial fibrillation
Abbreviations: **ECG**: electrocardiogram

5.1.5 Prescribed medications and nutritional supplements

Ninety-eight (92%) study participants took prescribed medications (median=5, range between 0 and 13). Among the female participants, five reported that they had taken hormone replacement therapy (HRT) in their lifetime with one still continuing. Medications were classified according to the World Health Organisation (WHO) Anatomical Therapeutic Chemical (ATC) Classification System. (http://www.whocc.no/atcddd/) The number of prescribed medications related to the cardiovascular system ranging from taking nothing (n=20) to as many as seven medications (n=1); median was

two. The most commonly-prescribed medication indicated for the cardiovascular system was aspirin. Use of aspirin was significantly more common among participants with CVD (57%) than no CVD (33%), p=0.021. The range of medications used as a consequence of health disorders related to the cardiovascular system is detailed in TABLE 5-2 (other medication use not presented).

TABLE 5-2: Classification of pharmacotherapy prescribed in relation to the cardiovascular system according to the WHO-ATC classification system

Therapeutic groups (ATC code)		Frequency n (%)
Antithrombotic agents (B01)		64 (59)
Platelet aggregation inhibitors excl. heparin - Aspirin*	53	
Vitamin K antagonists - Warfarin	13	
Platelet aggregation inhibitors excl. heparin - Dipyridamole	4	
Cardiac therapy (C01)		20 (19)
Organic nitrates - Isosorbide mononitrate	8	
Organic nitrates - Glyceryl trinitrate	7	
Digitalis glycosides - Digoxin	7	
Antiarrhythmics, class III - Amiodarone hydrochloride	2	
Antihypertensive (C02)		1 (1)
Alpha-adrenoreceptor antagonists - Doxazosin Mesylate	1	
Diuretics (C03)		30 (28)
Sulfonamides **-** Furosemide	26	
Thiazides - Bendroflumethiazide	4	
Aldosterone antagonists **-** Spironolactone	2	
Thiazides, combinations with other drugs - Hydrochlorothiazide; triamterene	1	
Beta blocking agents (C07)		40 (37)
Beta blocking agents, selective - Metoprolol succinate	29	
Beta blocking agents, selective - Atenolol	5	
Beta blocking agents, non-selective - Propranolol	2	
Beta blocking agents, non-selective - Sotalol	2	
Beta blocking agents, selective - Celiprolol	2	
Calcium channel blockers (C08)		19 (18)
Dihydropyridine derivatives - Felodipine	12	
Benzothiazepine derivatives - Diltiazem	6	
Phenylalkylamine derivatives - Verapamil	1	
Agents acting on the renin-angiotensin system (C09)		40 (37)
ACE inhibitors, plain - Cilazapril	16	
ACE inhibitors, plain - Quinapril	15	
ACE inhibitors, plain - Enalapril maleate	4	
Angiotensin II antagonists, plain - Candesartan cilexetil	4	
Angiotensin II antagonists, plain - Losartan	1	
Lipid modifying agents (C10)		29 (27)
HMG-CoA reductase inhibitors - Simvastatin	23	
Fibrates - Bezafibrate	3	
HMG-CoA reductase inhibitors - Atorvastatin	2	
Other lipid modifying agents - Ezetimibe	1	

Note: The majority of the participants used aspirin 100mg except for one participant (22703) who recorded using 300mg aspirin and it was not prescribed by the medical doctor. This same participant did not have other prescribed medications.

Half of the study participants used vitamin/mineral supplements (n=52, 50%) and 45 (42%) used natural/herbal products. Because of the varieties of supplements used by study participants, individual micronutrient dosages were not recorded but were grouped according to WHO ATC classification system into three categories: vitamin, minerals, and general nutrients. (TABLE 5-3) The impact of vitamin/mineral supplements and natural/herbal products on nutritional risk and nutritional biomarkers will be presented in the next chapter (Chapter Six).

TABLE 5-3: Nutritional supplements recorded from participants through face-to-face interviews

Therapeutic groups (ATC code)		n (%)
Vitamins (A11)		28 (26)
Multivitamins, plain	9	
Multivitamins, combinations	3	
Vitamin A and D, including combinations of the two	5	
Vitamin B1, plain and in combination with vitamin B6 and B12	3	
Vitamin B-complex, including combinations	3	
Ascorbic acid (vitamin C), including combinations	3	
Other plain vitamin preparations	4	
Other vitamin products, combinations	11	
Mineral supplements (A12)		19 (18)
Calcium	16	
Potassium	2	
Other mineral supplements	5	
General nutrients (V06)		31 (29)
Protein supplements	1	
Other nutrients*	30	

* Other nutrients include fish oil/omega-3 (n=19); glucosamine/supplement for joint care (n=13); garlic derivatives (n=7); co-enzyme Q10 (n=3); deer velvet (n=3); bee honey (n=2); capsicum derivatives (n=2); cranberry tablets (n=2); ginkgo biloba (n=1); HS-II (n=1); horseradish (n=1); trinovin 9 (n=1)

5.2 Discussion

5.2.1 Recruitment and completion rate

The response rate for this study was 60%. This was lower than expected and lower than the Newcastle 85+ study with a response rate of 66% (490), and the Leiden 85+ study with an 87% response rate. (491) The lower response rate in this study could potentially have been attributed to the long interview thus increasing respondent burden. The cross-sectional observation study also means there were no direct benefits for the age-eligible older adult. Additionally, there were limited resources constrained publicity and human resource effort at the outset, which limited the effort directed to recruitment. Recruitment strategies also influenced the response rate. For the 85-year-old group, they were recruited through direct mailing from the general practitioner; and for the

75-79-year-old group, the main recruitment strategy was the *whakawhenongatunga* (wider family connection) approach. The latter strategy could have lead to a sample selection bias for the age group as we do not know whether participants are the same or different from everyone who was not invited. This recruitment method evolved from extensive consultation with local *Kaumatua* (male elders) and *Kuia* (female elders) of respective *iwi* (tribes) about setting up and implementing the study. This referral/personal approach strategy yielded a higher response rate compared to the earlier strategy engaged for the 85-year-old group. This likely to suggest personal contact enhances understanding, and allowing ample time for older adults to discuss participation in the study with family members, caregivers or friends in order to make an informed decision. The referral/personal approach strategy may not only improve response rate but lessen the attrition rate. (490, 492)

5.2.2 Clinically manifest CVD

In this study, two-thirds of the participants had clinically manifest cardiovascular disease (CVD), which was equally distributed between men and women. Therefore, this study, supported by previous studies (493-495), refutes the notion that CVD is an 'old man's disease'. Although the prevalence of CVD is similar in older men and women, cardiovascular risk factors, both conventional and novel risk factors, are sex-specific. (496) In other words, pathology for cardiac disease differed between genders. After the loss of estrogens during menopause, body fat is redistributed to the abdominal region which is associated with increased insulin resistance, dyslipidemia, hypertension and diabetes. (496) Moreover, women are generally less likely to participate in leisure-time physical activities in the postmenopausal years. These risk factors may be responsible for the different manifestation of CVD between both sexes. Heart failure (HF) with reduced ejection fraction (EF) (also known as systolic HF) is more prevalent among men, whereas HF with preserved EF (diastolic HF) is more common in women. (445, 449, 497) Although the prognosis of mortality from diastolic HF was more favourable than systolic HF, in a group of more than six thousand HF patients at the Mayo Clinic Hospital in Olmsted County, it was found that diastolic HF was associated with higher morbidity compared to systolic HF. For example, those with preserved EF have a higher increase in the prevalence of diabetes over a 15-year period compared to those with reduced EF. (498) A review article by Mandinov *et al*. draws similar findings. (499) Hence, men and women in this study with CVD may carry a different CVD risk

burden, leading to adverse health outcomes. A similar hypothesis can be put forward for the remaining one-third of study participants without CVD. Nevertheless, a gender-specific analysis was not performed in this study because of the limited sample size. A larger study is needed to confirm whether the cardiovascular risk profile of men and women in advanced age differs. If so, there may be a need to have a sex-specific diagnostic criterion and treatment.

Māori have a less favourable cardiovascular risk factors profile and a higher mortality rate attributable to circulatory diseases at earlier ages. (42, 470) Therefore, in order to recruit a comparable age group of similar co-morbidities profile and chances of survival in the next year, the study chose a younger-age criterion for Māori participants compared to non-Māori. In this study, the prevalence of CVD was similar in Māori and non-Māori participants. However, this study cannot be certain that a 77-year-old Māori and an 85-year-old non-Māori share a similar biological age in terms of the cardiovascular system. Those living to advanced age are a particularly heterogeneous group. According to the "*heterogeneity"* hypothesis, survival selection is through the attrition of mortality, i.e. the frailer individuals are likely to die at younger ages and the survival of healthier individuals to older ages is attributable to more favourable genetic heredity and/or a healthy lifestyle. (500) The interactions between gene, lifestyle, and environmental factors produce survivors with diverse physical and cognitive functions. Therefore, comparing the health profile of older adults using chronological age would not be correct. Biological age, encapsulating the effect of gene and environmental factors, would be a better alternative indicator of cardiovascular health and the general health status of those of advanced age. (501). Owing to the small sample size, analyses were not completed separately for Māori and non-Māori. Future studies with a larger sample and a more population-representative sampling strategies would be able to determine the prevalence of CVD and the cardiovascular health profile of advanced-age Māori and non-Māori.

5.2.3 Prescribed medication: aspirin

Half of the study participants used aspirin. Aspirin is usually prescribed for secondary prevention of CVD as the benefit outweighs the adverse effects. (359, 502) Latest studies showed a similar beneficial effect of aspirin for primary prevention. (360, 503) A recent meta-analysis of six primary- and 16 secondary-prevention trials found, compared to the control group, aspirin used for primary prevention was associated with a 12% decrease in serious vascular events (mainly attributed to a 23% reduction in non-fatal myocardial infarction), no significant decrease in total

mortality, and an increase in major gastrointestinal and extracranial bleed. (361) For secondary prevention, compared to the control group, aspirin was associated with a 20% decrease in major coronary events, a significant 10% decrease in total mortality; and significant excess of major bleeds recorded in five of the 16 secondary-prevention trials (11 trials did not record events of major bleeds). (361) These reports were mostly constrained to individuals younger than 79 years old. In a prospective study of 75 octogenarians with permanent atrial fibrillation were randomised to receive either dose-adjusted warfarin (INR 2.0-3.0) or aspirin 300mg. The aspirin group had significantly more adverse events (gastrointestinal disturbances and serious bleeding) compared to the warfarin group. (504) The authors speculate this was possibly due to increasing intolerability of aspirin with increasing age. In an analysis of six primary prevention trials (using data from the Antithrombotic Trialists Collaboration meta-analysis), aspirin monotherapy used was likely to yield more harm than benefits among men aged 80 and above with five-year CVD risk of 15% and over. (505) Aspirin dose regimen for these trials (from the ATT Collaboration meta-analysis) varies between 100mg on alternate days and 500mg daily; and only three of the six trials have participants aged above 80 years but constitute only a small proportion. (45, 506) Hence, what would be the optimal aspirin dose for CVD prevention in advanced age? In a double-blind, randomised, placebo-controlled trial with patients 45 years or older (mean age 64 years) who had established atherosclerotic disease or were asymptomatic but had a combination of risk factors, aspirin doses of 75 to 81mg daily provide the optimal balance between efficacy and safety for patients requiring long term aspirin treatment for prevention of cardiovascular events. (507) A meta-analysis found aspirin doses of 75-150mg daily is as effective as higher daily doses for long-term use for secondary prevention of myocardial infarction and stroke. (359) This cross-sectional study was not able to ascertain when aspirin was prescribed, nor the treatment duration. Nevertheless, there were more participants with CVD on aspirin. This suggests that, in this sample, aspirin was prescribed for secondary prevention of CVD. Further investigations are needed to assess the risk benefit of aspirin for CVD prevention in advanced age. Exploring the long term effect of aspirin on cardiovascular health of those of advanced age would have important economical implications. This is because aspirin treatment is cost-effective for primary prevention of CVD in 75-year-old men and women. (360)

5.2.4 Nutritional supplements

Half of the study participants used nutritional supplements. This is indicative of a health-conscious sample. In a population-based cohort study of more than 2,100 adults aged between 43 and 86 years old, supplement use was more prevalent among individuals who were physically active, consumed less alcoholic beverages, had never smoked cigarettes, had a lower intake of fat, a higher intake of fruit, vegetables and dairy products, and had a lower BMI. (508) It is not possible to quantify intake of specific micronutrients in this sample due to the wide range of nutritional products. Information on micronutrients intake in advanced age may have clinical importance. Studies have shown vitamin D deficiency is a risk for CVD. (97) Hence, vitamin D supplementation may improve cardiovascular risk profile. In a randomised, double-blind, placebo-controlled study, participants with increased carotid intima-media thickness (a measure of sub-clinical atherosclerosis) receiving daily 2.5mg folic acid, 25mg Vitamin B_6 and 0.5mg Vitamin B_{12} for one year had a significant reduction in intima-media thickness. (404) Administration of micronutrients generally produces less adverse effects than pharmacologic intervention, but micronutrient-drug interactions may compromise the efficacy of chemical compounds. (509) Studying the effect of micronutrients on cardiovascular health in those of advanced age would be a significant challenge because: 1) compliance with other pharmacotherapy, as the number of prescribed medications can be high in older adults with co-morbidities; 2) the accuracy of dosage quantification due to the accessibility of a wide range of nutritional supplements over the counter. A sizeable proportion of this study sample used herbal/natural products. In a review article, Tachjian *et al*. reported that co-administration of herbal products with cardiovascular agents not only reduced bioavailability and altered the effectiveness of the pharmacologic agents, but found also that herbal-drug interactions may exacerbate existing health conditions. (510) Therefore, it was suggested that health professionals should attempt to collect this information, understand the use of the remedies, monitor and possibly identify the adverse herbal-drug interactions. In short, it is difficult to assess the benefit of nutritional supplements to cardiovascular health of those in advanced age. Perhaps it is the behavioural factors denoted by the use of supplements that plays an important role in determining cardiovascular health in this group.

In conclusion, the study sampling method may have recruited a very healthy group of those in advanced age. One-third of the participants did not have clinically manifest CVD. This exceptional health status, relative to chronological age, may be attributed to the interaction between genetic

inheritance and lifestyle-related health behaviour. Alternatively, those in advanced age are actually healthier and more robust than expected when considering media portrayals of the health of older people. This cross-sectional study will not be able to determine the cause-and-effect relationship between risk factors and clinically manifest CVD. The following chapters will describe the cardiovascular health status in a sample of New Zealanders of advanced age and the relationship between cardiovascular risk factors and cardiovascular health outcomes.

CHAPTER SIX: NUTRITIONAL RISK AND PHYSICAL ACTIVITY

This chapter will present the results of nutritional risk and physical activity ascertained in older people by self-report, and their association with clinically manifest cardiovascular disease (CVD). Nutritional risk was determined using SCREEN II (Seniors in the Community: Risk Evaluation for Eating and Nutrition, Version II). The SCREEN II score has a maximum score of 64, and a higher score means lower nutritional risk and vice versa. Individuals at nutritional risk are susceptible to development of sub-clinical and clinical malnutrition, evidenced by changes in biochemical and anthropometry measures. (80) The nutritional biomarkers measured in this study were pyridoxal 5' phosphate (PLP)/vitamin B_6, cobalamin/vitamin B_{12}, and 25-hydroxyvitamin D (25-OH D)/vitamin D; the anthropometry measure was body mass index (BMI). Low energy reserves may affect participation in physical activity, which is involved in the continuum of cardiovascular disease. Physical activity was determined by using the PASE (Physical Activity Scale for the Elderly) instrument. The PASE score can range from 0 to 793. A higher PASE score indicates a higher level of physical activity.

Descriptive statistics for nutritional risk, nutritional biomarkers, nutritional supplements, and physical activity is presented in this chapter. These results are followed by their association with clinically manifest CVD. The effects of potential moderators are considered. The findings of nutritional risk and physical activity in this sample of those living to advanced age will be discussed in the latter section of this chapter.

6.1 Result

6.1.1 Nutritional risk

One hundred and eight participants completed the questionnaire. SCREEN II score was missing for two participants and therefore SCREEN II score was available for 106 participants. Ninety participants gave blood sample for analysis of nutritional biomarkers. Eighty-eight participants had results for serum PLP (vitamin B_6) and 25-OH D (vitamin D); all 90 participants had results for serum cobalamin (vitamin B_{12}). Reasons for unavailability of biomarkers' results were: insufficient samples (from three participants), and a laboratory error being reported.

Serum 25-OH D (vitamin D) was distributed normally and there were no outliers. In contrast, the distribution of SCREEN II scores was skewed to the left of the median, i.e. the SCREEN II score had a long left tail, i.e. most values clustered toward the upper end of the scale with few at the lower end of the scale. The distribution for serum PLP, cobalamin, and BMI were skewed to the right of the median, i.e. a long right tail, i.e. most of the values clustered toward the lower end of the scale with few in the upper end of the scale. Ten participants had high PLP levels (nmol/L) (in descending order: >1000, 934, 564, 557, 477, 412, 400, 375, 327, and 322) and one participant had a high cobalamin level (1337pmol/L). Among the ten participants with high PLP levels, seven of them took at least one type of multivitamin. The participant with a high cobalamin level was treated with hydroxocobalamin by the general practitioner. BMI was markedly high in one female participant who weighed 156.7kg (BMI of 65.9kg/m^2).

Half of the study participants (n=52) used nutritional supplements. Serum PLP was significantly higher in supplements users than in non-users (p=0.018); serum cobalamin and 25-OH D did not differ between supplements users than non-users. (TABLE 6-1) In the sensitivity analyses conducted without the outliers, serum PLP and cobalamin did not differ between supplements users than non-users.

TABLE 6-1: Nutritional biomarkers between supplements users and non-users

	All	Nutritional supplements		P value[§]
		Users	Non-user	
Median (IQR)				
PLP (nmol/L)	76 (62)	82 (170)	72 (42)	0.018
Cobalamin (pmol/L)	266 (212)	259 (212)	265 (228)	0.695
Mean (SD)				
25-OH D (nmol/L)[a]	63 (22)	64.3 (20.6)	61.6 (24.6)	0.572[#]

Abbreviations: **25-OH D:** 25-hydroxyvitamin D); **PLP:** pyridoxal 5' phosphate (vitamin B_6)
[§]P value from Mann-Whitney U test unless stated otherwise
[#]P value from Independent t-test
[a] Sixteen participants used vitamin D/multivitamin supplement (which contains vitamin D). Serum 25-OH D concentrations of these 16 participants were higher than non-users of vitamin D/multivitamin supplement, mean (SD) nmol/L: 73.5 (12.9) vs. 60.4 (23.5) nmol/L, p=0.033

SCREEN II score, nutritional biomarkers and CV risk factors

In the univariate analysis, the SCREEN II score did not correlate significantly with nutrition biomarkers. Among the CV risk factors examined, the SCREEN II score was only correlated with the percentage of body fat (r=-0.361, p<0.001) (Appendix B: TABLE B-1, page 294). The SCREEN II score was not statistically correlated with BMI, but the proportion of participants with a SCREEN II

score less than 50, was lowest among participants with a normal BMI (18.5–<25kg/m^2) (46%) compared to other BMI categories (over 50% with SCREEN II <50) (Figure 6-1).

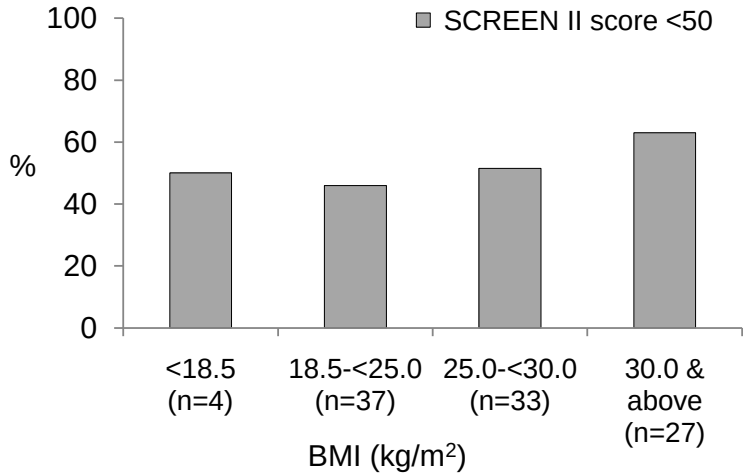


Figure 6-1: Proportion of participants with high nutritional risk (SCREEN II score <50) across BMI categories.

Since the percentage of body fat was likely to be different between the sexes (511) and between Māori- and non-Māori participants, the association between SCREEN II score and body fat percentage was controlled for sex and age-ethnicity. To determine if sex and age-ethnicity has an effect on the association between the SCREEN II score and body-fat percentage, the interaction term (body-fat percentage × sex, and body-fat percentage × age-ethnic) was added to the regression model. Both interaction terms body-fat percentage × sex (p=0.315) and body-fat percentage × age-ethnic (p=0.391) was not associated with SCREEN II score. This implied the association between the SCREEN II score and body-fat percentage was the same for both sexes and all ages. Hence, analysis was done with sex and age-ethnicity combines. The SCREEN II score was associated with body-fat percentage after adjusting for sex- and age-ethnicity (β=-0.280, p=0.025).

SCREEN II score and clinically manifest CVD

The median score for SCREEN II was 49 (IQR: 7; range 29–58) (TABLE 6-2). Fifty-five (52%) participants had a SCREEN II score below 50. Participants with CVD did not have a lower SCREEN II score compared to those without CVD, p=0.365. Similarly, levels of nutritional biomarkers did not differ between those with and those without CVD (TABLE 6-2).

TABLE 6-2: SCREEN II score and nutritional biomarkers

	Total n=108	No CVD n=36	Yes CVD n=72	P value[§]
Median (IQR)				
• SCREEN II score	49 (7)	51 (10)	49 (7)	0.365
• PLP (nmol/L)	76 (62)	74 (53)	77 (85)	0.267
• Cobalamin (pmol/L)	266 (212)	254 (220)	298 (214)	0.316
Mean (SD)				
• 25-OH D (nmol/L)	63 (22)	60 (21)	65 (23)	0.360[#]
N (%)				
• SCREEN II score <50	55 (52)	16 (47)	39 (54)	0.494[‡]
• Use vitamin & mineral supplements	52 (50)	16 (46)	36 (51)	0.581[‡]

Abbreviations: **25-OH D:** 25-hydroxy (vitamin D); **CVD**: cardiovascular disease; **IQR:** interquartile range; **SCREEN II:** Seniors in the Community: Risk Evaluation for Eating and Nutrition, version II); **SD:** standard deviation; **PLP:** pyridoxal 5' phosphate
[§]P value from Mann-Whitney U test unless stated otherwise
[#]P value from Independent t-test
[‡]P value from Chi-square test

The association between the SCREEN II score and CVD was explored controlling for sex, age-ethnicity, smoking status, and potential confounders. To determine if age-ethnicity has an effect on the association between CVD and the SCREEN II score, the interaction term (SCREEN II score × age-ethnicity) was added to the regression model. There was no association between the interaction term and CVD (p=0.350); this implied the association between the SCREEN II score and CVD was the same for all ages. Hence, analysis was done with age-ethnicity combined. Controlling for sex, age-ethnicity, and smoking status, the SCREEN II score was not associated with CVD [OR (95% CI): 0.960 (0.890–1.036), p=0.298]. Since nutritional biomarkers PLP, cobalamin, and 25-OH D may confound the relationship between the SCREEN II score and CVD, they were added to the model one at a time. These models were tested with and without outliers to rule out spurious effects attributable to outliers. Controlling for sex, age-ethnic group, smoking status, nutritional biomarkers, and supplements, there was no significant association between the SCREEN II score and CVD.

6.1.2 Physical Activity

One hundred and seven participants completed the PASE (Physical Activity Scale for the Elderly) questionnaire. The PASE score was not distributed normally, i.e. more values clustering toward the upper end of the scale with few at the lower end of the scale; there were no clear outliers. The median (IQR) for the PASE score was 84 (86), range 0–282. Seven participants had

a score of zero: three were wheelchair-bound, and four were in rest homes. Excluding these seven participants, the median (IQR) was 100 (85), range between 22–282; the distribution did not change with exclusion of the inactive group. Since it is possible to have a zero score for this instrument (questionnaire), the seven participants (6% of the total study sample) with a PASE score of zero were not excluded from the analysis.

The total PASE score constitutes three components, i.e. leisure-time physical activity, household related physical activity and work related physical activity. Using the mean value of the total PASE score (i.e. 93), household-related activities constituted the largest proportion of physical activities performed by the study participants (mean = 69; 74%), followed by leisure-time physical activities (mean = 21; 23%), and work-related physical activities (mean=3; 3%). (Figure 6-2)

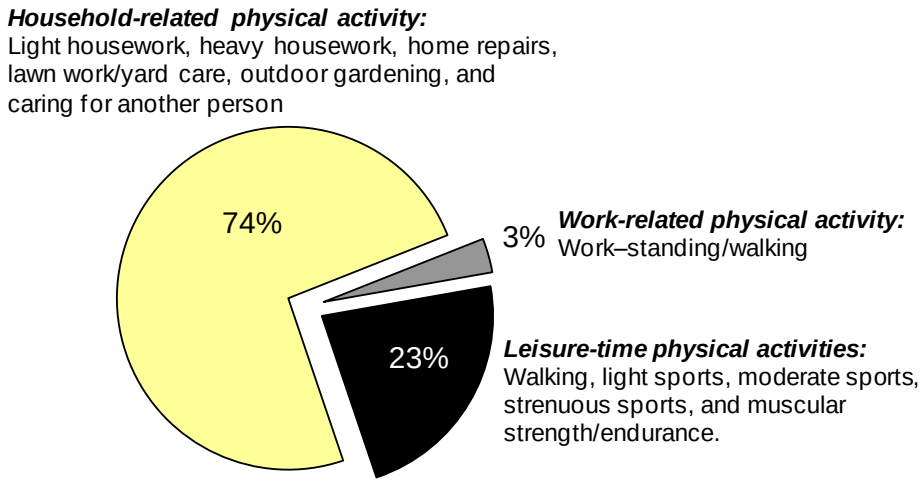


Figure 6-2: The three components of PASE score

PASE and CV risk factors

In univariate analyses, the PASE score was correlated with BMI (r=0.196, p=0.048) and fibrinogen (r=-0.243, p=0.027). There was one participant had markedly high fibrinogen level. To determine if this high fibrinogen value caused a spurious relationship, the analysis was re-run excluding this value. In the univariate analysis which excluded the high fibrinogen value, the PASE score tended to be correlated with fibrinogen (r=-0.215, p=0.052). Serum 25-OH D (vitamin D) tended to be correlated with the PASE score but did not reach statistical significance (r=0.188, p=0.080) (Appendix B: TABLE B-2, page 294). There was a linear correlation between the PASE score and BMI which was attributed to housework-related physical activity and this increased across BMI categories (Figure 6-3). Participants in the underweight category had the highest level

of leisure-time physical activity compared to other BMI categories, but the difference was not statistically significant. Work-related activities among the participants were equally low across BMI categories.

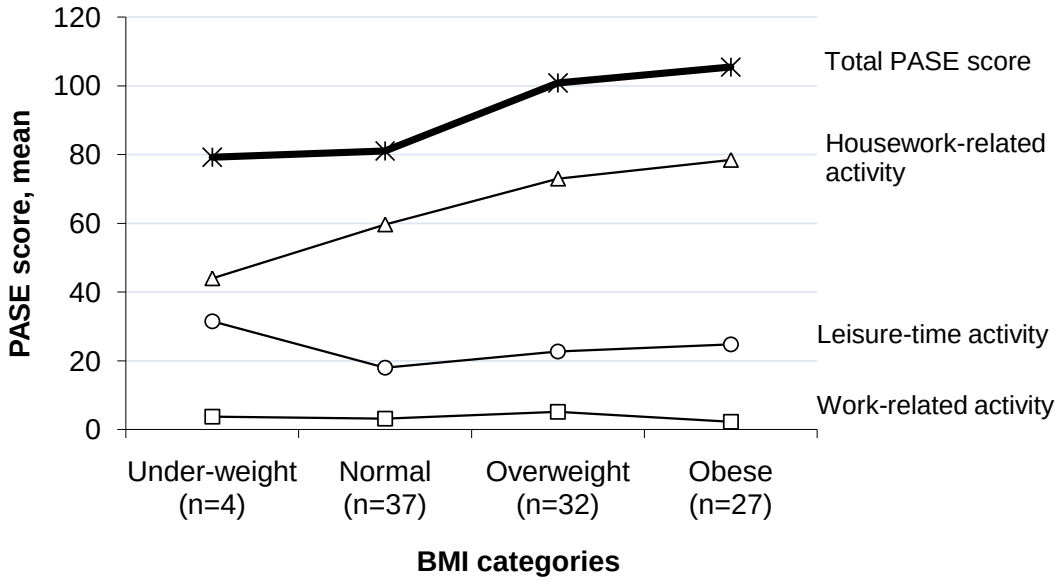


Figure 6-3: Mean PASE score according to BMI categories
Notes:
- Body Mass Index (BMI) was categorised according to the World Health Organisation (WHO) classification (236) : Underweight: BMI <18.5kg/m^2; Normal range: 18.5 to <25kg/m^2; Overweight: 25 to <30 kg/m^2; Obese: ≥30kg/m^2
- Spearman's correlation between PASE score and BMI, r=0.196, p=0.048
- Spearman's correlation between housework-related activity and BMI, r=0.211, p=0.035

Given that physical activity may be higher in men than in women, and in younger-age elderly adults than older-age elderly adults (117), and Māori participants had a higher BMI than non-Māori (p<0.01), the association between the PASE score and BMI was controlled for sex- and age-ethnicity. To determine if age-ethnicity had an effect on the association between the PASE score and BMI, the interaction term (BMI × age-ethnicity) was added to the regression model. The interaction term (BMI × age-ethnicity) was not associated with PASE score (p=0.770). This implied the association between the PASE score and BMI was the same for both age-ethnic groups. Hence, analyses were undertaken with age-ethnicity combined. The PASE score was not associated with BMI after adjusting for sex and age-ethnicity (p=0.500). The PASE score and its components between men and women across four BMI categories are shown in Figure 6-4.

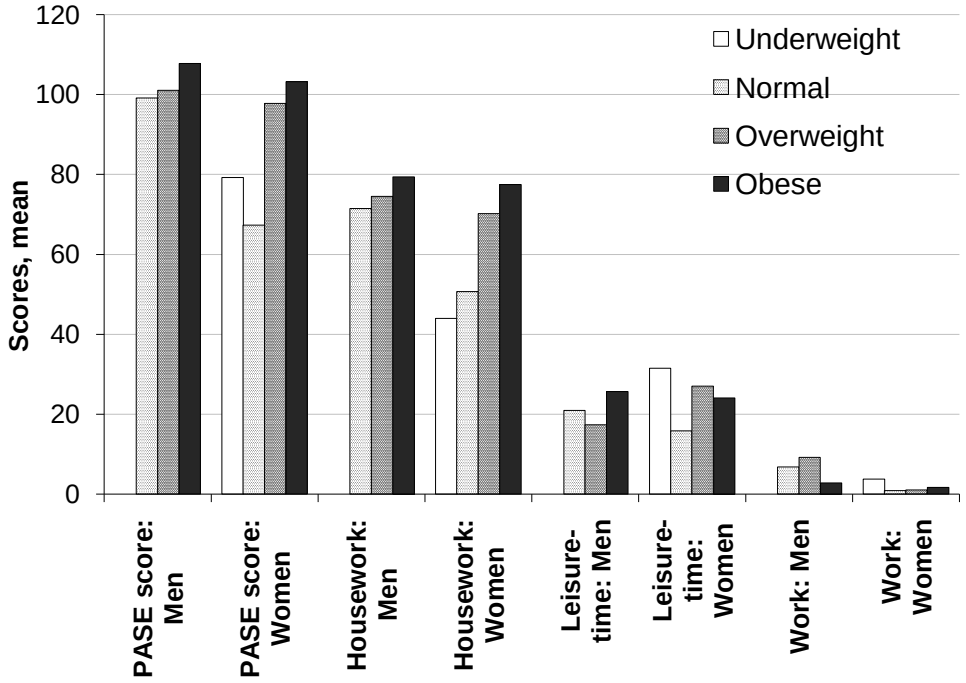


Figure 6-4: Physical activity scores for men and women across BMI categories
Notes: In univariate analysis, the PASE score (r=0.297, p=0.025) and housework-related activity (r=0.357, p=0.007) were correlated with BMI among women
(Additional information on the relationship between the PASE score and its component across BMI categories according to sex and age-ethnic groups are show in Appendix B: Figure B-1, page 295)

PASE and clinically manifest CVD

The total PASE score for participants with no CVD was 20% higher compared to those with CVD, median (IQR) 96 (111) vs. 80 (63), but it did not reach statistical significance (p=0.240). To identify the different physical activities performed between those with and those without CVD, the total PASE score was segregated into the three activity groups (i.e. leisure-time activity, household-related activity and work-related activity). Compared to participants with CVD, those without CVD tended to undertake more leisure-time physical activity but it did not reach statistical significance, p=0.073 (TABLE 6-3).

TABLE 6-3: PASE – Physical Activity Scale for the Elderly score according to CVD status

Activity group	Mean PASE score (% contribute to total PASE score)		
	No CVD n=35	Yes CVD n=72	P value[§]
Leisure-time physical activity	27 (26)	19 (21)	0.073
Household-related physical activity	73 (70)	67 (76)	0.398
Work-related physical activity	5 (4)	3 (3)	0.742
Total PASE score	104	88	0.240

[§]P value from Mann-Whitney U test unless stated otherwise

Since the use of prescribed medications may be associated with physical activity level among the very old (127), the PASE score for those with and those without CVD who used and did not use prescribed medication was determined. Participants with no CVD and not on any prescribed medication had higher PASE scores, median (IQR): 143 (73) compared to those with CVD and on prescribed medication, median (IQR): 79 (66), p=0.015 (Figure 6-5).

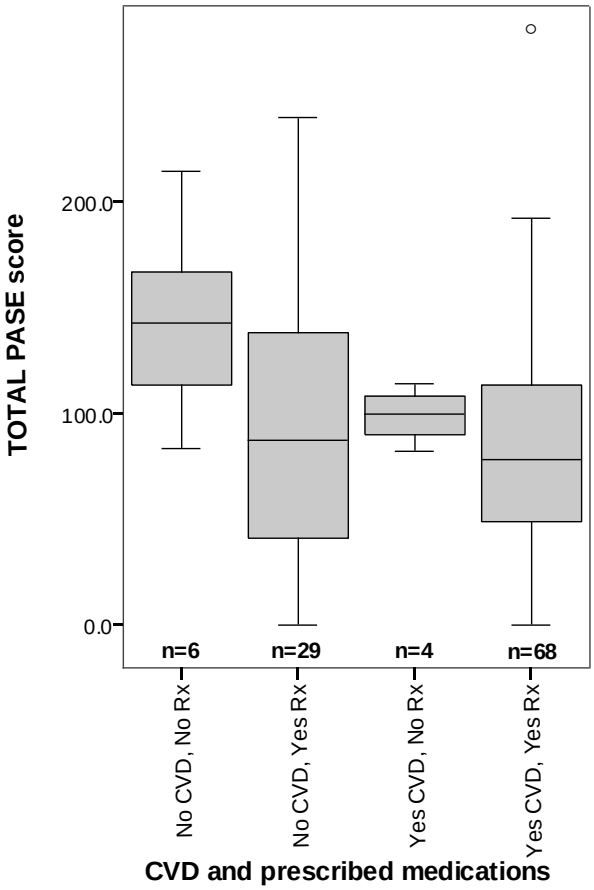


Figure 6-5: PASE score in four different groups of CVD status and medications
This box-plot showed the median of PASE score is greater in participants without CVD and not on any prescribed medication compared with the group of participants who had CVD and were on prescribed medications (p=0.015).

The association between the PASE score and CVD was explored, controlling for sex, age-ethnicity, smoking status, and potential confounders. As physical activity level was reported to be different between the sexes (117) and with younger-age elderly adults being more physically active (117), an interaction term was created to determine if the association between PASE and CVD was dependent on sex (PASE × sex) and age-ethnicity (PASE × age-ethnicity). The interaction terms (PASE × sex, p=0.127 and PASE × age-ethnicity, p=0.315) were not associated with CVD. This implied the association between the PASE score and CVD was the same, regardless of sex and

age-ethnicity. Controlling for sex, age-ethnicity, and smoking status, we found that a change of 10-units in the PASE score was associated with a reduction in the estimated risk of CVD, odds ratio (95% CI): 0.905 (0.831–0.986), p=0.022. (TABLE 6-4)

TABLE 6-4: Association between CVD and PASE controlled for sex, age-ethnic group and smoking status

Variables	Odds ratio (95% CI)	P value
Sex (ref: men)	0.445 (0.177–1.116)	0.084
Age-ethnicity (ref: NZ European)	2.706 (0.894 – 8.186)	0.078
Smoking, (ref: never)		0.663
Current	0.636 (0.122–3.303)	0.590
Former	1.235 (0.497–3.065)	0.649
PASE score	0.990 (0.982–0.999)	0.028
PASE score (change of 10-unit)	*0.905 (0.831–0.986)*	*0.022*
Nagelkerke R^2	0.098	

Abbreviations: **ref:** reference
Logistics regression model with CVD as the dependent variable

To determine whether the number of prescribed medications moderate the association between physical activity and CVD, an interaction term (PASE score × number of prescribed medications ≤5 vs. >5) was included in the regression model. Grouping of prescribed medications into ≤5 and >5 was based on the median number of prescribed medications used by study participants; median=5, range 0–13. There was significant association between the interaction term (PASE score × number of prescribed medications ≤5 vs. >5) and CVD (p=0.006). This implied the association between physical activity (as measured with PASE) and CVD differed between participants treated with more than five, and five or less, prescribed medications. Therefore, multivariate analysis examining the association between PASE score and CVD was done separately for these two groups. In the group of participants who used five or less prescribed medications, controlling for sex, age-ethnicity and smoking status, the PASE score tended to be associated with CVD [OR (95% CI): 0.99 (0.98–1.01), p=0.082]. However, for participants who used more than five prescribed medications, the PASE score was not associated with CVD [OR (95% CI): 1.01 (0.98–1.04), p=0.550]. Briefly, the association between physical activity level and CVD was moderated by the number of prescribed medications used.

Similar analytical procedures were carried out to determine the association between CVD and each of the three components of the PASE score, i.e. leisure-time, household-, and work-related

physical activity. Age-ethnicity did not have a modifying effect on the association between leisure-time, housework, or work- related activities with CVD. Sex of the participants did not have a modifying effect on the association between leisure-time or work-related activities with CVD, except for housework-related activities. The association between housework-related activities and CVD was dependent on sex. In separate analyses for men and women, whilst controlling for age-ethnicity and smoking status, housework-related activity was associated with CVD among women [OR (95% CI): 0.97 (0.95–0.99), p=0.006] but not men [OR (95% CI): 1.01 (0.99–1.02), p=0.604]. The number of prescribed medications (≤5 vs. >5) have a modifying effect on the association between leisure-time and housework-related activities with CVD (but not work related activities). Therefore, a separate analysis was completed for both groups (number of prescribed medications ≤5 and >5). In the group of participants who used ≤5 prescribed medications, controlling for sex, age, and smoking status, leisure-time activity tended to be associated with CVD [OR (95% CI): 0.97 (0.95–1.01), p=0.055] but not in the group who used >5 prescribed medications [OR (95% CI): 1.01 (0.95–1.08), p=0.694]. In both groups (number of prescribed medications ≤5 and >5), controlling for sex, age-ethnicity, and smoking status, housework-related activity was not associated with CVD. In brief, housework-related activities was associated with CVD among women (not men) and leisure-time activities tended to be associated with CVD in participants who used ≤5 prescribed medications after taking into account sex, age-ethnicity, and smoking status.

6.2 Discussion

6.2.1 Nutritional risk

In this study, half of the study participants were at high risk for poor nutrition (SCREEN II score less than 50), which would not be unexpected. In a group of 158 younger-age elderly participants (mean age 79.5 years) living in the community, consisting of mainly New Zealand European, one-third was identified to be at high risk of poor nutrition. (58) This study sample of those living to advanced age also included Māori participants. In New Zealand, older Māori are less likely to consume the recommended servings of fruit and vegetables per day compared to older non-Māori. (470) The current sample of Māori participants were also found to be at risk of inadequate intake of fruit and vegetables, and more Māori tended to skip meals compared to non-Māori participants (Appendix B: Figure B-2, page 296; article comparing nutritional risk factors amongst Māori and

non-Māori of Advanced Age has been submitted for publication). Fruit and vegetables intake and skipping meals are two items are among the 14-item SCREEN II questionnaire. In a Canadian study with 367 vulnerable older adults (mean age 79.3 years) living in the community, more than two-thirds were found to be at high risk of poor nutrition. (57) Collectively, these studies showed nutritional risk are prevalent among older adults; people of advanced age could be more vulnerable.

One initial clinical manifestation of malnutrition (results of undernutrition) is weight loss. (79, 80) In this study, only a small fraction (4%) of study participants was underweight (BMI <18.5kg/m^2) but half of them were at high risk of poor nutrition. These results seem inconsistent but they are not contradictory. It possibly suggests the state of undernutrition is yet to be manifested clinically. Alternatively, loss in body weight is obscured by replacement of muscle mass with fat mass, a physiological change associated with ageing. (234) Excess of fat mass coupled with loss of muscle mass leads to sarcopenic obesity. (512) This study was not designed to determine the prevalence of sarcopenic obesity in those of advanced age but found a positive relationship between body-fat percentage and nutritional risk. In a Finnish population with ages ranging between 56 and 70 years old, fat mass index was associated with lower social class and physical inactivity. (511) Possibly socioeconomic status is associated with nutritional risk in older adults, but this will need to be confirmed in future studies. Inability to consume a wide variety of foods suggests one may not have balanced nutrients for proper physiological function. In middle-aged and older adults, vitamin B_6 and C intake has been shown to be significantly and inversely associated with inflammatory markers (84, 85, 87). Elevated inflammatory markers are associated with increased CVD risk. (270, 328, 340, 384, 513) Hence, undernutrition may exacerbate deterioration of cardiovascular health in those of advanced age.

This study found nutritional risk did not differ between those with and those without CVD. It may be a type II error due to the small sample size. Other possibilities contributing to the null association between CVD and nutritional risk in this advanced-age sample has been discussed in the published article. (514)

The changes in body composition with ageing and its relationship with nutrition and CVD risk is complex. In this study, half of the study participants who were underweight were at high risk of undernutrition. For those with ideal body weight (BMI 18.5–25kg/m^2), more than half of them were not at high risk of undernutrition. At the opposite end of the spectrum, more than half of the study

participants with BMI>30kg/m^2 were at high risk of undernutrition. With these findings, it is tempting to suggest a J-shape relationship between nutritional risk and BMI but this study cannot confirm the J-shape relationship. Studies have shown older adults with a healthy BMI range have a reduced risk of CVD and all-cause mortality compared to those with very low or high BMI. (244, 515, 516) In an article published from this study, the proportions of participants with clinically manifest CVD across BMI categories mirrored the proportions of malnutrition risk across BMI categories. Controlling for CV risk factors, SCREEN II scores trended towards an inverse association with CVD. (514) Therefore, from this study it could be hypothesised that nutritional risk is the mechanism for the J- or U-shaped relationship between BMI and CVD observed in older adults. (238, 517) Future studies are needed to confirm this.

In summary, nutritional risk is common among people of advanced age. The cardiovascular health of those in advanced age may be affected by inadequate nutrients intake for recuperation. Assessment of nutritional risk in those of advanced age is perhaps the first step in exploring ways in which nutritional strategies could impact on CVD related morbidity. Understanding of the relationship between nutritional risk and body composition may elucidate mechanisms involved in the development/progression of CVD in those of advanced age. Findings from future research on the relationship between nutritional risk and cardiovascular health may assist in the development of nutrition strategies and policy.

6.2.2 Physical activity

In this study, most of the study participants performed some level of physical activity except for seven (6%) who were wheelchair-bound or lived in a rest home. Most of the activities performed were housework-related activities followed by leisure-time activities, with minimal work-related activities. In the 2006/07 New Zealand Health Survey, regularity of leisure-time physical activity declined after 65 years of age and the prevalence of a sedentary lifestyle was highest in those aged 75 years plus. (118) Findings from the New Zealand Health Survey suggest older New Zealanders did not often meet the recommended requirement of at least 30 minutes per day of moderate-intensity physical activity (brisk walking) at least five days per week. (118) For older adults, overall health state is likely to be an important determinant of participation in leisure-time physical activity. In this study, among participants who used five or less prescribed medications and enjoyed a greater amount of leisure-time activity tended to have a lower likelihood of CVD after adjusting for

age, sex, and smoking status. No association was found between leisure-time activity and CVD among those who used more than five prescribed medications. These two important observations, i.e. use of prescribed medications and the possibility of an inverse relationship between leisure-time physical activity and CVD risk, merit further discussion.

Co-morbidities are common in older adults and likely to affect the activities of daily living. Heart failure and stroke are among the common health conditions limiting the activity of daily living and are associated with disability. (72-75) As mentioned, no association was found between leisure-time physical activities with CVD among participants who used more than five prescribed medications. This may suggest participants with co-morbidities, which can be reasonably assumed by increased used of prescribed medications, were less likely to participate in leisure-time physical activities. For older adults with co-morbidities, maintaining activity for daily function is the foremost priority. In the Jerusalem Longitudinal Cohort Study, comparing participants aged between 70 and 78 years old who were physically active to sedentary participants, the former group had significantly less deterioration in ease of performing the activities of daily living (ADLs) than the later group. (127) In the Perth Community Stroke Study which followed 362 patients (mean age 73±13 years) for up to five years, a low level of physical activity prior to stroke was one of the major predictors of surviving in a disabled or dependent state. (73) These studies suggest leisure-time physical activity level has a role in determining functional status and survival in older adults. There is also a strong epidemiological connection between high levels of physical activity throughout the lifetime and low levels of morbidity, higher levels of survival and wellbeing. Those who naturally increase their level of activity improve their chance of survival. (518) The current cross-sectional study was not able to determine prior physical activity levels. Prospective studies are needed to determine the effect of physical activity on long-term cardiovascular health of advanced age, whether they do or do not have clinically manifest CVD.

In this study, participants who had fewer co-morbidities, as indicated by fewer prescribed medications, increased leisure-time activity tended to be related to lower likelihood of having CVD after adjusting for age, sex, and smoking status. This supports the positive association between physical activity and CVD extending into advanced age. The better cardiovascular health profile of the participants engaging in physical activity is likely to be mediated through multiple mechanisms. This study found fibrinogen levels appear to be inversely related to physical activity levels. This is

in line with the Cardiovascular Health Study which showed increased leisure-time physical activity was associated with significantly lower levels of inflammatory markers (CRP, fibrinogen, Factor VIII activity and white blood cell count). (355) Elevated levels of inflammatory markers are associated with increased risk of CVD. (270, 328, 340, 384, 513) The current study did not find an association between leisure-time physical activity with HDL level observed in studies with young (519, 520) and older adults. (105, 109, 355) Information related to the relationship between physical activity and HDL in very old age is yet to be reported. Perhaps there will be no overt relationship in this sample of people of advanced age due to the homogeneity of physical activity variety, i.e. that is mostly involves low-intensity physical activity such as walking or gardening. In a cross-sectional study of 3,255 adults aged between 65 and 93 years living in Pianoro (northern Italy), HDL was positively correlated with housework-related activity. (521) The cause-and-effect relationship between HDL levels and housework-related activity is uncertain. Prospective studies are needed to address the cause-and-effect relationship between HDL and physical activity in advanced age.

This study found a positive correlation between physical activity levels with BMI; more precisely, housework-related physical activity and higher BMI was observed in women. The positive correlation between physical activity levels and BMI may indicate energy reserves (of which BMI is a good indicator) are needed to maintain performance of housework-related activity. However, in the analysis adjusting for sex and age-ethnicity, physical activity was not associated with BMI. In a study of 190 older adults aged between 55 to 77 years (mean age 66 years old), women were more likely to engage in light housework whereas men were more likely to do more home repair and lawn work/yard care. (117) This may explain why physical activity was not associated with BMI after adjusting for sex. In this study, the overall levels of activity were similar between men and women, meaning substitution in types of activity between the sexes was common. This study acknowledged the small sample size is likely to have contributed to a type II error. Future studies are needed to understand and demonstrate the relationship between energy reserves and physical activity in those of advanced age.

The benefit of physical activity in those of advanced old age is likely to be multi-factorial. The 18-year Jerusalem Longitudinal Cohort Study demonstrated that being physically active into advanced old age (88 years) improved function and remained a strong predictor of survival. (127) Together with nutritional status, physical activity is possibly instrumental in delaying the onset and

exacerbation of the downward spiral of the cardiovascular health status. Additionally, the cardio-protective effects of physical activity are likely to continue into advanced old age potentially through reduction of inflammatory markers. Results from this study should be interpreted cautiously. Studies with a larger sample size are needed to confirm these findings.

CHAPTER SEVEN: CARDIOVASCULAR RISK FACTORS

This chapter will present the conventional cardiovascular (CV) risk factors and the inflammatory markers of the study sample. The conventional CV risk factors are smoking status, fasting serum glucose, blood pressure, anthropometry measures (body mass index, waist circumference, waist-to-hip ratio, and body fat percentage), and lipid profile (total cholesterol, triglyceride, high-density lipoprotein, low-density lipoprotein, and total cholesterol/high-density lipoprotein ratio). The inflammatory markers are C-reactive protein, interleukin-6, tumour necrosis factor-alpha, fibrinogen, and erythrocyte sedimentation rate. Descriptive statistics will be presented for each of the risk factors; these are followed by their association with clinically manifest cardiovascular disease (CVD). Age is known to be a major contributor to increased CVD risk. Hence, the effect of age on each of the cardiovascular risk factors will be explored. An association between the interaction term (age $\times$ variable of interest) with CVD at $p<0.05$ indicates the effect of the study variable on CVD is moderated by age. In this situation, a separate analysis was performed for each age-ethnic group. Otherwise, analysis was combined for both age-ethnic groups. The findings of CV risk profile in this group of people in advanced age will be discussed in the latter section of this chapter.

7.1 Results

7.1.1 Smoking

Smoking was not common in this sample. Half of the study participants (n=55) had never smoked tobacco cigarettes, and 41% (n=44) had stopped smoking for more than 12 months (former smokers). Only a small number of participants were current smokers (n=8). There was no difference in the distribution across three smoking categories in any of the participants' characteristics and CVD status (TABLE 7-1).

TABLE 7-1: Participants' characteristics according to smoking status.

Variable, n (column %)	Smoking			P value†
	Never, n=55	Current, n=8	Former, n=44	
Sex				
- Men	19 (34)	3 (38)	25 (57)	0.077
- Women	36 (66)	5 (62)	19 (43)	
Age-ethnicity				
- 75-79 years old	16 (29)	5 (62)	11 (25)	0.122
- 85 years old	39 (71)	3 (38)	33 (75)	
Marital status				
- Married	18 (33)	2 (25)	21 (48)	0.306
- Widowed	32 (58)	6 (75)	18 (41)	
Education				
- Secondary	24 (44)	2 (25)	15 (34)	0.577
- Tertiary	15 (28)	4 (50)	18 (41)	
CVD				
- No	19 (35)	3 (38)	13 (30)	0.812
- Yes	36 (65)	5 (62)	31 (70)	

† P values are from Fisher's exact test because 60% of the expected frequencies were less than 5

7.1.2 Diabetes and serum glucose

Ascertainment of diabetes mellitus

The definition for diabetes mellitus was described in Chapter Three: Methods (Section 3.9, page 96). Diabetes was ascertained by: self-report, on prescribed medications for diabetes, a fasting serum glucose ≥7.0mmol/L, or hospitalisation records indicated diabetes. The majority of the diabetes cases were self-reported (n=16), followed by hospitalisation records (n=14), medication for diabetes (n=9), and serum glucose ≥7.0mmol/L (n=8). All cases were type 2 diabetes mellitus. Ten of the 16 participants with self-reported diabetes had also another method confirming their diabetes status (Figure 7-1). There were six participants unaware of their diabetes condition: two of them had serum glucose ≥7.0mmol/L, three had hospitalisation records indicated diabetes, and one female participant had both serum glucose ≥7.0mmol/L and a hospital record of diabetes. Overall, 22 (20%) of participants had diabetes mellitus.

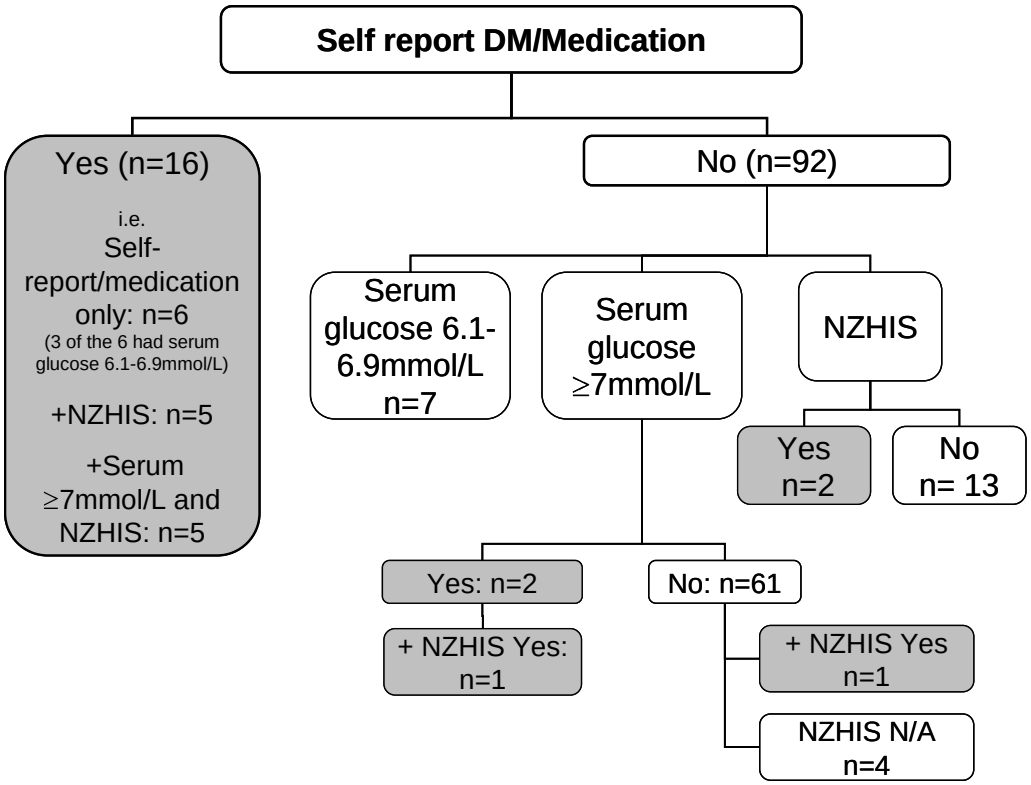


Figure 7-1: Ascertainment of diabetes mellitus
Abbreviation: **DM**: diabetes mellitus; **N/A**: not available; **NZHIS**: New Zealand Health Information service
Shaded boxes were number of participants with diabetes mellitus.

Diabetes, participants' characteristics and CVD

The participants' characteristics and CVD status between those with and without diabetes are presented in TABLE 7-2. In this sample, of the 22 participants with diabetes, 41% were men and 59% were women. There was no difference in the distribution of diabetes in any of the participants' characteristics and CVD status.

TABLE 7-2: Participants' characteristics and CVD status by diabetes status.

Variable, n (column %)	Diabetes mellitus		P value‡
	No n=86	Yes n=22	
Sex			
- Men	39 (45)	9 (41)	0.708
- Women	47 (55)	13 (59)	
Age-ethnicity			
- 75-79 years old	23 (27)	10 (46)	0.089
- 85 years old	63 (73)	12 (55)	
Marital status			
- Married	32 (37)	9 (41)	0.871†
- Widowed	44 (51)	13 (59)	
Education			
- Secondary	34 (40)	7 (32)	0.723
- Tertiary	30 (35)	8 (36)	
Smoking status			
- Current	7 (8)	1 (5)	0.674
- Former	36 (42)	8 (36)	
CVD			
- No	31 (36)	5 (23)	0.237
- Yes	55 (64)	17 (77)	

‡P values are from Pearson chi-square test, unless specified otherwise
†Examined with Fisher's exact test because 60% of the expected frequencies were less than 5

Fasting serum glucose

A total of 90 participants contributed fasting blood samples for analysis of serum glucose. Eighteen participants chose not to give blood samples for analysis. Of the 90 who gave blood samples, glucose analysis was not done for one participant because there was insufficient serum. Thus, the total number of serum glucose samples available for statistical analysis was 89. The distribution of the serum glucose was skewed to the right of the median (positively skewed), i.e. the majority of serum glucose values were clustered toward the lower end of the distribution scale with few in the upper end of the scale. The median (IQR) was 5.2(0.9)mmol/L. One high value of 14.5mmol/L was from an 85-year old woman with diabetes and treated with metformin. The next value following 14.5mmol/L was 9.6mmol/L.

Glucose-lowering medication, diabetes and serum glucose

There were nine participants reported to be on prescribed medications for diabetes. All of them were on metformin: four had metformin alone, three had metformin and glipizide, one had metformin and insulin, and one had metformin, insulin, and gliclazide. According to the World Health Organisation/International Diabetes Federation criteria of diabetes (481), seventy-one participants (66%) had normal fasting serum glucose (<6.1mmol/L), ten (9%) participants had impaired fasting serum glucose (6.1–7.0mmol/L), and eight (7%) participants had diabetes (≥ 7.0mmol/L). Half of

the participants with diabetes were treated with glucose-lowering medication (TABLE 7-3). Serum glucose levels for the remaining half not treated for the condition (diabetes) ranged between 7.3 and 9.6mmol/L. Participants on medication had significantly higher fasting serum glucose than those not on medication, median (IQR): 8.3(5.5) vs. 5.2(0.9), p=0.030.

TABLE 7-3: Glucose-lowering medication and fasting serum glucose according to diabetes status[27]

	Normal fasting glucose (<6.1mmol/L)	**Impaired fasting glucose (6.1–6.9mmol/L)**	**Diabetes (≥ 7.0mmol/L)**	**Serum glucose not available**
n (%)	71 (66)	10 (9)	8 (7)	19 (18)
Medication for diabetes, n	2	0	4	3
Fasting glucose median (IQR)	5.1 (0.6)	6.6 (0.5)	8.5 (1.7)	-

Abbreviations: **IQR:** Interquartile range
Note: Six of the ten participants with impaired fasting glucose and five of the eight participants with serum glucose ≥7.0mmol/L had CVD.

Serum glucose and CVD

Serum glucose levels were not different between those with and those without CVD, median (IQR): 5.2(0.8) vs. 5.3(1.1), p=0.593. The association between serum glucose and CVD was examined using logistic regression. To determine if age-ethnicity has an effect on the relationship between serum glucose and CVD, the interaction term (age-ethnicity × serum glucose) was included into the regression model. There was no significant association between the interaction term and CVD (p=0.280). This indicates the association between serum glucose and CVD was the same for all ages. Therefore, analysis was combined for both age-ethnic groups. Controlling for sex, age-ethnicity, and smoking status, fasting serum glucose was not associated with CVD. When glucose-lowering medication was added to the model, fasting serum glucose tended to be associated with CVD, p=0.060 [OR (95% CI): 0.642 (0.405–1.018)]. (Appendix B: TABLE B-3, page 297) This is probably because by controlling for the drug used, the glucose level was more homogenous.

[27] Diabetes mellitus classification based on a report from WHO/IDF consultation 2006 (461)

7.1.3 Hypertension and blood pressure

Ascertainment of hypertension

The definition for hypertension was described in Chapter Three: Methods (Section 3.9, page 96). Participants with any one of the five criteria were considered as having hypertension (TABLE 7-4). Forty-nine (45%) participants self-reported to have hypertension and 47 (44%) participants had hospitalisation records indicating hypertension. Twenty-four (23%) participants had systolic/diastolic blood pressure ≥140/90mmHg, and 47 (46%) had systolic blood pressure (SBP) ≥140mmHg but diastolic blood pressure (DBP) <90mmHg. All 34 participants on prescribed medication indicated for hypertension had one or more of the criteria defining hypertension, except for one participant who had only a record of receiving prescribed medications for hypertension. She was on Triamizide tab (180) (hydrochlorothiazide; triamterene) indicated for blood pressure and fluid retention. Overall, 91 (84%) study participants had hypertension.

TABLE 7-4: Ascertainment of hypertension

	Self report n=49	**NZHIS records n=47**	**SBP/DBP≥140/90 n=24**	**SBP≥140 n=47**	**Medication indicated for hypertension n=34**
Self report	49				
Self report or NZHIS records		65			
Self report or NZHIS records or SBP/DBP≥140/90			73		
Self report or NZHIS records or SBP/DBP≥140/90 or SBP≥140				90	
Self report or NZHIS records or SBP/DBP≥140/90 or SBP≥140 or medication indicated for hypertension					91

Abbreviations: **DBP**: diastolic blood pressure; **HTN**: hypertension; **NZHIS**: New Zealand Health Information System; **SBP**: systolic blood pressure

Hypertension, participants' characteristics and CVD

The participants' characteristics and CVD status between those with and those without hypertension are presented in TABLE 7-5. There was a difference in the distribution of hypertension between men and women (p=0.018). The distribution of hypertension was not different in any other of the participants' characteristics or CVD status.

TABLE 7-5: Participants' characteristics and CVD status by hypertension status

Variable, n (column %)	Hypertension		P value‡
	No n=17	Yes n=91	
Sex			
- Men	12 (71)	36 (40)	0.018
- Women	5 (29)	55 (60)	
Age-ethnicity			
- 75-79 years old	4 (24)	29 (32)	0.493
- 85 years old	13 (76)	62 (68)	
Marital status			
- Married	11 (65)	30 (33)	0.202†
- Widowed	6 (35)	51 (56)	
Education			
- Secondary	5 (29)	36 (40)	0.258
- Tertiary	9 (53)	29 (32)	
Smoking status			
- Current	1 (6)	7 (8)	0.627
- Former	5 (31)	39 (43)	
CVD			
- No	5 (29)	31 (34)	0.709
- Yes	12 (71)	60 (66)	

‡P values are from Pearson chi-square test, unless specified otherwise
†Examined with Fisher's exact test because 60% of the expected frequencies were less than 5

Systolic and diastolic blood pressure

A total of 103 participants had three-sitting blood pressure measurements. Both systolic and diastolic blood pressure was distributed normally and data exploration did not show any outliers. The mean (SD) for systolic blood pressure (SBP) was 151(21) mmHg, and mean (SD) for diastolic blood pressure (DBP) was 83(12) mmHg. Participants with hypertension had significantly higher SBP than those without hypertension, 155(20)mmHg vs. 127(9)mmHg, $p<0.001$. However, the mean difference of DBP between the two groups missed the statistical significance level of $p<0.05$, 84mmHg (13) vs. 77mmHg (6), $p=0.051$.

Power calculation for blood pressure: In this study the sample size of 108 participants comprised a 2:1 ratio of participants with and without CVD. It had 21% and 52% power respectively to detect a clinically meaningful difference of 5mmHg of SBP and DBP. To have 80% power to detect the difference of 5mmHg for SBP with the same ratio of participants with and without CVD of 2:1, 630 participants would have been needed. To detect a similar difference of DBP for those with and those without CVD, 210 participants would have been needed.

Blood pressure-lowering medications, hypertension and blood pressure

One-third of the study participants (n=34) were on prescribed medication indicated for hypertension. The number of blood pressure-lowering medications ranged from one to three: 25 of them were on one medication, eight of them were on two medications, and one participant had three medications. Medications indicated for treatment of hypertension observed to be taken by study participants and recorded in the questionnaire are listed in TABLE 7-6. Among those with hypertension, nearly two-thirds were not receiving treatment indicated for the condition. However, in the total study sample, with or without hypertension, there were 69 (64%) participants on medications that could possibly be used to treat hypertension but were not recorded as such in the self-report medication table.

TABLE 7-6: Medications for treatment of hypertension and medications that have an effect on the blood pressure

List of medications	Reported by participant for treatment of hypertension	Have impact on blood pressure level
	N	N
Metoprolol succinate	8	29
Quinapril	6	15
Felodipine	5	12
Atenolol	4	5
Bendroflumethiazide	4	4
Celiprolol	2	2
Cilazapril	2	16
Enalapril maleate	2	4
Diltiazem	1	6
Losartan	1	1
Hydrochlorothiazide; triamterene	1	1
Doxazosin mesylate		1
Verapamil		1
Spironolactone		2
Propranolol		2
Sotalol		2
Candesartan cilexetil		4

The mean (SD) for SBP and DBP values for participants with hypertension and on medication indicated for hypertension (n=34) were 158 (21) mmHg and 84 (14) mmHg. The mean (SD) for SBP and DBP values for participants with hypertension but not on medication indicated for hypertension (n=57) were 153 (20) mmHg and 83 (12) mmHg. Blood pressure values did not differ between hypertensive participants receiving medication indicated for hypertension compared to those not receiving medication indicated for hypertension, SBP: p=0.215, DBP: p=0.995. For the 69 participants on medications that have an impact on blood pressure, the mean (SD) for SBP and

DBP values were 150(23) mmHg and 81(13) mmHg. These values did not differ from participants who were not on these medications, 151(18) and 85(10) mmHg, p>0.05.

Blood pressure and CVD

Systolic and diastolic blood pressure did not differ between those with and those without CVD (TABLE 7-7). The association between systolic and diastolic blood pressure with CVD was examined using logistic regression. To determine if age-ethnicity has an effect on the relationship between blood pressure and CVD, the interaction term (age-ethnicity × SBP) and (age-ethnicity × DBP) was included in the regression model separately. There was no association between the interaction terms and CVD (p=0.289, p=0.442). Therefore, analysis was combined for both age-ethnic groups. Controlling for sex, age-ethnicity, smoking status and medication indicated for hypertension or medication that has an effect on blood pressure, SBP and DBP were not associated with CVD. (Appendix B: TABLE B-4, page 298 and TABLE B-5, page 299)

TABLE 7-7: Blood pressure between those with and those without CVD, mean (SD)

	All n=108	**No CVD n=35**	**Yes CVD n=68**	**P value[§]**
Systolic BP (mmHg)	151 (21)	153 (18)	150 (23)	0.457
Diastolic BP (mmHg)	83 (12.2)	84 (12)	82 (12)	0.303

Abbreviations: **BP**: blood pressure; **CVD**: cardiovascular disease
[§] P values are from Independent t-test

7.1.4 Anthropometry measures

The anthropometry measures examined are body mass index (BMI, kg/m^2), waist circumference (WC, cm), waist-to-hip ratio (WHR) and body fat percentage (BF%). A total of 103 participants completed measurements of height, weight and body composition. Due to physical incapacity, the heights of four participants were calculated using demispan, and their weights were obtained from the most recent measurement done in a nursing home or hospital. One participant did not have her waist and hip circumference measured and another participant did not have his hip circumference measured, because both were not able to co-operate physically. Body fat percentage was estimated from measures of body composition using the Tanita scale. Six participants did not have their body composition measured because they were unable to co-operate physically (n=5), and one participant had a body weight exceeding the measurable limit on the Tanita scale (maximum limit 150kg) (her weight was measured using a SECA mechanical weighing scale at the health

centre). Thus, BMI, WC, WHR and BF% were available for 103, 102, 101 and 97 participants, respectively.

Distribution of anthropometry measures

The distribution of BMI was skewed to the right of the median (positively skewed), i.e. the majority of the values clustered toward the lower end of the scale with few having high values. One female participant weighed 156.7kg, with a BMI of 65.9kg/m^2, an outlier in the sample. The next value after this was 46.2kg/m^2. Waist circumference (WC), waist-to-hip ratio (WHR) and body fat percentage (BF%) had a normal distribution.

Body mass index (BMI)

A total of 103 participants had a BMI calculated. The median (IQR) for BMI was 27.1 (7.1) kg/m^2. According to the WHO classification (236), four (4%) study participants were in the underweight category, 37 (36%) had a normal BMI, 34 (33%) were overweight, and 28 (27%) were obese. All four participants with BMI <18.5 were women aged 85 years old; three were widowed; three were former smokers; and three had hypertension. Three of four participants in this underweight category had CVD (Figure 7-2). Mean BMI for this group was 17.8 kg/m^2 (SD=0.55).

In the obese category (BMI≥30 kg/m^2) (n=28), there was an equal number of men and women, 19 (68%) of them were aged between 75 and 79 years old, 15 (54%) were widowed, eight (30%) participants had received tertiary education, three (11%) were current smokers, and 11 (41%) were former smokers. Twenty-four of the 28 obese participants (86%) had hypertension, six of the 28 participants (21%) had diabetes, and 22 of the 28 participants (79%) had CVD (Figure 7-2). Mean BMI for the obese group was 35.7 kg/m^2 (SD=7.2).

There was a difference in the distribution across four BMI categories between participants aged 75-79 and 85 years ($p<0.001$), i.e. the proportion of participants aged 75-79 increased across the BMI category but there was a reverse trend for participants aged 85 years old. The distribution of BMI was not different in any other of the participants' characteristics, medical history and CVD status. Comparing BMI between participants with and without CVD revealed there was no significant difference between the two groups, median (IQR) 27.4 (8.4) vs. 24.7 (5.6), $p=0.120$.

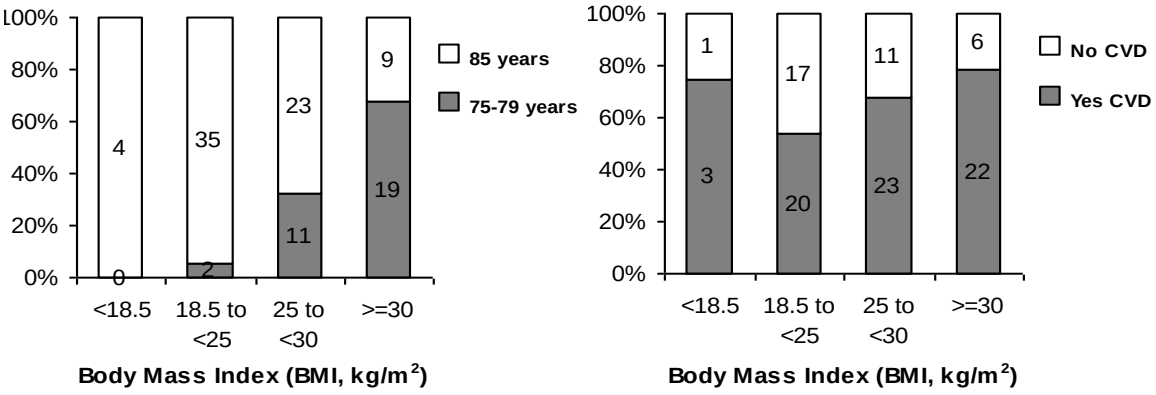


Figure 7-2: BMI classification by age-ethnic groups and CVD

Waist circumference (WC)

A total of 102 participants had a waist circumference (WC) measurement. The mean (SD) for WC was 95 (15) cm. Twenty-five participants (24%) had a normal WC, and 77 participants (76%) had increased WC (men ≥94cm and women ≥80cm). The participants' characteristics and medical history between those with normal WC and increased WC are presented in TABLE 7-8. There was a difference in the distribution of normal and increased WC between participants aged 75-79 and 85 years (p=0.021). The distribution of normal and increased WC was not different in any other of the participants' characteristics and medical history. Comparing WC between participants with and without CVD revealed that participants with CVD had a larger WC compared to those without CVD, mean (SD) 97.3 (15.7) vs. 91 (13.8), p=0.047.

TABLE 7-8: Participants' characteristics and medical history by two groups of WC measurements

Variable, n (column %)	Normal WC[a] n=25	Increased WC[b] n=77	P value[‡]
Sex			
- Men	10 (40)	36 (47)	0.555
- Women	15 (60)	41 (53)	
Age-ethnicity			
- 75-79 years old	3 (12)	28 (36)	0.021
- 85 years old	22 (88)	49 (64)	
Marital status			
- Married	10 (40)	28 (36)	0.963[†]
- Widowed	14 (56)	40 (52)	
Education			
- Secondary	9 (36)	31 (41)	0.346
- Tertiary	12 (48)	25 (33)	
Smoking status			
- Current	2 (8)	4 (5)	0.814
- Former	11 (44)	31 (41)	
Hypertension			
- No	4 (16)	10 (13)	0.704
- Yes	21 (84)	67 (87)	
Diabetes			
- No	21 (84)	63 (82)	0.804
- Yes	4 (16)	14 (18)	
CVD			
- No	12 (48)	23 (30)	0.097
- Yes	13 (52)	54 (70)	

Abbreviations: **WC**: waist circumference
[‡]P values are from Pearson chi-square test, unless specified otherwise
[†]Examined with Fisher's exact test because 60% of the expected frequencies were less than 5
[a] Normal WC: men<94cm; women<80cm
[b] Increased WC: men≥94cm; women≥80cm

Waist-to-hip ratio (WHR)

A total of 101 participants had a waist-to-hip ratio (WHR) calculated. The mean (SD) for WHR was 0.89 (0.08). Based on the WHO classification, 69 (68%) participants had a normal range WHR and 32 (32%) participants had high WHR (men >1.0 and women >0.85). The participants' characteristics and medical history between those with normal WHR and high WHR are presented in TABLE 7-9. There was a difference in the distribution of normal and high WHR between men and women (p=0.002). The distribution of normal and increased WC was not different in any of the participants' characteristics and medical history. Comparing WHR between participants with and without CVD revealed that participants with CVD did not have a higher WHR compared to those without CVD, mean (SD) 0.90 (0.08) vs. 0.88 (0.09), p=0.356.

TABLE 7-9: Participants' characteristics and medical history by two groups of WHR measurements

Variable, n (column %)	Normal WHR[a] n=69	High WHR[b] n=32	P value‡
Sex			
- Men	38 (55)	7 (22)	0.002
- Women	31 (45)	25 (78)	
Age-ethnicity			
- 75-79 years old	21 (30)	10 (31)	0.934
- 85 years old	48 (70)	22 (69)	
Marital status			
- Married	30 (44)	7 (22)	0.104†
- Widowed	33 (48)	21 (66)	
Education			
- Secondary	25 (37)	14 (44)	0.665
- Tertiary	25 (37)	12 (38)	
Smoking status			
- Current	4 (6)	2 (6)	0.317
- Former	32 (47)	10 (31)	
Hypertension			
- No	11 (16)	3 (9)	0.374
- Yes	58 (84)	29 (91)	
Diabetes			
- No	59 (86)	24 (75)	0.199
- Yes	10 (14)	8 (25)	
CVD			
- No	23 (33)	12 (38)	0.682
- Yes	46 (67)	20 (62)	

Abbreviations: **WHR**: waist-to-hip circumference
‡P values are from Pearson chi-square test, unless specified otherwise
†Examined with Fisher's exact test because 60% of the expected frequencies were less than 5
[a] Normal: men≤1.0; women≤0.85
[b] High: men>1.0; women>0.85

Body fat percentage (BF%)

The body fat percentage (BF%) was measured by two different machines (a bioimpedance analyser in the pilot study and a Tanita Inner Scan Body Composition monitor in the main study). To determine whether BF% values from the pilot study would affect results of the overall study sample, all analyses were done with and without data from the pilot study. In all variables, the level of association between BF% and the variable of interest did not differ when analyses were done with or without data from the pilot study. Therefore, the following results included data from all participants.

The mean (SD) for BF% was 32(8). Women had a significantly higher BF% compared to men, mean (SD): 36(8) vs. 27(6), p<0.000. Those aged between 75 and 79 years old had a significantly higher BF% compared to those aged 85 years old, 36(9) vs. 30(8), p=0.005. There was no significant difference in BF% between groups of marital status, smoking status, hypertension and

diabetes mellitus. Similarly, participants with CVD did not have a higher BF% than participants without CVD (p=0.634).

Anthropometry measurements and CVD

The association between anthropometry measures and CVD was examined using logistic regression controlling for sex, age-ethnicity, and smoking status. Collinearity between anthropometric measures was examined using a correlation test. Among all anthropometry measures, BMI was most strongly correlated with WC (r=0.832, p<0.001), followed by BF% (r=0.518, p<0.001), and WHR (r=0.324, p=0.001). Waist circumference (WC) was also significantly correlated with WHR (r=0.664, p<0.001) and BF% (r=0.267, p=0.009). There was no correlation between WHR and BF% (r=-0.154, p=0.135) (Figure 7-3).

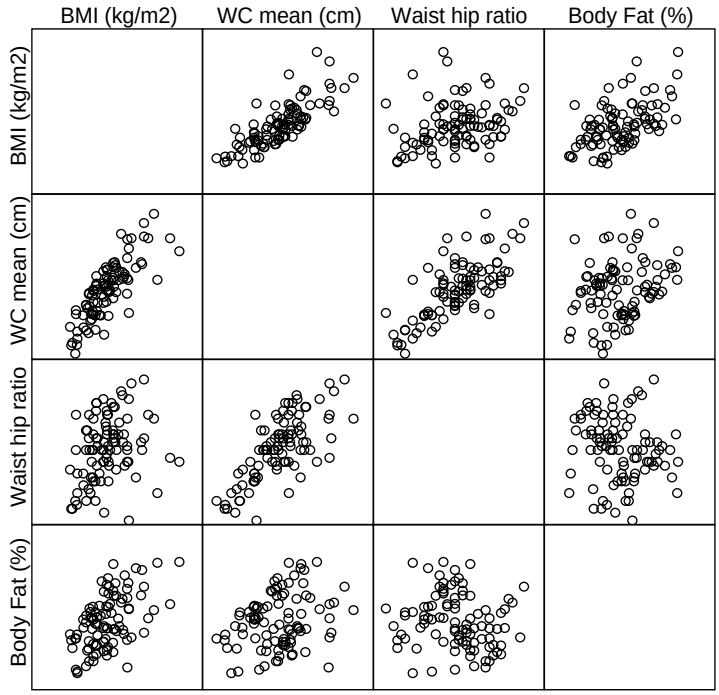


Figure 7-3: Scatter plots showing the correlation between anthropometry measurements
Abbreviations: **BMI**: Body mass index; **WC**: waist circumference

Due to the highly-correlated relationship between BMI, WC and WHR, each of these variables was entered separately into the regression model. Interaction terms were created using each of the anthropometry variables with age-ethnicity, to assess for any significant interactions between these variables in examining a potential association with CVD. There were no significant association between interaction terms and CVD (p>0.05). This finding implied that the association between anthropometry variables and CVD was the same for the two age-ethnic groups. Controlling for sex,

age-ethnicity and smoking status, there were no significant association between CVD and BMI [OR (95% CI): 1.08 (0.99–1.19), p=0.098]; WC [OR (95% CI): 1.023 (0.99–1.06), p=0.131]; WHR [OR (95% CI): 2.03 (0.003–1637.15), p=0.835]; and BF% [OR(95%CI): 1.003 (0.94–1.07), p=0.912]. (Appendix B: TABLE B-6 to TABLE B-9, page 300)

7.1.5 Dyslipidemia and lipid profile

Results of the lipid profile to be presented here are total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and TC/HDL ratio.

Ascertainment of dyslipidemia

The definition of dyslipidemia was described in Chapter Three: Methods (Section 3.9, page 96). The study defined dyslipidemia as one of the following criteria: participants receiving lipid-lowering medications, having a hospitalisation record of hyperlipidemia, or having an abnormal level of any type of fasting serum lipid according to the New Zealand Heart Foundation (NZHF) recommendation. (469) The NZHF recommendation was chosen over the less stringent laboratory cut-off values because the NZHF classification is the recommended optimal lipid level for adults aged 75 years and above.

In the sample, 29 (27%) participants were on prescribed medication for lipid metabolism disorder. Eighteen (17%) participants had hospitalisation records indicating the presence of lipid metabolism disorders. Based on the NZHF recommendation, 82 of the 90 participants who gave blood sample (91%) had at least one unfavourable lipid profile (TABLE 7-10). Combining the three methods of identifying dyslipidemia in the study sample, i.e. prescribed medication, hospitalisation records related to lipid metabolism disorder, and NZHF classification of unfavourable lipid profile, revealed that 85% (92 participants of the total sample of 108) of the study sample had dyslipidemia.

TABLE 7-10: Number of participants with abnormal lipid level according to the New Zealand Heart Foundation recommendation and the laboratory reference range

	NZHF [a]	n (%)	Laboratory [b]	n (%)
At least one abnormal lipid value		82 (91)		53 (59)
TC (mmol/L)	≥4.0	78 (87)	≥5.0	40 (44)
TG (mmol/L)	≥1.7	19 (21)	>2.0	9 (10)
LDL-C (mmol/L)	≥2.5	61 (68)	>4.0	29 (32)
HDL-C (mmol/L)	≤1.0	12 (13)	Similar to NZHF recommendation	
TC:HDL ratio	≥4.5	16 (18)		

Abbreviations: **HDL**: high-density lipoprotein; **LDL**: low-density lipoprotein; **NZHF**: New Zealand Heart Foundation; **TC**: total cholesterol; **TG**: triglyceride
A total of 90 participants gave blood sample for analysis
[a] The NZHF classification is the recommended optimal lipid level for adults aged 75 years and above
[b] Combining laboratory classification of an unfavourable lipid profile with the other two methods in ascertainment of dyslipidemia (i.e. lipid-lowering medication and hospitalisation record), revealed that 70% (76 participants of the total sample of 108) of the study sample had dyslipidemia.

Dyslipidemia, participants' characteristics and medical history

The participants' characteristics and medical history between those with and without dyslipidemia are presented in TABLE 7-11. There was no difference in the distribution between the two dyslipidemia groups in any of the participants' characteristics and medical history.

TABLE 7-11: Participants' characteristics and medical history by dyslipidemia status.

Variable, n (column %)	Dyslipidemia		P value[‡]
	No, n=16	Yes, n=92	
Sex			
- Men	8 (50)	40 (44)	0.628
- Women	8 (50)	52 (56)	
Age-ethnicity			
- 75-79 years old	6 (38)	27 (29)	0.514
- 85 years old	10 (62)	65 (71)	
Marital status			
- Married	8 (50)	33 (36)	0.181[†]
- Widowed	6 (38)	51 (55)	
Education			
- Secondary	5 (31)	36 (40)	0.531
- Tertiary	5 (31)	33 (36)	
Smoking status			
- Current	2 (13)	6 (7)	0.704
- Former	6 (37)	38 (42)	
Hypertension			
- No	3 (19)	14 (15)	0.715[†]
- Yes	13 (81)	78 (85)	
Diabetes			
- No	13 (81)	73 (79)	1.000[†]
- Yes	3 (19)	19 (21)	
CVD			
- No	4 (25)	32 (35)	0.444
- Yes	12 (75)	60 (65)	

[‡]P values are from Pearson chi-square test
[†]Examined with Fisher's exact test because 60% of the expected frequencies were less than 5

Distribution of lipid variables

All 90 participants who gave blood samples for analysis had results for all lipid parameters. Serum TC, HDL and LDL were distributed normally, whereas both TG and TC/HDL ratio had a distribution curve with a long right tail (skewed to the right of the median), i.e. most of the values clustered toward the lower end of the distribution scale with few in the upper end of the scale. There were two extreme outliers in the TG distribution: 4.8 and 4.0mmol/L from the two women who were not on a lipid-lowering medication; the 85-year-old woman has had a cardiac arrest and the 77-year-old woman has had myocardial infarction, angina, heart failure, ischemic heart disease, hypertensive heart disease, and abdominal aneurysm. The next lowest TG value after 4.8 and 4.0 was 3.1mmol/L. There were no extreme outliers in the TC/HDL ratio distribution.

Lipid profile and lipid lowering medications

The descriptive results for TC, TG, HDL, LDL, and TC/HDL ratio for all 90 participants who gave blood sample are presented in TABLE 7-12.

Power calculation for HDL: In this study the sample size of 108 participants comprised a 2:1 ratio of participants with and without CVD. This sample size had 98% power to detect a clinically meaningful difference of 0.33mmol/L[28] in HDL. To have 80% power to detect a difference of 0.33 mmol/L in HDL with the same 2:1 ratio of participants with and without CVD, only 54 participants are needed.

[28] In a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths, a 0.33 mmol/L higher HDL level was associated with about a third lower ischemic heart disease mortality. (262)

TABLE 7-12: Lipid level of the total study sample and among participants with dyslipidemia treated and not treated with lipid-lowering medications

	All participants n=90 [a]	Participants with dyslipidemia (n=87)		P value[‡]
		No medication n=62	Yes medication n=25	
Mean (SD)				
TC (mmol/L)	5.0 (1.1)	5.3 (1.1)	4.6 (0.8)	0.003
HDL (mmol/L)	1.5 (0.4)	1.5 (0.5)	1.4 (0.3)	0.663
LDL (mmol/L)	2.9 (0.9)	3.2 (0.9)	2.5 (0.7)	0.001
Median (IQR)				
TG (mmol/L)	1.2 (0.6)	1.2 (0.6)	1.3 (0.6)	0.382[#]
TC-HDL ratio (mmol/L)	3.5 (1.3)	3.6 (1.3)	3.1 (1.2)	0.053[#]

Abbreviations: **HDL**: high-density lipoprotein; **IQR**: interquartile range; **LDL**: low-density lipoprotein; **NZHF**: New Zealand Heart Foundation; **SD**: standard deviation; **TC**: total cholesterol; **TG**: triglyceride

[‡] P values are from Independent T-test, unless specified otherwise

[#] P values are from Mann-Whitney U test

[a] Three of the 90 participants who gave blood sample did not have dyslipidemia

A total of 29 participants were on prescribed lipid-lowering medications. The most common lipid-lowering medication used was simvastatin (n=23), followed by bezafibrate (n=3), atorvastatin (n=2), and ezetimibe (n=1). Of the 29 participants receiving treatment, 25 participants had blood lipid levels analysed; the remaining four participants declined to give blood samples for analysis. The lipid levels of participants with dyslipidemia receiving treatment compared to those not on treatments are showed in TABLE 7-12. The TC and LDL level was significantly lower in participants receiving medication compared to those not on medication (p=0.003 and p=0.001, respectively). In spite of the pharmacology treatment, TC and LDL levels were still above the NZHF recommended level.

Association between lipid profile and CVD

Comparing each of the lipid parameters between participants with CVD and those without CVD, HDL levels were significantly lower in participants with CVD than those without CVD, 1.4 (0.7) vs. 1.6 (0.4), p=0.041 (TABLE 7-13). No difference in other lipid parameters between the two groups.

TABLE 7-13: Lipid levels between those with and those without CVD

	All n=90	No CVD n=32	Yes CVD n=58	P value‡
Mean (SD)				
TC (mmol/L)	5.0 (1.1)	5.3 (1.0)	4.9 (1.1)	0.056
HDL (mmol/L)	1.5 (0.4)	1.6 (0.4)	1.4 (0.7)	0.041
LDL (mmol/L)	2.9 (0.9)	3.1 (1.0)	2.8 (0.9)	0.147
Median (IQR)				
TG (mmol/L)	1.2 (0.6)	1.3 (0.7)	1.2 (0.6)	0.532#
TC-HDL ratio (mmol/L)	3.5 (1.3)	3.6 (1.4)	3.6 (1.3)	0.578#

Abbreviations: **CVD**: cardiovascular disease; **HDL**: high-density lipoprotein; **IQR**: interquartile range; **LDL**: low-density lipoprotein; **NZHF**: New Zealand Heart Foundation; **SD**: standard deviation; **TC**: total cholesterol; **TG**: triglyceride
‡ P values are from Independent T-test, unless specified otherwise
# P values are from Mann-Whitney U test

The association between lipid parameters and CVD was examined using logistic regression controlling for sex, age-ethnicity, smoking status, and lipid-lowering medications. Due to the high correlation between these lipid variables (Figure 7-4), each of the variables was entered separately into the regression model. To determine if age-ethnicity has an effect on the relationship between each of the lipid variables with CVD, the interaction term (age-ethnicity × lipid variable) was included in the regression model. There was no association between each of the five interaction terms with CVD ($p>0.05$). This indicates the association between the lipid variable and CVD was the same for all ages. Therefore, analysis was combined for both age-ethnic groups. Controlling for sex, age-ethnicity, smoking status and lipid-lowering medication, revealed that TC, TG, LDL and TC/HDL ratios were not associated with CVD. HDL tended to be associated with CVD [OR (95%): 0.316 (0.100–1.000, p=0.050)]. (Appendix B: TABLE B-10 to TABLE B-14, page 301-302)

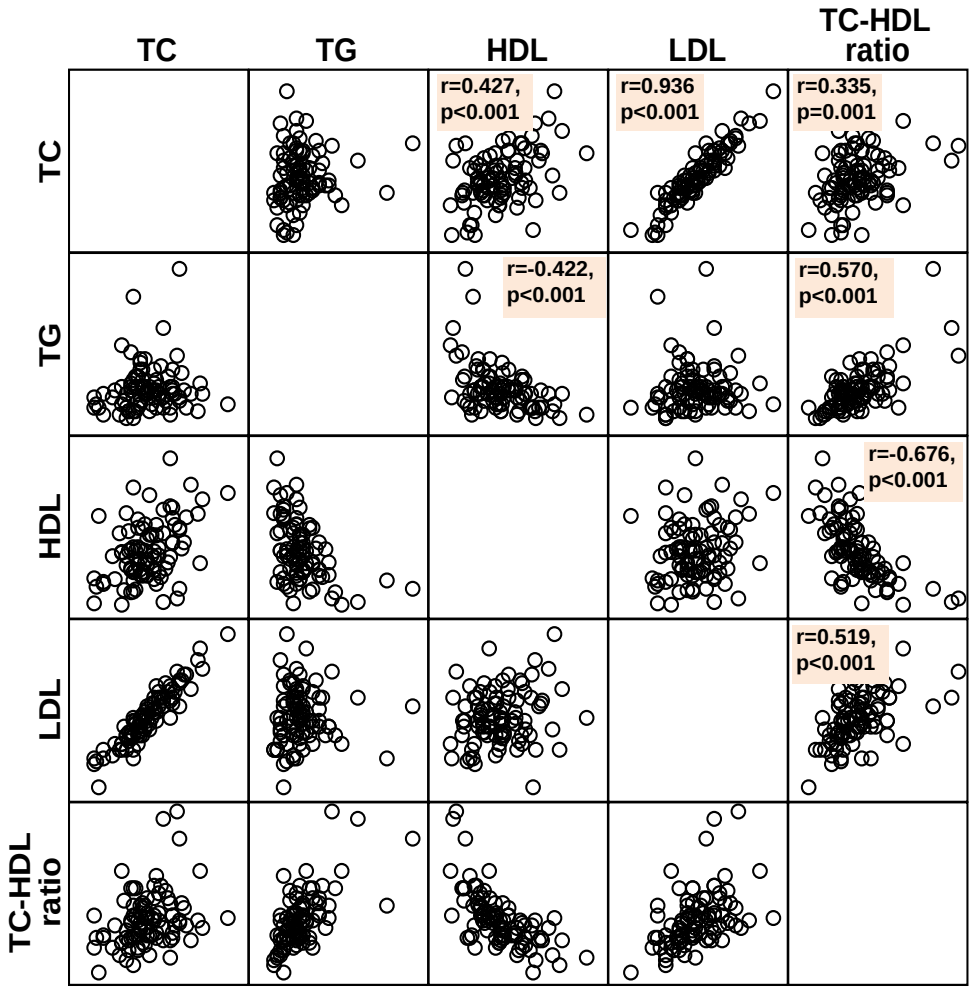


Figure 7-4: Scatter plots showing the correlation between TC, TG, HDL, LDL and TC-HDL ratio

Abbreviations: **HDL**: high-density lipoprotein; **LDL**: low-density lipoprotein; **TC**: total cholesterol; **TG**: triglyceride

7.1.6 Inflammatory markers

The results of the inflammatory markers to be presented are C-reactive protein (CRP), interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), fibrinogen, and erythrocyte sedimentation rate (ESR). Histograms showed all of the inflammatory markers were skewed to the right of the median (positively skewed), i.e. the majority of the values clustered toward the lower end of the distribution scale with few in the upper end of the scale. Tumour necrosis factor-alpha (TNF-α) results were presented as binary data because only seven of the 75 results available (9%) had a distinct reading; the majority were reported as <1.0pg/mL. There were six extreme outliers for CRP, one for IL-6, one for fibrinogen, and two for ESR. Participants' characteristics and clinical profile for each of these cases are presented in the following sections.

C-reactive protein (CRP)

Results for CRP were available for all 90 study participants who had blood analysis completed. There were 26 participants with CRP results reported as <1.0mg/mL. CRP value for this group was imputed with a random number between 0.15 and 1.0. The lower limit of 0.15 was used because it is the lowest quantification at which serum CRP concentration can be reliably measured. (522)

The median (IQR) for CRP level was 1.8 (3.2) mg/L. Six participants had CRP readings that were more than three times the IQR from the third quartile. The readings in decreasing order were: 97.0mg/L, 17.0mg/L (2 participants), 16.0mg/L, and 13.0mg/L (2 participants). The clinical profile for these six participants with high CRP values is presented in TABLE 7-14. The participant with the highest CRP level, 97.0 mg/L, is a 79-year-old woman who has hypertension and asthma, has had breast cancer, has a BMI of 31.4kg/m^2, and has hypercholesterolemia – her total cholesterol level was 7.3mmol/L and LDL 5.3mmol/L. She also had other inflammatory markers that were above the study sample median: her IL-6 level was 8.26pg/mL, the median was 1.14pg/mL; her fibrinogen was 6.9g/L, the median was 3.75g/L, and her ESR was 75mm/hr, the median was 8mm/hr. The next value following 97mg/L was 17mg/L.

TABLE 7-14: Clinical profile of the six participants with CRP readings more than three times the IQR from the third quartile

Women (n=5)	Former smokers (n=2)	Asthma (n=3)
Aged 75-79 year (n=5)	BMI< 18.5 (n=1)	Breast cancer (n=3)
CVD (n=4)	BMI=25-29.9 (n=2)	Prostate cancer (n=1)
Hypertension (n=4)	BMI≥30 (n=3)	
Diabetes (n=1)		

Abbreviations: **BMI**: body mass index; **CVD**: cardiovascular disease; **CRP**: C-reactive protein; **IQR**: interquartile range

Power calculation for CRP: In this study, the standard deviation of the log CRP was 0.5 which corresponds to a usual CRP value of 3.2mg/L. In this study the sample size of 108 participants comprised a 2:1 ratio of participants with and without CVD of 2:1. It had a 44% power to detect a difference of 1.2mg/L of CRP. To have an 80% power to detect the difference of 1.2mg/L of CRP with the same ratio of participants with and without CVD of 2:1, 254 participants would have been needed.

According to the recommendations from the Centers for Disease Control and Prevention and the American Heart Association (281), there were 26 (29%) participants considered to have a CRP level associated with a low relative risk of CVD (<1.0mg/L), 38 (42%) had intermediate levels (1.0-3.0mg/L), and 26 (24%) had CRP levels associated with high CVD risk (>3.0mg/L). These cut-points correspond to approximate tertiles of CRP in this study population. The participants' characteristics, medications and medical history across three CRP categories are shown in TABLE 7-15. There was no difference in the distribution across three CRP categories in any of the participants' characteristics, medications, and medical history.

TABLE 7-15: Participants' characteristics, medications and medical history by C-reactive protein (CRP) categories

Variable, n (column %)	CRP level (mg/L)			P value‡
	<1.0 n=26	1.0–3.0 n=38	>3.0 n=26	
Sex				
- Men	14 (54)	18 (47)	8 (31)	0.220
- Women	12 (46)	20 (53)	18 (69)	
Age-ethnicity				
- 75-79 years old	9 (35)	8 (21)	9 (35)	0.374
- 85-years old	17 (65)	30 (79)	17 (65)	
Smoking status				
- Current	1 (4)	1 (3)	3 (11)	0.622†
- Former	12 (48)	16 (42)	9 (35)	
Use aspirin	11 (42)	19 (50)	12 (46)	0.831
Use lipid-lowering medication	11 (42)	9 (24)	5 (19)	0.135
Use vitamin & mineral supplements	13 (52)	18 (47)	11 (44)	0.961
Hypertension				
- No	5 (19)	5 (13)	3 (12)	0.801†
- Yes	21 (81)	33 (87)	23 (88)	
Diabetes				
- No	23 (89)	29 (76)	21 (81)	0.555†
- Yes	3 (11)	9 (24)	5 (19)	
CVD				
- No	9 (35)	13 (34)	10 (39)	0.934
- Yes	17 (65)	25 (66)	16 (61)	

‡P values are from Pearson chi-square test, unless specified otherwise
†Examined with Fisher's exact test because more than 20% of the expected frequencies were less than 5

Interleukin 6 (IL-6)

Results for IL-6 were available for 75 of the 90 participants (83%) who gave a blood sample for analysis. Interleukin-6 analysis was not done for two participants because the test was not requested on the laboratory request form. The remaining 13 participants did not have enough stored serum sample for a re-test using the extended 10-point standard curve[29]. Of the 75

[29] As mentioned in Chapter 3 (section 3.8.2, page 87), three-quarters of the way through serum analysis for IL-6 and TNF-α, the standard curve for measuring these cytokines concentrations was extended from an 8-point standard curve to a 10-point curve so that lower levels of IL-6 and TNF-α could be detected with an absolute value. Samples not run with the extended range were repeated where possible.

participants who had results for IL-6, 20 (27%) of them were reported with a value of <0.2pg/mL. For this group, a random imputation was carried out. (The process of this data imputation has been described in Chapter Three (Section 3.8.2, page 87)

The median (IQR) for IL-6 level was 1.14 (3.05) pg/mL. An 85-year-old woman had a high IL-6 reading of 40.40pg/mL. Her medical records showed she has had a cardiac arrest and transient cerebral ischemia, has hypertension, arthritis, breast cancer and was a former smoker. Her BMI was marginally above the underweight category, 19.3kg/m^2. She also had a very high TNF-α level (73.1pg/mL). Her other inflammatory markers were all above the study sample median: her CRP was 4.2 mg/L, the median being 1.8mg/L; her fibrinogen was 4.3g/L, the median being 3.75g/L; and her ESR was 33mm/hr, the median being 8mm/hr. This high IL-6 value, 40.40pg/mL, was followed by 9.19pg/mL.

Interleukin-6 readings were categorised into tertiles: $\leq$0.41 (n=27), 0.42–1.72 (n=23) and $\geq$1.73pg/mL (n=25). The participants' characteristics, medications and medical history across IL-6 tertiles are shown in TABLE 7-16. There was a difference in the distribution across IL-6 tertile for hypertension (p=0.022). The distribution across IL-6 tertile was not different in any of other participants' characteristics, medication and medical history.

TABLE 7-16: Participants' characteristics, medications and medical history by interleukin-6 (IL-6) tertiles

Variable, n (column %)	Tertile of IL-6 (pg/mL)			P value‡
	Low n=27	Mid n=23	High n=25	
Sex				
- Men	10 (37)	13 (57)	12 (48)	0.383
- Women	17 (63)	10 (43)	13 (52)	
Age-ethnicity				
- 75-79 years old	5 (19)	5 (22)	10 (40)	0.176
- 85 years old	22 (83)	18 (78)	15 (60)	
Smoking status				
- Current	0	1 (5)	3 (12)	0.255†
- Former	15 (56)	10 (46)	8 (32)	
Use aspirin	17 (63)	9 (39)	11 (44)	0.197
Use lipid-lowering medication	8 (30)	7 (30)	6 (24)	0.860
Use vitamin & mineral supplements	20 (74)	9 (41)	7 (29)	0.015
Hypertension				
- No	2 (7)	8 (35)	2 (8)	0.022†
- Yes	25 (93)	15 (65)	23 (92)	
Diabetes				
- No	25 (93)	19 (83)	21 (84)	0.530†
- Yes	2 (7)	4 (17)	4 (16)	
CVD				
- No	10 (37)	6 (26)	8 (32)	0.710
- Yes	17 (63)	17 (74)	17 (68)	

‡P values are from Pearson chi-square test, unless specified otherwise
†Examined with Fisher's exact test because more than 20% of the expected frequencies were less than 5

Tumour necrosis factor-alpha (TNF-α)

Results for TNF-α were available for 75 of the 90 participants (83%) who gave a blood sample for analysis. TNF-α analysis was not done for two participants because the test was not requested on the laboratory request form. The remaining 13 participants did not have enough stored serum sample for re-test using the extended 10-point standard curve[30]. Of the 75 participants who had a serum sample reanalysed, 68 (91%) participants had TNF-α readings of <1.0pg/mL and seven (9%) participants had an absolute values. The median (IQR) was 12.0 (33.0)pg/mL.

This paragraph will detail the relevant clinical profile of the seven participants with an absolute TNF-α reading. TNF-α values (pg/mL) in ascending order: 1.9, 2.9, 7.2, 12.0, 12.2, 35.9, and 73.1. In this, four were women, six were aged 85 years old, four were widowed, two had received tertiary education, four were former smokers (none were current smokers), five had hypertension, none had diabetes, and six had CVD. Additionally, four of these seven participants had arthritis, three had skin cancer, two had depression, and one had asthma. In terms of their BMI, four were obese, two

[30] As mentioned in Chapter 3 (section 3.8.2, page 87), three-quarters of the way through serum analysis for IL-6 and TNF-α, the standard curve for measuring these cytokines concentrations was extended from an 8-point standard curve to a 10-point curve so that lower levels of IL-6 and TNF-α could be detected with an absolute value.

had a normal BMI and one was underweight. The participant with the highest TNF-α reading (73.1pg/mL) also had a very high IL-6 concentration (40.40pg/mL). Her clinical profile has been mentioned in the previous section (page 156).

Fibrinogen

Results for fibrinogen were available for 84 of the 90 participants (93%) who gave a blood sample for analysis. The remaining six participants did not have fibrinogen results because of insufficient samples (five cases) and miscommunication (one case). The median (IQR) was 3.8 (1.1)g/L. One participant had a very high fibrinogen reading of >18g/L, a value that deviated more than three times from the IQR from the third quartile. He is an 85-year-old man who has had myocardial infarction, heart failure, angina, ischemic heart disease, arteriosclerosis, atrial fibrillation, hypertension, a kidney problem, arthritis, and was obese (BMI=39.6kg/m^2). He also had elevated concentrations of CRP (5.7mg/L) and ESR (22mm/hr). This high fibrinogen value of >18g/L was followed by 6.9g/L.

Fibrinogen levels were categorised according to tertiles: $\leq$3.5g/L (n=35), 3.6–4.1g/L (n=23) and $\geq$4.2g/L (n=26). The participants' characteristics, medications and medical history across fibrinogen tertiles are shown in TABLE 7-17. There was an increased prevalence of diabetes across fibrinogen tertiles (p=0.042). The distribution across fibrinogen tertile was not different in any of other participants' characteristics, medication and medical history.

TABLE 7-17: Participants' characteristics, medications and medical history by fibrinogen tertiles

Variable, n (column %)	Tertile of fibrinogen (g/L)			P value‡
	Low n=35	Mid n=23	High n=26	
Sex				
- Men	20 (57)	10 (44)	9 (35)	0.207
- Women	15 (43)	13 (56)	26 (65)	
Age-ethnicity				
- 75-79 years old	9 (26)	7 (30)	7 (27)	0.923
- 85 years old	26 (74)	16 (70)	19 (73)	
Smoking status				
- Current	1 (3)	2 (9)	2 (8)	0.828†
- Former	15 (43)	9 (41)	12 (46)	
Use aspirin	17 (49)	10 (43)	15 (58)	0.596
Use lipid-lowering medication	9 (26)	7 (30)	9 (35)	0.751
Use vitamin & mineral supplements	21 (60)	8 (36)	10 (40)	0.288
Hypertension				
- No	6 (17)	3 (13)	3 (12)	0.810†
- Yes	29 (83)	20 (87)	23 (88)	
Diabetes				
- No	32 (91)	18 (78)	17 (65)	0.042
- Yes	3 (9)	5 (22)	9 (35)	
CVD				
- No	11 (31)	10 (44)	8 (31)	0.569
- Yes	24 (69)	13 (56)	18 (69)	

‡P values are from Pearson chi-square test, unless specified otherwise
†Examined with Fisher's exact test because more than 20% of the expected frequencies were less than 5

Erythrocyte sedimentation rate (ESR)

Results for ESR were available for all 90 participants who gave blood samples for analysis. The median (IQR) for ESR level was 8 (17) mm/hr. Two participants had ESR readings that were more than three times the IQR from the third quartile. These readings, 101 and 71mm/hr, were from two women aged 75-79 years. One of them had CVD, both had hypertension, both had breast cancer, and both were obese. They also had levels of CRP, IL-6 and fibrinogen above the sample median. These high values (101 and 71mm/hr) were followed by 52mm/hr.

ESR levels were categorised into tertiles: ≤7mm/hr (n=40), 8–18mm/hr (n=20) and ≥19mm/hr (n=30). The participants' characteristics, medications and medical history across ESR tertiles are shown in TABLE 7-18. The distribution across ESR tertile was not different in any of participants' characteristics, medication and medical history.

TABLE 7-18: Participants' characteristics, medications and medical history by ESR tertiles

Variable, n (column %)	Tertile of ESR (mm/hr) Low n=40	Mid n=20	High n=30	P value‡
Sex				
- Men	20 (50)	11 (55)	9 (30)	0.140
- Women	20 (50)	9 (45)	21 (70)	
Age-ethnicity				
- 75-79 years old	10 (25)	5 (25)	11 (37)	0.516
- 85 years old	30 (75)	15 (75)	19 (63)	
Smoking status				
- Current	2 (5)	0	3 (10)	0.593†
- Former	15 (38)	8 (42)	14 (47)	
Use aspirin	20 (50)	7 (35)	15 (50)	0.495
Use lipid-lowering medication	13 (33)	6 (30)	6 (20)	0.497
Use vitamin & mineral supplements	19 (48)	13 (68)	10 (35)	0.170
Hypertension				
- No	9 (23)	1 (5)	3 (10)	0.151†
- Yes	31 (77)	19 (95)	27 (90)	
Diabetes				
- No	32 (80)	17 (85)	24 (80)	0.881
- Yes	8 (20)	3 (15)	6 (20)	
CVD				
- No	16 (40)	6 (30)	10 (33)	0.712
- Yes	24 (60)	14 (70)	20 (67)	

Abbreviations: **ESR**: Erythrocyte sedimentation rate
‡P values are from Pearson chi-square test, unless specified otherwise
†Examined with Fisher's exact test because more than 20% of the expected frequencies were less than 5

Inflammatory markers and medications

Nearly half of the participants who had inflammatory markers measured used aspirin, one-quarter used lipid-lowering medications and more than one-fifth used both aspirin and lipid-lowering medications. Levels of CRP, IL-6, fibrinogen and ESR were similar in participants who were treated and those who were not treated with these pharmacologic interventions. Similar analyses were repeated without the outliers. In these sensitivity analyses, levels of each inflammatory marker were not different between those who were treated and those who were not treated with these pharmacologic interventions.

Association between inflammatory markers and CVD

Comparing each of the inflammatory markers between participants with CVD and participants without CVD, there were no differences between the two groups (TABLE 7-19).

TABLE 7-19: Inflammatory markers levels between those with and those without CVD

Median (IQR)	**No CVD**	**Yes CVD**	**P value**[#]
CRP (mg/L)	2.2 (3.1)	1.6 (2.5)	0.479
IL-6 (pg/mL)	0.8 (3.3)	1.2 (2.4)	0.691
Fibrinogen (mg/L)	3.8 (1.0)	3.7 (1.2)	0.891
ESR (mm/Hr)	8 (18)	10 (17)	0.642

Abbreviations: **CRP**: C-reactive protein; **CVD**: cardiovascular disease; **ESR**: Erythrocyte sedimentation; **IL-6**: interleukin-6; **IQR**: interquartile range
[#] P values are from Mann-Whitney U test, unless specified otherwise

Univariate analysis was used to measure associations between all types of inflammatory markers. C-reactive protein (CRP) was most strongly correlated with fibrinogen ($r=0.545$, $p<0.001$), followed by ESR ($r=0.512$, $p<0.001$), and IL-6 ($r=0.295$, $p=0.010$). ESR was strongly correlated with fibrinogen ($r=0.584$, $p<0.001$).

The potential association between each inflammatory marker and CVD was examined using logistic regression controlling for sex, age-ethnicity and smoking status. Due to collinearity between inflammatory markers, each of the variables was examined separately. To determine if age-ethnicity has an effect on the relationship between each of the inflammatory markers with CVD, the interaction term (age-ethnicity $\times$ inflammatory marker) was included in the regression model. There was no association between each of the five interaction terms with CVD ($p>0.05$). This indicates the association between the inflammatory marker and CVD was the same for all ages. Therefore, the analysis was combined for both age-ethnic groups.

In all five regression models controlling for sex, age-ethnicity and smoking status, the associations between CVD and CRP, IL-6, TNF-α, fibrinogen, and ESR were not statistically significant. (Appendix B: TABLE B-15–TABLE B-19, page 303–305). The Nagelkerke R^2 for each of these models was small, ranging between 0.020 and 0.073. As aspirin has both anti-inflammatory (523) and anti-platelet (365) properties, it has been reported that aspirin may lower CRP, IL-6, fibrinogen, and ESR levels (368, 373). Lipid-lowering medications were also found to reduce CRP and IL-6 levels. (368, 373) Hence, these medications were added separately to the covariates list. Including aspirin and lipid-lowering medication separately into the model did not alter the associations between each inflammatory marker and CVD, but Nagelkerke R^2 increased when aspirin was added to the model (ranging between 0.166 and 0.193). The largest Nagelkerke R^2 difference observed was when analysing the two models examining the association between CVD

and IL-6 controlling for sex, age-ethnicity and smoking status, with and without aspirin added to the model; Nagelkerke R^2 increased from 0.020 (aspirin not included in the model) to 0.182 when aspirin was added to the model. Nevertheless, this difference was not significant, $\chi^2 = 9.225$, p=0.10. In short, no inflammatory markers were found to be associated with CVD.

The chapter had presented results of conventional CV risk factors: smoking (Section 7.1.1), diabetes and fasting serum glucose (Section 7.1.2), hypertension and blood pressure (Section 7.1.3), anthropometry measures (Section 7.1.4), and dyslipidemia and lipid profile (Section 7.1.5). The emerging CV risk factors presented are the inflammatory markers (Section 7.1.6). The following section (Section 7.1.7) will present the correlation between conventional CV risk factors and inflammatory markers.

7.1.7 Correlation between cardiovascular risk factors

In univariate analyses, fasting serum glucose was correlated positively with waist-to-hip ratio (WHR) and triglyceride (TG) levels. There were significant correlations between anthropometry measures. BMI was correlated with TG, HDL and TC-HDL ratios. Waist circumference (WC) was correlated with HDL and TC-HDL ratio. Body fat percentage (BF%) was correlated with TG, TC and TC-HDL ratio (TABLE 7-20).

TABLE 7-20: Correlation between conventional cardiovascular risk factors

	SBP	DBP	BMI	WC	WHR	BF%	TG	TC	HDL	LDL	TC-HDL ratio
Glucose	0.158	0.065	0.112	0.148	0.213*	-0.090	0.224*	0.450	-0.133	-0.137	0.011
SBP		0.587**	-0.041	0.015	0.134	0.069	-0.016	0.090	0.144	0.034	-0.112
DBP			0.010	0.009	0.059	-0.084	-0.139	0.090	0.037	0.099	0.010
BMI				0.832**	0.324**	0.518**	0.291**	-0.071	-0.398**	-0.005	0.310**
WC					0.666**	0.223*	-0.129	0.187	-0.336**	-0.098	0.212*
WHR						-0.227*	0.036	-0.106	-0.070	-0.149	-0.031
BF%							0.415**	0.246*	-0.095	0.186	0.253*
TG								0.157	-0.422**	0.107	0.570**
TC									0.382**	0.932**	0.335**
HDL										0.174	-0.676**
LDL											0.519**

Abbreviations: **BF%**: percentage of body fat; **BMI**: body mass index; **DBP**: diastolic blood pressure; **HDL**: high-density lipoprotein; **LDL**: low-density lipoprotein; **SBP**: systolic blood pressure; **TC**: total cholesterol; **TG**: triglyceride; **WC**: waist circumference; **WHR**: waist-to-hip ratio

* $p<0.05$

** $p<0.01$

Among the inflammatory markers examined, fibrinogen correlated with most conventional cardiovascular risk variables, followed by ESR, CRP and IL-6 (TABLE 7-21). Owing to the presence of outliers in CRP (97mg/L), IL-6 (40.40pg/mL), ESR (101mm/Hr) and fibrinogen (18.1g/L), a sensitivity analysis was performed by excluding these values from the correlation test. The IL-6 and fibrinogen outliers caused an apparent spurious effect on the relationship between these two markers with conventional cardiovascular risk variables, i.e. the correlation between IL-6 and WHR lost significance, in turn, IL-6 was correlated with BMI (r value increased from 0.190 to 0.235) (TABLE 7-21). The correlation between fibrinogen and TG lost significance (r value decreased from 0.232 to 0.206). In the sensitivity analyses, IL-6 was the only inflammatory marker correlated with BMI (r=0.235, p=0.046), and fibrinogen was the only inflammatory marker correlated with BF% (r=0.304, p=0.007). Inflammatory markers were not correlated with WC and WHR. For lipid profile, CRP and fibrinogen were correlated positively with TC (r=0.216, p=0.042; r=0.250, p=0.023), LDL (r=0.283, p=0.007; r=0.289, p=0.008), and the TC-HDL ratio (r=0.317, p=0.002; r=0.322, p=0.003). ESR was correlated positively with TG (r=0.275, p=0.009), LDL (r=0.231, p=0.029), and the TC-HDL ratio (r=0.357, p=0.001), but inversely with HDL (r=-0.243, p=0.022). In brief, IL-6 and fibrinogen were associated with anthropometry measures; CRP, fibrinogen, and ESR were associated with lipid variables.

TABLE 7-21: Correlations between inflammatory markers and conventional cardiovascular risk factors

	CRP		IL-6		TNF-α		Fibrinogen		ESR	
	All	**Ssvity. A.**	**All**	**Ssvity. A.**	**All**	**Ssvity. A.**	**All**	**Ssvity. A.**	**All**	**Ssvity. A.**
Glucose	0.134	0.160	0.043	0.048	0.065	0.001	0.085	0.088	0.090	0.128
SBP	0.066	0.067	-0.114	-0.161	0.156	0.156	0.082	0.060	-0.054	-0.035
DBP	0.154	0.160	0.016	-0.024	0.218	0.218	0.138	0.130	-0.018	0.011
BMI	0.071	0.053	0.190	0.235*	0.040	0.040	0.198	0.170	0.052	0.019
WC	0.045	0.027	0.175	0.202	0.127	0.127	0.151	0.118	0.010	-0.017
WHR	-0.044	-0.079	0.249*	0.225	0.184	0.184	-0.015	-0.038	-0.118	-0.106
BF%	0.165	0.149	-0.126	-0.116	0.073	0.073	0.314**	0.304**	0.176	0.147
TG	0.188	0.176	-0.034	-0.016	-0.053	-0.052	0.232*	0.206	0.290**	0.275**
TC	0.241*	0.216*	0.197	0.164	0.064	0.064	0.215*	0.250*	0.195	0.180
HDL	-0.205	-0.201	-0.036	-0.078	0.005	0.005	-0.167	-0.137	-0.245*	-0.243*
LDL	0.306**	0.283**	0.201	0.168	0.068	0.068	0.258*	0.289*	0.246*	0.231*
TC-HDL ratio	0.339**	0.317**	0.125	0.121	0.008	0.008	0.346**	0.322**	0.371**	0.357**

Abbreviations: **BF%**: percentage of body fat; **BMI**: body mass index; **CRP**: C-reactive protein; **DBP**: diastolic blood pressure; **ESR**: erythrocyte sedimentation rate **HDL**: high-density lipoprotein; **IL-6**: Interleukin-6; **LDL**: low-density lipoprotein; **SBP**: systolic blood pressure; **Ssvity. A.**: sensitivity analysis; **TC**: total cholesterol; **TG**: triglyceride; **TNF-α**: tumour necrosis factor-alpha; **WC**: waist circumference; **WHR**: waist-to-hip ratio

* $p<0.05$

** $p<0.01$

7.1.8 Associations between cardiovascular risk factors and CVD

A multiple logistic regression model was developed using p≤0.2 as criteria for entry and p>0.2 for removal. From the individual logistic regression model presented earlier, controlling for sex, age-ethnicity, smoking status, and relevant medication, four conventional cardiovascular risk factors were found to contribute to the regression model that is to be associated with CVD with at least a level of significance of ≤0.2: HDL (p=0.050), serum glucose (p=0.060), BMI (p=0.098), and WC (p=0.131). Since BMI and WC are highly correlated (r=0.832, p<0.001), they were not entered simultaneously in the model. Glucose-lowering medication was also highly correlated with serum glucose but it was forced into the model to control for the effect of treatment. (Appendix B: TABLE B-3, page 297) Therefore, variables included in the models are sex, age-ethnicity, smoking status, fasting serum glucose, glucose-lowering medication, HDL, and BMI (Model 1) / WC (Model 2) (TABLE 7-22).

TABLE 7-22: Variables included in the logistic regression model examining the association between conventional CV risk factors with CVD controlling for sex, age-ethnicity and smoking status.

Variables	Model 1		Model 2	
	OR (95% CI)	P value	OR (95% CI)	P value
Sex (ref: men)	0.396 (0.114–1.376)	0.145	0.513 (0.123–2.146)	0.361
Age-ethnicity (ref: NZ European)	0.989 (0.192–5.079)	0.989	1.268 (0.267–6.030)	0.765
Smoking (ref: never)		0.342		0.355
- Current	0.134 (0.009–1.995)	0.144	0.134 (0.009–2.067)	0.150
- Former	0.912 (0.274–3.036)	0.881	0.859(0.258–2.855)	0.804
Glucose-lowering med (ref: no)	85.277 (0.443–6399.424)	0.098	44.099 (0.162–12027.424)	0.186
Serum glucose	0.487 (0.271–0.875)	0.016	0.507 (0.283–0.905)	0.022
HDL	0.270 (0.062–1.185)	0.083	0.241 (0.056–1.040)	0.057
BMI	1.121 (0.975–1.290)	0.109		
WC			1.029 (0.982–1.078)	0.235
Nagelkerke R^2	0.316		0.293	

Abbreviations: **BMI:** Body mass index; **CVD**: cardiovascular disease; **HDL:** high-density lipoprotein; **med**: medications; **OR:** odds ratio; **ref**: reference; **WC:** waist circumference

Both Model 1 and 2 in TABLE 7-22 were unstable evidenced by large confidence interval in glucose-lowering medication. A further investigation was done and it found that the number of people treated with glucose-lowering medication was small (n=9). The results of lower odds ratio for CVD with increase serum glucose (TABLE 7-22, Model 1: p=0.016 and Model 2: p=0.022) is

possibly distorted by a high serum glucose level of 14.5mmol/L from an 85-year-old woman treated with glucose-lowering medication but no record of having CVD (TABLE 7-23). A sensitivity analysis excluding this high value (14.5mmol/L) was completed. The significance of the association between serum glucose and CVD reduced but the odds ratio did not change materially. (Appendix B: TABLE B-20, page 306) Moreover, excluding the high value further reduced the sample size that caused the model to become more unstable. The rarity of treatment with glucose-lowering medications contributed to the wide variation of serum glucose in the CVD group (standard deviation=2.54, as shown in TABLE 7-23). This also contributed to the wide confidence interval observed for variable glucose-lowering medications in both Model 1 and Model 2 in TABLE 7-22.

TABLE 7-23: Descriptive results of serum glucose in participants with and without CVD receiving glucose-lowering medications.

		n	Mean (SD)	Min	Max
No CVD	No glucose-lowering med	29	5.63 (0.94)	4.50	8.20
	Yes glucose-lowering med	1	14.50	14.50	14.50
Yes CVD	No glucose-lowering med	62	5.37 (0.93)	3.90	9.60
	Yes glucose-lowering med	8	6.82 (2.54)	3.00	9.00

Therefore, from a statistical perspective, glucose-lowering medication was removed from the model. Although R^2 appeared to reduce significantly when glucose-lowering medication was removed from the model, this does not imply glucose-lowering medications have a substantial explanatory effect in the model because the model was unstable, attributable to the small number of treatments with the medications. Since fasting serum glucose was not associated with CVD at $p \leq 0.2$ when glucose-lowering medication was not taken into account, from a statistical perspective, fasting serum glucose was also removed from Models 1 and 2 in TABLE 7-22.

There were collinearity between HDL, BMI, and WC (HDL was correlated with BMI r=-0.398; and WC r=-0.336 at $p<0.01$). The association between CVD and each of these separate variables (BMI, WC, HDL) controlling for sex, age-ethnicity, and smoking status are shown in TABLE 7-24. The effect of lipid-lowering medication on HDL level was examined (Model 3a) and found lipid lowering medication did not have an apparent effect on HDL level. Therefore, among the first three models in TABLE 7-24, Model 3 has the highest R^2 value, i.e. sex, age-ethnicity, smoking status, and HDL explained 11% of the variance of having CVD. Controlling for sex, age-ethnicity, and smoking status, HDL was marginally associated with CVD (p=0.043).

TABLE 7-24: Logistic regression model examining the association between CVD with conventional CV risk factors

Model	Variables	Odds ratio (95% CI)	P value	R^2
1	BMI	1.083 (0.985 – 1.190)	0.098	0.074
2	WC	1.027 (0.992 – 1.063)	0.131	0.063
3	HDL	0.306 (0.097 – 0.965)	0.043	0.110
3a	HDL*	0.316 (0.100 – 1.000)	0.050	0.129
4	HDL	0.354 (0.105 – 1.192)	0.094	0.173
	BMI	1.090 (0.975 – 1.218)	0.128	
5	HDL	0.291 (0.086 – 0.986)	0.047	0.162
	WC	1.023 (0.984 – 1.064)	0.246	

Abbreviations: **BMI:** Body mass index; **CVD**: cardiovascular disease; **HDL:** high-density lipoprotein; **WC:** waist circumference
All models were adjusted for sex, age-ethnic group, and smoking status
* Model 3a was adjusted for sex, age-ethnic group, smoking status and lipid-lowering medication

Since BMI and WC are important CV risk factors, BMI and WC were added separately to Model 3 of TABLE 7-24. Together with sex, age-ethnicity, smoking status, HDL, and BMI, Model 4 explained 17.3% of the variance of having CVD. (TABLE 7-24) In Model 5, similar covariates were entered but BMI was replaced with WC; the model explained 16.2% of the variance of having CVD. Controlling for WC in addition to sex, age-ethnicity, and, smoking status, HDL remains to be independently associated with CVD.

Concerning blood pressure, although both SBP and DBP were not associated with CVD at p≤0.2 but it is known to be important variables related to CVD risk, they were added separately to the Model 3 (TABLE 7-24). Controlling for sex, age-ethnicity, smoking, and SBP, HDL remains to be associated with CVD [OR (95% CI): 0.296 (0.090–0.976), p=0.046]. Replacing SBP with DBP, HDL missed the significant statistical association with CVD [OR (95% CI): 0.314 (0.096–1.028), p=0.056].

7.1.9 Summary of cardiovascular risk factors

The conventional cardiovascular risk factors presented in this chapter were smoking status, diabetes, hypertension, obesity (determined by BMI), and dyslipidemia. The most prevalent CV risk factor in this sample was dyslipidemia (85%), followed by hypertension (84%), obesity (BMI>30kg/m^2) (27%), diabetes (20%), and cigarette smoking (8%) (Figure 7-5). When abdominal obesity was considered, 71% of the participants had increased waist circumference and 29% had

increased waist-to-hip ratio. More than two-thirds of participants with a particular cardiovascular risk factor had CVD. Similar pattern was observed in participants with top tertile inflammatory markers who had CVD, i.e. between 62% and 77% of the participants with top tertile inflammatory markers had CVD.

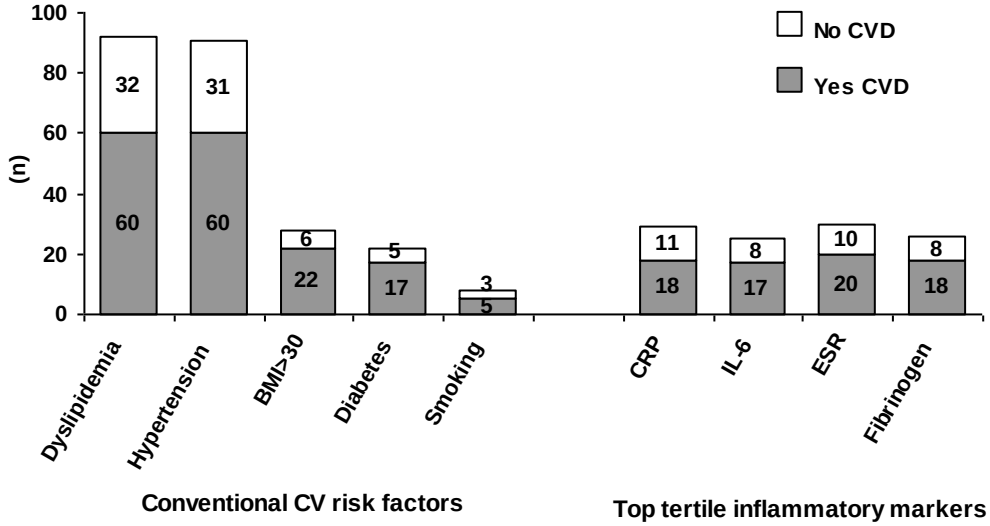


Figure 7-5: Cardiovascular risk factors according to CVD status
Abbreviations: **BMI**: body mass index; **CRP**: C-reactive protein; **CVD**: cardiovascular disease; **ESR**: erythrocyte sedimentation rate; **IL-6**: interleukin-6

The number of conventional CV risk factors ranges between zero and four; median was two (Figure 7-6). Overall, participants with CVD did not have a higher number of conventional CV risk factors than those without CVD; mean: 4.3 vs. 4.1. Eighteen percent of participants with CVD had one risk factor, compared to 14% without CVD. A similar trend was observed between those with and those without CVD in the category of two (47% vs. 56%), three (24% vs. 22%), and four risk factors (11% vs. 6%) (Figure 7-6). Fifty-seven percent of participants with CVD had at least one inflammatory marker in the top tertile, compared to 44% among those with no CVD.

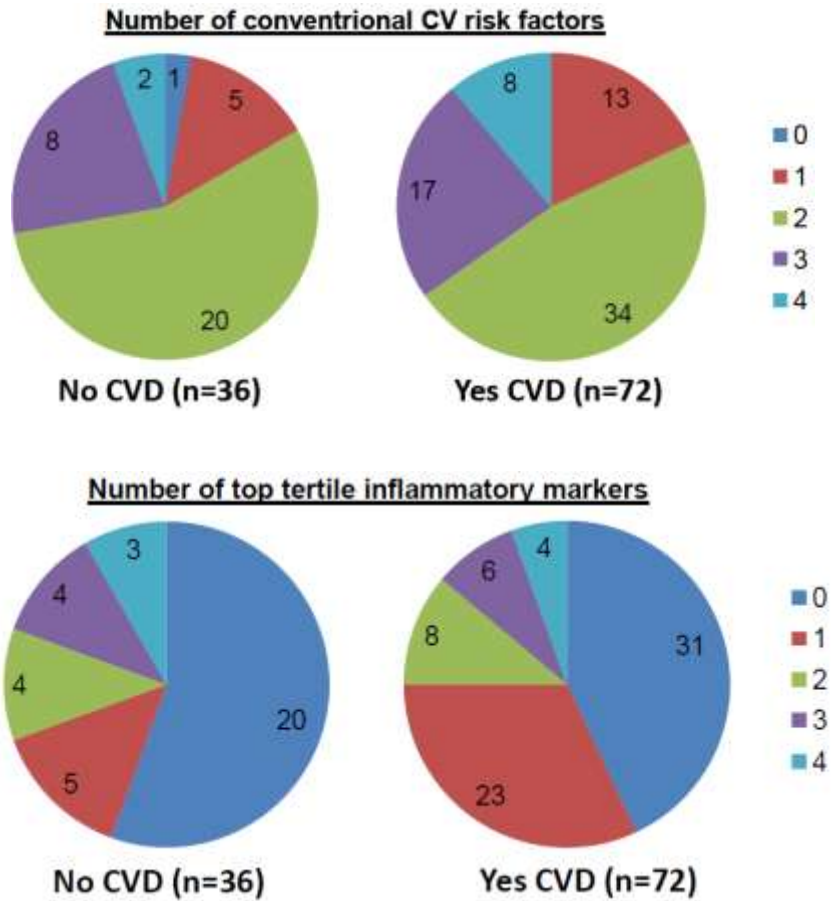


Figure 7-6: Number of cardiovascular risk factors between participants with and participants without cardiovascular disease.
Abbreviations: **CVD**: cardiovascular disease; **CV RFc:** cardiovascular risk factors
Note:
- Conventional CV risk factors included in this figure are cigarette smoking, diabetes, hypertension, BMI>30kg/m^2, and dyslipidemia.
- An 85-year-old man with no records of CVD had no known conventional CV risk factors (plus a normal WC and WHR) and he did not give blood sample for analysis.

In examining the association between CV risk factors and CVD, HDL was the only CV risk factor found to be associated with CVD. Controlling for sex, age-ethnicity, smoking status, and waist circumference, HDL level was inversely associated with CVD. When waist circumference is replaced with SBP, HDL remained to be inversely associated with CVD.

7.2 Discussion

Cardiovascular (CV) risk profile increased with age. The most prevalent CV factor was dyslipidemia, closely followed by hypertension. Cigarette smoking was observed in only eight percent of the sample. This section aims to discuss each of the CV risk factors, following the order presented in the results section.

7.2.1 Smoking

In this study, cigarette smokers constitute only a small proportion (8%) of the sample. Abroad, the prevalence of current smokers in the oldest of the elderly participants (85 years old plus) ranged between 11% (432) and 16% (36). The prevalence of smokers is lower in older adults than in the younger population. This may be due to smokers dying at a younger age than non-smokers. (161) Education has a role in smoking behaviour. This sample is a relatively well-educated group with three-quarters of them having a minimum of secondary education (one-third had tertiary education). Cigarette smoking and tobacco use is less frequent in more educated men and women than in their less educated counterparts. (524)

This study did not find an association between cigarette smoking and CVD. Former smokers in this study sample may have started smoking during their service in World-War II where cigarettes were 'prescribed' to alleviate stress (personal communication with study participants). This suggests the initiation of cigarette smoking is for 'medicinal' purposes and therefore differs from the addiction-based intention of smoking in the present time. (525) Hence, smoking behaviour may differ between the older population and the younger population. Furthermore, the excess risk of CVD mortality decreased to the level of a never-smoker 20 years after stopping. (526) In this study, the average duration since study participants gave up smoking is 35 years (data not presented). Or perhaps they (the study sample) carried certain genes which conferred protection against the harmful chemical of cigarettes? The interaction between smoking and C4B gene has been explored, and shows that smokers who carried the silent allele C4B*Q0 of the C4B gene have increased susceptibility to angina and acute myocardial infarction than a non-smoker carrier of genotype C4B*Q0. (527) There was also evidence for a contribution of specific genes to smoking behaviour but it remains modest. (528) This cross-sectional study with a small sample size is not able to demonstrate whether the lack of association between CVD and smoking was attributed to the beneficial impact of smoking cessation or the healthy cohort effect. A larger study could provide a better understanding between cigarette smoking and CVD in those of advanced age.

7.2.2 Diabetes and serum glucose

Prevalence of diabetes

In this sample, one-fifth of the study participants had diabetes. This is similar to the findings in the Third National Health and Nutrition Examination Survey, reporting 21% of men and 18% of women aged 75 years and above having diabetes (176), and in the 85-year-plus age group, 16% had diabetes. (529) The prevalence of impaired fasting glucose (6.1–6.9mmol/L) in this study (9%) was lower than the prevalence reported in other studies with adults aged 60–79 years and 75 years plus, 18% and 14%, respectively. (175, 176) Undiagnosed diabetes in this study sample was low (i.e. two percent) and four percent had a medical record for diabetes but were unaware of it. These findings were similar to the British Regional Heart Study and the British Women's Heart and Health Study which reported five to six percent of men and women aged 60–79 years old have undiagnosed diabetes (175). Similarly, five to seven percent of American men and women aged 75-years-plus have undiagnosed diabetes. (176) Although results from this study cannot be generalised to the wider population of the advanced age group, it certainly provides an indication that diabetes and impaired fasting glucose is prevalent in this population. This study has a robust technique in identifying cases of diabetes.

Treatment rate for diabetes

In this study, two-fifths of the study participants with diabetes were treated with pharmacotherapy for the condition. In the National Health and Nutrition Examination Survey (NHANES), between 70% and 73% of those diagnosed with diabetes (based on fasting serum glucose) were treated with insulin or an oral glucose-lowering drug. (530) The low percentage of participants receiving pharmacotherapy for diabetes in the current study sample of those living to advanced age could mean more than half of them were probably on diet therapy. Unfortunately, this study was not able to confirm this because the information was not collected. Early detection of diabetes through screening and monitoring of serum glucose for good glycaemic control in older adults could prevent pathogenesis of diabetic vasculopathy and further exacerbation of the existing condition. Nevertheless, management of diabetes and impaired glucose regulation in those of advanced age is difficult. This is because they often have multiple cardiovascular risk factors accompanied by co-morbidities. Intensive treatment aims to achieve the treatment goal (i.e. HbA1c <7.0%) are commonly accompanied with hypoglycaemic episodes. (193) In view of this complexity,

better understanding of the circumstances of treatment and lifestyle intervention in those of advanced age with diabetes would inform prevention of cardiovascular events.

Fasting serum glucose and CVD

This study found an inverse association between fasting serum glucose and CVD, independent of sex, age-ethnicity, smoking status, glucose-lowering medication, HDL level, BMI, and WC. Studies have shown a positive association between fasting serum glucose and cardiovascular disease, independent of other CV risk factors. (190, 531) In a prospective study with more than 20,000 adults aged 50 years and above, followed up for an average of seven years, each 0.56mmol/L (=10mg/dL) increase in fasting serum glucose was found to be associated with an 8% increase in the risk of heart failure in non-diabetic adults (mean age 64 years), independent of the risk factor of heart failure. (191) Similarly, in the Reykjavík Study of nearly 3,200 participants aged 33–84 years with an average follow-up duration of 13±8 years, each 1mmol/L increase in fasting serum glucose level was associated with a 14% increase risk of heart failure, independent of ischemic heart disease and other CV risk factors. (190) The inverse association between fasting serum glucose and CVD found in this study is likely to be a spurious relationship attributed to the small number of participants treated with glucose-lowering medications. A prospective observational study with a representative sample is needed to validate the association between fasting glucose levels and CVD, and whether increased glucose levels over time is predictive of CVD (first episode or recurrent) among non-diabetic people of advanced age.

7.2.3 Hypertension and blood pressure

Prevalence of hypertension

The prevalence of hypertension increased with advancing age. (532) In this sample, 84% of study participants had hypertension. This is within the expected trend. In the Three-City Study with more than 7,600 participants with a mean age of 74 years old, 77% of the study sample had hypertension. (533) Contrary to result of this thesis, hypertension observed in the Leiden 85+ and the Newcastle 85+ study cohort, was lower with a range between 44% and 64%. (432, 465) This is most likely due to the different definition of hypertension adopted by different studies. The Three-City study and the Framingham study defined hypertension as SBP/DBP ≥140/90mmHg or

receiving medication specifically for the indication of hypertension; the Leiden 85+ study defined hypertension as SBP/DBP >160/90mmHg; whereas the Newcastle 85+ study defined hypertension as SBP/DBP ≥140/90mmHg. The current study has a robust method for identifying hypertension and these criteria are believed to present a more accurate picture of the prevalence of hypertension in those of advanced age.

At younger ages (<60 years old), the prevalence of hypertension was higher in men than in women, whereas in older adults (≥60 years), the prevalence was higher in women than in men. (534, 535) Among the older participants in the National Health and Nutrition Examination Survey (NHANES), the prevalence of hypertension in every age group was higher in women than in men: 60 to 69 years – 62% vs. 57%; 70 to 79 years – 78% vs. 64%; and ≥80years – 82% vs. 67%. (536) In this study of those in advanced age, the prevalence of hypertension was higher in women than in men (91% vs. 75%). Unexpectedly, with a similar definition of hypertension, the Three-City study reported a reverse prevalence rate. In that study, with participants' mean age being 74 years, the prevalence of hypertension was lower in women than in men (75% vs. 83%)[31]. (537) Could this be a regional difference where the NHANES study is a U.S.A. based study, whereas the Three-City study is comprised of French participants? In a population-based study of older Italian adults (mean age 73 years), there was a similar finding to the NHANES study, i.e. the prevalence of hypertension[32] was higher in women than men (73% vs. 61%). (538) This difference may be due to different sample characteristics attributed to the recruitment procedure and the definition of hypertension adopted by the respective studies. Nonetheless, these population-based studies, with this current study of those in advanced age, are consistent in the finding that the prevalence of hypertension increases with age, and the increase is more pronounced in women, to some degree, than men.

Awareness of hypertension

In the general population, one in four adults is unaware of their high blood pressure. (212) This prevalence of unawareness increased to nearly one-third in adults aged 65 years and above. (537)

[31] In the Three-City Study, hypertension was defined by two set of criteria, i.e. 1) SBP/DBP ≥160/95mmHg or use of an anti-hypertensive drug; 2) SBP/DBP ≥140/90mmHg or use of an anti-hypertensive drug. When hypertension was defined as SBP/DBP ≥160/95mmHg or use of an anti-hypertensive drug, the prevalence of hypertension for women was 60% and for men, 66%.

[32] In the Italian population-based study, hypertension was defined as SBP/DBP >160/90 mmHg or with normal blood pressure during anti-hypertensive therapy.

In this sample of those in advanced age, one-third (35%) of the participants were unaware that they have hypertension. The awareness rate differs between subtypes of hypertension, i.e. the awareness of essential hypertension (SBP/DBP ≥140/90mmHg) was significantly higher than the awareness of isolated systolic hypertension (ISH) (SBP≥140 and DBP<90mmHg). (539) Since 'white-coat' hypertension is common among older adults, 24-hour blood pressure monitoring in a subgroup of the oldest of the elderly participants in future studies would approximate the prevalence of this condition and its impact on cardiovascular health of those in advanced age. Raising awareness of hypertension is an imperative preliminary step in the prevention of adverse effects on cardiovascular health.

Isolated systolic hypertension

Isolated systolic hypertension (ISH) is the predominant hypertension subtype in older adults, accounting for 65% of hypertension. This increases to 87% in those older people having hypertension by the sixth decade of life. (212, 539) In the current study, ISH accounted for 52% of observed hypertension. Older adults (mean age 73 years) with ISH had a significantly increased risk of heart failure than those without ISH. (213) Hence, treating ISH would be one of the strategies to prevent increased incidences of heart failure among the older adults.

The treatment benefit for ISH is similar to the benefit observed in essential hypertension. (44, 540) In the Systolic Hypertension in the Elderly Program (SHEP), older adults (mean age 72 years) treated for ISH had a 55% reduction in the incidence of heart failure. (215) In the HYVET study, older adults (mean age 84 years) treated for essential hypertension resulted in a 64% reduced risk of fatal and non-fatal heart failure. (202) Despite the unequivocal benefit of blood pressure reduction in patients with hypertension, there are uncertainties for treatment of ISH among the oldest elderly. In at least one study, ISH was associated with increased risk of heart failure in adults younger than 78 years old but there was no association for adults 78 years and above. (213) The pharmacological treatment goal for ISH is to lower systolic blood pressure; this naturally lowers diastolic blood pressure. Diastolic blood pressure is the driving pressure for coronary circulation. (541) With the reduction of diastolic blood pressure, coronary flow is decreased and therefore may increase the risk of acute myocardial infarction. (541) In the SHEP study, every 5mmHg decrease in diastolic blood pressure was associated with increased risk of stroke, coronary heart disease,

and cardiovascular disease seen only among participants receiving active treatment for ISH and not in the placebo group. (542) Nevertheless, the benefit of treatment for ISH outweighs the harmful effect.

Treatment rate for hypertension

In this study, nearly two-thirds of study participants with hypertension did not have medications indicated for the treatment of hypertension. This, however, does not imply that two-thirds of participants with hypertension were untreated. Medication information in this study was obtained through face-to-face interview and many participants were unable to provide the medical indication pertaining to the particular medication. For those with a clear indication of treatment for hypertension, the mean systolic blood pressure was 13% above the recommended treatment goal of <140mmHg, but the diastolic blood pressure was in accordance with the treatment goal of <90mmHg. This is not unexpected, as other studies have shown the control rate in attaining the treatment goal was low in adults 80 years and above. (532) Moreover, this recommendation of a treatment goal of SBP/DBP <140/90mmHg in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure may not be applicable to the oldest elderly. As mentioned earlier, in an attempt to lower systolic blood pressure the diastolic blood pressure will fall, with the risk of a J-shape curve effect, which the SHEP study and several other studies had demonstrated. (542-544) Therefore, lower blood pressure is not always better for the oldest elderly. The goal for treatment of blood pressure should be balanced between the benefits and harmful effects to sufficiently prevent worsening of the existing condition and to avert future cardiovascular events. New therapies may be needed for those in advanced age which differentially lower systolic blood pressure over diastolic.

Hypertension and CVD

One-third of study participants with hypertension had no clinically manifest CVD. This group probably represents hypertensive participants with subclinical CVD. The adverse effect of high blood pressure on cardiovascular profile is through various pathways. It has been reported that high blood pressure was associated with increased thickness of the carotid intima-media layer (391) and left ventricular mass. (434, 545) Nonetheless, the pathogenesis of hypertension remains largely unidentified. Recently the Multi-Ethnic Study of Atherosclerosis (MESA) study found that

structural and functional vascular abnormalities were independent predictors of incident hypertension. (546) This finding confirmed the inter-relationship between hypertension and subclinical CVD and that the presence of subclinical CVD is commonly present in older adults, probably more so in those of advanced age. (332) The association between hypertension/blood pressure and carotid intima-media thickness and left ventricular mass is presented and discussed in Chapter 8.

Blood pressure and CVD

This study did not find an association between systolic and diastolic blood pressure and CVD. The null association between diastolic blood pressure and CVD was not unexpected because diastolic blood pressure rises only until 50 years of age and decreases thereafter. (198) The null association between systolic blood pressure and CVD was somewhat unexpected but not too surprising. This is probably a type II error (false negative) attributable to the small sample size. Although systolic blood pressure increases with age and therefore is a better indicator of increased CV risk in older adults (compared to diastolic blood pressure), it is possible the association between systolic blood pressure and CVD attenuates (weakens) with age, as found in the Cardiovascular Health Study (CHS). The CHS found that ISH was not associated with heart failure in adults 78 years and above. (213) Pulse pressure has been reported to predominate over systolic blood pressure in predicting coronary heart disease in older adults, probably due to the discordant decrease of diastolic blood pressure and increased systolic blood pressure with age. (213, 547, 548) Future studies are needed to examine the predictive value of pulse pressure on CVD risk in advanced age.

Summary for hypertension, blood pressure and CVD

Hypertension is one of the major risk factors for CVD. The prevalence of hypertension increased with age. As many as three-quarters of septuagenarians and octogenarians had hypertension. (532, 533) In this sample of those living to advanced age, more than three-quarters of participants had hypertension. Early detection of this health problem enables initiation of treatment interventions. However, due to the diversity in the oldest of the elderly population, the management of hypertension for people of advanced age is a challenge. Integration of individualised treatments and education to encourage lifestyle changes, e.g. including functional

foods in the diet along with appropriate physical activities, would be the ideal approach in managing hypertension in those of advanced age. Regular contact with a general practitioner would be an important determinant of both awareness and treatment of hypertension in those of advanced age. Prospective cohort studies are ideal to examine and establish the association between systolic blood pressure and CVD, and whether the degree of this relationship changes in the remaining years of life.

7.2.4 Anthropometry measures

Prevalence of obesity

In this study, more than one-quarter of the study participants were obese (BMI≥30kg/m^2). In the Canadian National Population Health Survey of more than 12,800 adults over 65 years old, 12% of those aged between 75 and 79 years old and 5% over 80 years old were obese. (549) In Australia, 14% of those over 75 years old were obese. (460) In New Zealand, 22% of men and 20% of women over 75 years old were obese. (118) The higher prevalence of obesity in New Zealand is probably due to the diverse ethnic groups in New Zealand. In this study, obesity was associated with age-ethnicity. Three-fifths of Māori participants aged 75-79 years, as opposed to one-tenth of the 85-year-old New Zealand European participants, were obese. Findings from the 2006/07 New Zealand Health Survey showed 42% of adult Māori and 24% of adult NZ Europeans were obese. (118) This difference may be due to hereditary of genetic material predisposing to obesity. In a genome-wide search for type-2 diabetes-susceptibility genes, it was identified that a common variant in the fat mass and obesity-associated gene was strongly associated with increased BMI. (550) Adults who are homozygous for this risk allele had nearly 1.7-fold increased odds of obesity compared with those not inheriting the risk allele. In this group of people living to advanced age with supposedly similar CVD profiles, there were more Māori than non-Māori (NZ European) participants with observed obesity.

Relationship between BMI, WC, WHR and CVD

There were more than twice as many participants in this study with increased waist circumference rather than obesity (BMI>30kg/m^2). This study also found participants with CVD had a higher waist circumference than those without CVD. There was no difference in BMI and WHR

between the two groups. Weight tends to reduce with age. (551) In New Zealand, the prevalence of obesity peaks at middle age (55-64 years) and declines thereafter. (118) On the contrary, abdominal adiposity increases with ageing due to the redistribution of body fat to the abdominal region occurring at middle age, particularly for women. (234, 551) In a large study with participants over 75 years old in the United Kingdom, BMI was inversely associated with mortality. (242) It has been reported that WC was a better indicator of health problems in older adults compared to BMI. (223, 224, 229, 232) In another study of more than 14,800 adults aged 75 years and over, WHR was positively related to circulatory mortality; the same association was not observed in waist circumference. (242) These findings reiterate that there is no one anthropometry measure that can correctly predict cardiovascular health outcomes in older adults. Those in advanced age often constituted only a small proportion of study samples, and perhaps body fat distribution and its contribution to cardiovascular risk differs for those in advanced age compared to younger groups. This cross-sectional study was not designed to establish the predictability of anthropometry measures on CV risk among those of advanced age. However, it probably indicates that the positive association between waist circumference and increased risk of CVD observed in younger adults continues into advanced age.

In addition, this study shed some light on the specificity of anthropometry measures for CV health indicators in those of advanced age. Of the four anthropometry measures examined, BMI and WC demonstrated some relevance in assessing CV health with specific contribution in the pathophysiology of CVD in those of advanced age. BMI is a measure of general obesity and also a clinical manifestation of malnutrition. Factors favouring higher BMI in older adults are positive energy reserves (552) and low BMI was related to risk of fall and fracture. (553) Risk factors for malnutrition include disability and depression following clinical manifestation of CVD. (554, 555) A prolonged state of malnutrition may exacerbate existing CV health problems due to low energy reserves when reserves are needed for recuperation, (556) thus leading to a downward spiral of general health status and wellbeing. Waist circumference, on the other hand, is a measure of abdominal obesity. In the National Institutes of Health-American Association of Retired Person Diet and Health Study with more than 245,500 adults aged 50-71 years, persons with a normal BMI but large waist circumference had up to a fifty-percent increase in their risk of mortality. (226) This is probably due to a greater number of systemic inflammation markers secreted by adipose tissue in the abdominal region than in subcutaneous adipose tissues. (239) Hence, visceral adipose tissue

may have a critical correlation with inflammation that is not completely accounted for by BMI alone. (557) Increased systemic inflammation is associated with prevalence of frailty (558) and increased risk of CVD. (239) Therefore, this study hypothesised BMI as a better indicator for risk of malnutrition, whereas waist circumference may be a better indicator, with or without nutritional risk, of increased risk of CVD.

Body fat percentage and inflammatory markers

In this study, body fat percentage (BF%) (measure of overall adipose tissue) was correlated with fibrinogen. Studies have shown that adipose tissue correlates positively with systemic inflammatory markers (241, 297, 557) and possibly up to 30% of circulating IL-6 is released from adipose tissue. (154, 221) In the Framingham Offspring Multi-Detector CT-scan study of 1,250 adults, mean aged 60(±9) years, comparing subcutaneous and visceral adipose tissue in the abdominal compartment, controlling for BMI and waist circumference, it was revealed that subcutaneous adipose tissue was associated with fibrinogen, and visceral adipose tissue was associated with CRP and IL-6. (557) Visceral adiposity increases with age and the loss of muscle mass with ageing may be replaced with adipose tissue. (234) In other words, older adults not only have more fat gathering in the abdominal region, they also have more adipose tissue in other parts of the body. This probably explains why inflammatory markers increase with age. (154, 466) In this study, the Tanita scale was chosen to provide an estimation of body composition. This study acknowledges the inadequate accuracy of BF% generated from this device. The ideal assessment of body composition is the dual energy X-ray absorptiometry (DEXA) or computed tomography (CT) method (559). These methods are expensive and have limited accessibility outside the main cities in New Zealand and so were beyond the scope of the study. Future research are needed to explore further the role of visceral and subcutaneous adipose tissue in people of advanced age and their association with inflammation, and establish how they impact on cardiovascular health.

7.2.5 Lipid profile

Prevalence of dyslipidemia

In this study, five of six participants had dyslipidemia. In the Diabetes Heart and Health Survey (DHHS) carried out in Auckland, New Zealand, with participants aged 35 to 74 years, over 90% of the study population had dyslipidemia. (25) In the Multi-Ethnic Study of Atherosclerosis (MESA),

the primary care setting in Germany, and the NHANES study, the prevalence of dyslipidemia for age ranges between 75 and 90 years was between 38% and 88%. (26, 27, 560) These considerably varied prevalence rates between studies are due to the different definitions used. The DHHS defined dyslipidemia according to the New Zealand Heart Foundation (NZHF) recommendation; the MESA and NHANES study defined dyslipidemia according to the Adult Treatment Panel III recommendation, and the German study according to the European Society of Cardiology guidelines. (25-27, 560) This study with a thorough method in defining dyslipidemia indicates that dyslipidemia is prevalent among those living to advanced age.

Treatment rate for dyslipidemia

Despite the high prevalence of dyslipidemia in older adults, treatment for the condition remains low. In the current study, only one-quarter of those with dyslipidemia were on lipid-lowering medications. In the 2006/07 New Zealand Health Survey, 23% of adults above 75 years old were treated with lipid-lowering medications. (118) Studies abroad showed treatment of dyslipidemia for adults aged 80 years and above ranges between 18% and 24% (27, 560). In addition to the low treatment rate, effective lipid-lowering is low for those receiving treatment. In this study, two-thirds of participants treated with lipid-lowering medications still have total and LDL cholesterol above the optimal level recommended by the NZHF. The control rate observed in this study was lower than observed in the NHANES study of participants aged 85 years and above. (560) In the NHANES study, one-third of study participants did not achieve the treatment goal. This variance is probably due to different recommendations of the treatment goal. In brief, dyslipidemia is common among those in advanced age but the proportion of this age group treated for the condition remains low. Moreover, only small numbers of those treated for the condition have optimal lipid levels as recommended by the NZHF.

Treatment strategy for dyslipidemia

Treatment of dyslipidemia with statin has been proven to be effective in primary and secondary prevention of CVD. Nonetheless, under-treatment of this condition remains widespread in the very old. There are several reasons contributing to this circumstance. Firstly, the current evidence supporting medical therapy of dyslipidemia in older patients was limited to younger elderly (65 to 74 years) and middle elderly (75 to 84 years). (561, 562) Debate continues as to the utility of

cholesterol-lowering in old age. (563) It is uncertain if this treatment benefit persists in the very old (85 years plus), particularly for those with co-morbidities. The adverse effect of pharmacotherapy for dyslipidemia may be increased in the very old due to drug-drug interaction as a consequence of polypharmacy. In the JUPITER (Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) study, 5,695 adults aged 70 to 97 years (median age 74 years) were randomised into the 20mg rosuvastatin group or the placebo group, and followed up for 5 years (median follow-up 2 years). Over the study duration, compared to the placebo group, the rosuvastatin group had increased risk of myopathy (31%), newly-diagnosed diabetes (25%), bleeding event (18%), renal disorder (14%), and gastrointestinal disorder (6%). (564) To date, the target of pharmacotherapy for dyslipidemia is to lower total and LDL cholesterol levels.

In this cross-sectional study, HDL was the only lipid profile found to be lower in those with CVD compared to those without CVD (p=0.041); and was inversely associated with CVD (p=0.047) independent of sex, age-ethnicity, smoking status, and waist circumference. This finding is in line with prospective studies abroad. In a study of 432 adults aged 75 years old, followed up for 10 years, men (but not women) with low HDL levels were significantly more likely to have increased cardiovascular morbidity and mortality. (565) Conversely, the levels of total and LDL cholesterol had no significant impact on the long-term prognosis in either men or women. (565) In the Leiden 85+ study, low HDL was associated with a 2- to 3-fold increased risk of mortality from coronary artery disease and stroke; total and LDL cholesterol was not associated with coronary artery disease or stroke. (24) Findings from this study and prospective studies abroad imply that a low HDL level continues to be an important cardiovascular risk factor in those of advanced age, but the strong and graded association between total and LDL cholesterol and CVD loses its significance with advanced ageing. So, is the current medical treatment aiming for lower total and LDL cholesterol suitable for the oldest elderly? Should they be offered lipid-lowering medications?

Rather than lowering total and LDL cholesterol, increasing the HDL level to reduce CVD risk is perhaps a better strategy for older adults. In a population study with 256,000 adults aged between 50 and 84 years old (mean age 59 years), it was estimated that for every increase of 0.13mmol/L HDL level, the risk of major cardiovascular events decreased by 6.5% during the 5-year study period. (113) The cardio-protective role of HDL is limited not only to its role in reverse cholesterol transport (from the arterial wall's foam macrophages to the liver, bile and faeces), but also its anti-

inflammatory, antiapoptotic, antioxidative and antithrombotic actions (i.e. HDL particles can transport antioxidant enzymes which can break down oxidised lipids and neutralise the proinflammatory effects). (89, 112, 566) In the InChianti study of older adults with an average age of 76 years, low HDL levels were associated with increased inflammatory markers. (567) Among older adults (mean age 80 years) with low HDL levels, inflammatory markers (IL-6 and CRP) were strongly associated with decreased levels of physical function. (568) The ageing and longevity study in the Sirente geographical area (ilSIRENTE study) drew a similar finding: that octogenarians living in the community with higher levels of HDL have better functional performance (569). Hence, increasing the HDL level probably is as important for good cardiovascular health of those in advanced age as observed in younger adults.

Strategies to increase HDL levels include both pharmacological and non-pharmacological intervention. Aerobic exercise and dietary consumption with the right kind of fat (i.e. n-3 polyunsaturated fat) had been found to elevate HDL levels. (112, 570) Raising HDL levels through pharmacology intervention has been less successful than lowering total and LDL cholesterol. (112) To date, niacin (nicotinic acid) is the most effective pharmacological agent available to increase HDL levels by up to 35%. (566, 571, 572) Patients with a low HDL level (<1.0mmol/L), treated with modified release niacin 2g daily (in addition to statin) showed atheroma regression of the carotid arteries as opposed to progression seen in the placebo group. (572) Nonetheless, the major drawback of niacin is the adverse effect of flushing that occurs in up to 80% of patients (depending on the formulation) which often leads to discontinuation of the treatment. (112, 566, 572) Not only did these clinical trials have a limited number of people in advanced age, their use was mostly combined with other pharmacological agents (commonly a statin). (573) Would this treatment suit older adults with multiple morbidity and probably multiple pharmacotherapy treatments? Clearly, it is warranted that the risk-benefit equilibrium of the existing strategies be assessed for increasing HDL levels in those of advanced age.

A longitudinal study of greater numbers will assist in answering this question. Randomised trials enrolling those of advanced age are really needed to determine the risk-benefit of both pharmacologic and non-pharmacologic intervention in improving HDL level.

7.2.6 Inflammatory markers

In this study, inflammatory markers did not differ between those with and those without CVD, but they were correlated with a selection of conventional CV risk factors.

Inflammatory markers and diabetes

This study found fibrinogen was associated with diabetes status. Fibrinogen is a strong predictor of atherosclerotic CVD in patients with diabetes. (574, 575) In the ARIC (Atherosclerosis Risk in Communities) study, fibrinogen was independently associated with coronary heart disease in patients with diabetes after adjustment with conventional risk factors. (576) There are several pathways linking inflammation and diabetes. In the diabetic state, macromolecules were modified, leading to formation of advanced glycation end products (AGEs). Increased serum AGEs in diabetes patients is associated with elevated levels of CRP (577), and augments the production of other proinflammatory cytokines. (89) Additionally, the diabetic state enhances monocytes binding to the vascular smooth muscle cells. (172) Hyperglycaemia or insulin resistance also generates oxidative stress. (89, 575) These interactions are key regulatory signals promoting macroangiopathy. In a group of 100 newly-diagnosed diabetes patients, CRP and fibrinogen were strongly associated with increased intima-media thickness (IMT >1.5mm), a value indicating the presence of asymptomatic carotid lesions by the European Society of Hypertension/European Society of Cardiology. (578) Therefore, elevated levels of inflammatory markers may be implicated as a causal mechanism contributing to increased risk of CVD in patients with diabetes.

Inflammatory markers and hypertension

This study also found IL-6 was associated with hypertension. The association between low-grade inflammation and hypertension has been proposed but it is yet to determine whether low-grade inflammation precedes hypertension or is a consequence of increased blood pressure. Arterial stiffness, thought to be a consequence of hypertension, is due to changes of the vasculature through the remodelling process precipitated by mechanical stresses. (181) Angiotensin II (a humoral factor of the RAAS[33]) has an important mediating role linking inflammation and hypertension. (89, 182) Angiotensin II (Ang II) induces synthesis of TNF-α and IL-6, and stimulates adhesion molecules and pro-inflammatory transcription factors (e.g. nuclear factor κB,

[33] **RAAS**: renin-angiotensin-aldosterone

which regulates adhesion molecule and cytokine expression in cell). (182, 579, 580) These molecules induce and sustain inflammation within the vascular wall, stimulate deposition of extracellular matrix and promote hypertrophy and hyperplasia of vascular smooth muscle cells (VSMCs). Within the inflamed vascular wall (consisting of monocytes/macrophages) and hypertrophied VSMCs, NADPH[34] oxidase is expressed. NADPH oxidase is a major source of vascular reactive oxygen species (ROS) (182), which modulate vascular tone and structural changes of the vessels and stimulate the production of endothelin (ET)-1. (182) Endothelin-1 in turn activates NADPH oxidase, besides inducing oxidative stress which precipitates inflammatory response and contributes to the vascular remodelling and endothelial dysfunction. (182) In brief, Ang II seems to be the precursor within the RAAS contributing to vascular inflammation.

So, what triggers Ang II to produce cytokines and adhesion molecules? In an experimental study testing the role of IL-6 in mediating hypertension caused by high-dose Ang II and a high-salt diet, IL-6 knockout mice had significantly lower mean arterial pressure compared to wild-type mice during two weeks of Ang II infusion. The study demonstrates that hypertension caused by chronic Ang II excess may depend on the presence of IL-6. (580) Hence, there may be a vicious cycle that potentiates the inflammatory effect linking hypertension to CVD.

The relationship between IL-6 and hypertension is more complex with the discovery of a pleiotropic function of IL-6. IL-6 was found to have a wide range of biological activities consisting of both pro-inflammatory and anti-inflammatory action. (581, 582) The cause-and-effect association between inflammatory markers and hypertension requires further investigation, particularly in those of advanced age. This is important because inflammatory markers and the prevalence of hypertension increase with advancing age. (343, 466, 532)

Inflammatory markers and lipid profile

Additionally, this study found that CRP, fibrinogen, and ESR correlated positively with lipid parameters, and inversely with HDL levels. In younger-aged elderly adults, similar trends of association were observed between CRP and fibrinogen with total cholesterol and HDL. (326, 583) However, in the ilSIRENTE cohort study involving community-dwelling adults aged 85 years and above (mean age 90 years), the CRP level was inversely associated with all lipid parameters (i.e.

[34] **NADPH**: nicotinamide adenine dinucleotide phosphate

total cholesterol, HDL, LDL and triglycerides). (293) This suggests inflammation linking the association between lipid parameters and CVD changes with advancing age.

In the article by Esteve *et al.*, the evidence linking inflammation and dyslipidemia was reviewed and described explicitly. (584) Inflammation, a compensatory response, triggers an acute phase response (APR) aiming to protect tissues from injury and facilitating the mechanism of repair. During acute infection, lipoproteins are directed to injured sites for repair and regeneration of damaged membranes. Consequently, less lipoprotein is excreted through the liver. The role of lipoprotein as a host defence might be the reason why an increased total cholesterol level is protective for nonagenarians. (465) However, prolonged inflammation causes disturbances of the lipid metabolism, i.e. the HDL level is reduced, the anti-oxidant properties of HDL are modified; production of lipoprotein (triglycerides-rich particles) increases but clearance is decreased; and clearance of LDL changes, and the size and LDL protection from oxidation is modified. (584) Evidence from the work of Dichtl *et al.* found triglyceride-rich protein (VLDL) activates the pivotal transcriptional regulator of inflammation nuclear factor-kappa B (NF-κB regulates adhesion molecule and cytokine expression in cell). (585) These evidence suggest that lipoprotein properties and lipid metabolism incite inflammation via several pathways during atherogenesis. (586)

In brief, the relationship between inflammation and lipid parameters is complex, particularly in those of advanced age who have already undergone significant physiological change. Experimental studies are still underway, elucidating the cause-and-effect relationship between inflammation and dyslipidemia. This study contributes to the limited body of evidence that the association between inflammatory markers and lipid parameters in those of advanced age is similar to those of younger-aged elderly adults. However, these results should be interpreted cautiously as the sample size was small.

Inflammatory markers and anthropometry measures

Lastly, this study showed IL-6 is correlated with BMI, and fibrinogen is correlated with percentage of body fat. Numerous studies has showed that increased BMI is correlated with increased circulating systemic inflammatory markers such as CRP, IL-6, plasminogen activator inhibitor-1 (PAI-1), P-selectin, vascular cell adhesion molecule 1 (VCAM-1), fibrinogen, and angiotensinogen. (239) With age, there is an increase in body fat ratio as loss of muscle mass is

replaced with fat mass. (234) Adipose tissue has been reported to synthesise cytokines IL-6 and TNF-α. (154, 221, 239) In fact, adipose tissue infiltrated with macrophages was thought to be responsible for the expression of IL-6 and TNF-α, and the number of adipose tissue macrophages increased with obesity. (587) In this study, IL-6 and TNF-α did not correlate with percentage of body fat. This is not unanticipated because body fat percentage was estimated using the Tanita scale. DEXA is considered to be a gold standard in measuring body composition. However, due to logistical issues, measurement of body fat in this study was limited to the simpler device. Additionally, the null correlation between body fat percentage, IL-6 and TNF-α may be due to advancing ageing. It has been reported that the mononuclear cells of older adults may have an increased capability of producing pro-inflammatory cytokines, overtaking adipose tissue as the important source of cytokine production observed in younger adults. (64) In short, obesity is an important triggering factor for increased inflammatory markers. The interaction between the physiological changes due to obesity and the multifaceted highly complex inflammatory cascade will require further investigations in those of advanced age.

Explorative treatment influencing inflammatory markers

To date, there are less than a handful of inflammation-targeted therapies for prevention of CVD. Aspirin is the most commonly-prescribed medication for prevention of CVD due to its anti-inflammatory and anti-platelet properties. (365, 523) It has been found to reduce CRP, IL-6, fibrinogen, and ESR levels. (368, 373) Statin, which lowers cholesterol by inhibiting the enzyme HMG-CoA reductase, has also been found to reduce CRP and IL-6 levels. (368, 373) In this study, neither of these agents was associated with inflammatory markers, but use of vitamin and mineral supplementation was associated with IL-6. This finding is unexpected but The Health, Aging and Body Composition (Health ABC) study found similar results; use of a multivitamin, vitamin C, vitamin E or its derivatives, or beta-carotene or its derivatives was significantly associated with IL-6 but not with CRP or TNF-α. (354) This study agreed with the Health ABC study that nutritional supplement use could be a marker of an overall healthier lifestyle. However, the study cannot rule out the possibility of type I error. Hence, this finding may merit further exploration in a larger study. The challenges in examining the association between nutritional supplementation and cardiovascular health in those of advanced age were mentioned in Chapter 5.

Other factors influencing inflammatory markers levels

Inflammation is involved in various pathophysiological pathways during the restorative process. The probable link between chronic low-grade inflammation and CVD elicited by CV risk factors has been described earlier. Acute infection or the presence of autoimmune diseases such as rheumatoid arthritis causes a sharp rise in inflammatory markers. (270, 309) In this study, there were several high values of CRP, IL-6, fibrinogen, and ESR. These high values are probably reflective of acute infection or the presence of autoimmune diseases. The seasonal flu variation on CRP levels would be minimal, as almost three-quarters of the blood samples were drawn during autumn and summer season. (Statistical tests showed no difference in the CRP level between different seasons, Appendix TABLE B-21, page 306). As the CRP level is sensitive to acute infection, it was recommended that CRP values above 10mg/L be repeated in two weeks to allow acute inflammation to subside before retesting; this will rule out acute infection. (281) In this study, six participants (7%) had a CRP level above 10mg/L. Nonetheless, CRP levels, and other inflammatory markers, were not repeated. Therefore the presumption of acute infection in these participants cannot be disregarded in this study. Collection of medical history in this study did not include autoimmune diseases (e.g. rheumatoid arthritis). Therefore, it is not known whether participants with these high levels of inflammatory markers were attributed to autoimmune diseases. Nonetheless, arthritis, cancer (skin, breast, and prostate cancer) and asthma seem to be prevalent among those with high levels of inflammatory markers. These observations, although not definite, are possible in view of the function of the immune system.

As mentioned in Chapter Three, analysis of TNF-α and IL-6 in this study encountered some challenges, i.e. the standard clinical reference range was not able to detect the low levels of TNF-α and IL-6. The samples were reanalysed and measured with an extended standard curve (i.e. increasing the detection sensitivity). Nevertheless, eighth-tenths of the study sample still have an undetectable TNF-α level. TNF-α is a cytokine that initiates the inflammatory cascade and is involved in the amplification of inflammatory reactions. (309) It is detected not only in diseased adults but also in healthy older adults aged 65–80 years old (588) suggesting low-grade inflammation is present in older adults who have aged "successfully" (i.e. absence of disease). It is quite surprising that TNF-α levels were not detected in this group of advanced-age older adults. This is probably because TNF-α is a cytokine mainly produced locally and working *in-situ*, and

having a limited half-life (589), making it difficult to detect in the circulation unless it is produced in large amounts. (270) It is tempting to report people of advanced age as having a very low TNF-α level, but this needs to be verified in a larger study. TNF-α has pleiotropic function (308) and, therefore, may have different detectable concentrations in different states of health. Additionally, the availability of several methods in measuring TNF-α level (i.e. enzyme-linked immunosorbant assay (ELISA) kit; radioimmunoassays and spontaneous production of TNF-α by peripheral blood mononuclear cells) (35, 304, 590) makes it more difficult to compare TNF-α levels between studies. In the midst of these complexities, this study has endeavoured measuring TNF-α levels in a group of people living to advanced age. The undetectable TNF-α concentrations in this sample possibly indicate other cytokines stimulated by TNF-α (e.g. IL-6, which had a longer half-life) (589) may be a more appropriate biomarker relating to cardiovascular health in those living to advanced age.

Summary for inflammatory markers (Section 7.2.6)

In summary, inflammation is most likely an inevitable process linking conventional cardiovascular risk factors to CVD. Inflammation is part of the homeostatic process. This study did not find an association between inflammatory markers and CVD but did find an association between inflammatory markers and cardiovascular risk factors, which also have been observed in younger adults. An unexpected association between nutritional supplements and IL-6 was found. This, however, was in agreement with a larger study of more than 3000 older adults aged between 70 and 79 years old. With advancing age, significant physiological changes have taken place, and the inflammatory cascade is involved in these changes. Therefore, inflammatory markers, which denote the activities of inflammation, warrant further research to understand the cause and consequences of these biomarkers in the pathogenesis of CVD in those of advanced age. In the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), Sattar *et al*. shows IL-6 and CRP are more strongly associated with fatal than non-fatal cardiovascular events, suggesting inflammation may have a mechanistic role in the promotion of serious vascular disease leading to death. (591) The small study sample size may contribute to Type II error. Nevertheless, every possible step has been considered, i.e. sensitivity analyses of high value and seasonal flu variation, to minimise spurious relationships. These results need to be interpreted cautiously. A longitudinal cohort study will add significant understanding and evidence to the relationship between inflammatory markers, cardiovascular risk factors and CVD in those of advanced age.

CHAPTER EIGHT: CAROTID INTIMA-MEDIA THICKNESS AND ECHOCARDIOGRAPHIC MEASURES

This chapter will present the descriptive statistical results examining CIMT, echocardiographic measures and Brain natriuretic peptide (NT-proBNP). The descriptive results are followed by examination of the association between CIMT and echocardiographic measures with clinically manifest CVD.

The second section of this chapter presents and discusses the association between CIMT and LVM (the secondary outcomes) with other cardiovascular risk factors.

8.1 Results

8.1.1 Carotid intima-media thickness

A total of 103 participants agreed to physical assessments. One hundred (97%) participants had ultrasound images of the common carotid intima-media thickness (CIMT); three participants did not have CIMT images taken due to timing and logistical issues. Of these 100 participants, CIMT measures were available for 98 participants. Images of the remaining two participants were not digitally stored correctly and were not available for analysis. The distribution of CIMT values were skewed to the right of the median (positively skewed), i.e. most of the values clustered toward the lower end of the distribution scale with few in the upper end of the scale. In this sample of people in advanced age the CIMT median (IQR) was 1.07 (0.27)mm. Two participants, a man and a woman, had high CIMT value, 2.30 and 2.33mm respectively. Both participants were aged 85 years, had hypertension, and a BMI of 27kg/m^2 (for both participants). The male participant also had clinically manifest CVD and a previous pulmonary embolus; the female participant had diabetes and skin cancer. The next highest value after these two outliers (i.e. 2.33 and 2.30mm) was 1.92mm.

CIMT, participants' characteristics and medical history

In this sample, the 75th percentile of CIMT was equivalent to 1.206mm. The participants' characteristics, medications and medical history between those with CIMT above and below the 75th percentile are presented in TABLE 8-1. Using the 75th percentile to define abnormality (≥1.206mm) (480), 24 participants had an abnormal CIMT. There was a difference in the distribution between

normal and abnormal CIMT in smoking status (p=0.026). There was no difference in the distribution between the two CIMT groups in any of the participants' characteristics, medications and medical history.

TABLE 8-1: Participants' characteristics, medications and medical history between those with carotid intima-media thickness (CIMT) below and above the 75th percentile

Variable, n (column %)	CIMT		
	Below 75th percentile, n=74	Above 75th percentile, n=24	P value‡
Sex			
- Men	32 (43)	14 (58)	0.198
- Women	42 (57)	10 (42)	
Age-ethnicity			
- 75-79 years old	21 (28)	9 (37)	0.399
- 85-years old	53 (72)	15 (63)	
Smoking status			
- Current	1 (1)	4 (17)	0.026†
- Former	33 (45)	9 (38)	
Use aspirin	33 (45)	11 (46)	0.916
Use lipid-lowering medication	20 (27)	5 (21)	0.545
Use vitamin & mineral supplements	38 (53)	12 (50)	0.814
Hypertension	64 (87)	20 (83)	0.741†
Diabetes	11 (15)	7 (29)	0.135
Clinically manifest CVD	47 (64)	16 (67)	0.779
Atherosclerotic CVD	38 (51)	12 (50)	0.908

‡P values are from Pearson chi-square test, unless specified otherwise
†P values are from Fisher's exact test

CIMT and medication

Blood pressure- and lipid-lowering medications may regress CIMT. (378, 381) Of the 98 participants who had their CIMT measured, 25 (26%) participants were on lipid-lowering medication and 32 (33%) were being treated for hypertension. There were another 30 participants on medications that may affect blood pressure. Therefore, there were a total of 62 participants taking medications that may have an impact on blood pressure and subsequently would have the potential to regress CIMT. In this sample, CIMT was similar between participants who were on lipid-lowering or blood pressure-lowering medication compared to those not on these medications. (Appendix B: TABLE B-22, page 306)

CIMT and CVD

Of the 98 participants who had CIMT measured, 63 (64%) participants had clinically manifest CVD; 35 (36%) did not have CVD. The CIMT median (IQR) for participants with and without CVD

was 1.06 (0.29) and 1.07 (0.20) mm, respectively. CIMT did not differ between those with and those without CVD, p=0.932. Since CIMT is a measure of the thickness of the arterial wall and implicated in the development of atherosclerosis, analysis of the association between CIMT and CVD was reanalysed, limiting the analysis to those with atherosclerotic CVD. Atherosclerotic CVD includes all forms of CVD listed in Table 3.3 (page 92) except for cardiac arrest, heart failure, cardiomegaly, aortic valve replacement, abdominal aneurysm, cardiac catheterisation, and insertion of a pacemaker. Fifty-nine of the 108 participants (55%) had atherosclerotic CVD. Among those who had CIMT measured, 50 of the 98 participants (51%) had atherosclerotic CVD. The median for those with atherosclerotic CVD did not differ from those with clinically manifest CVD (p=0.649) (Figure 8-1).

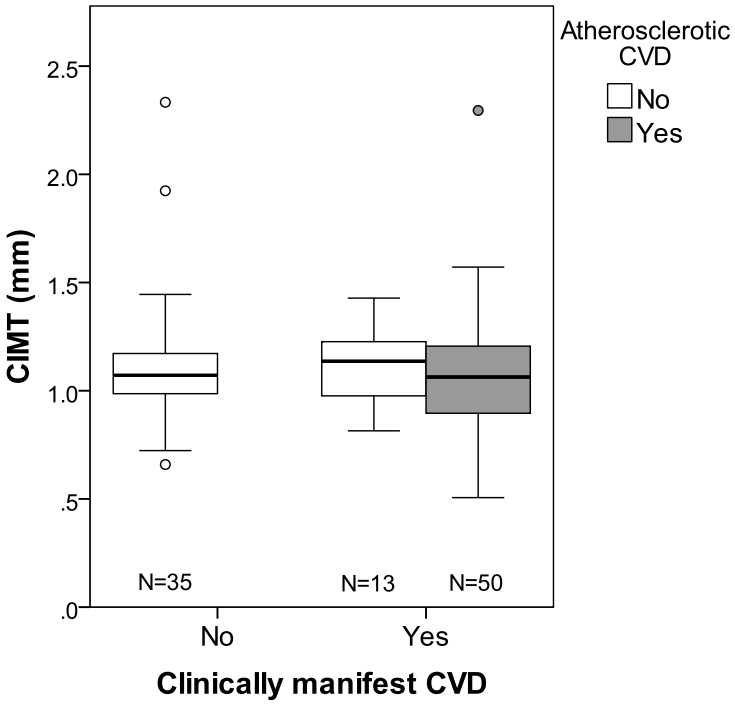


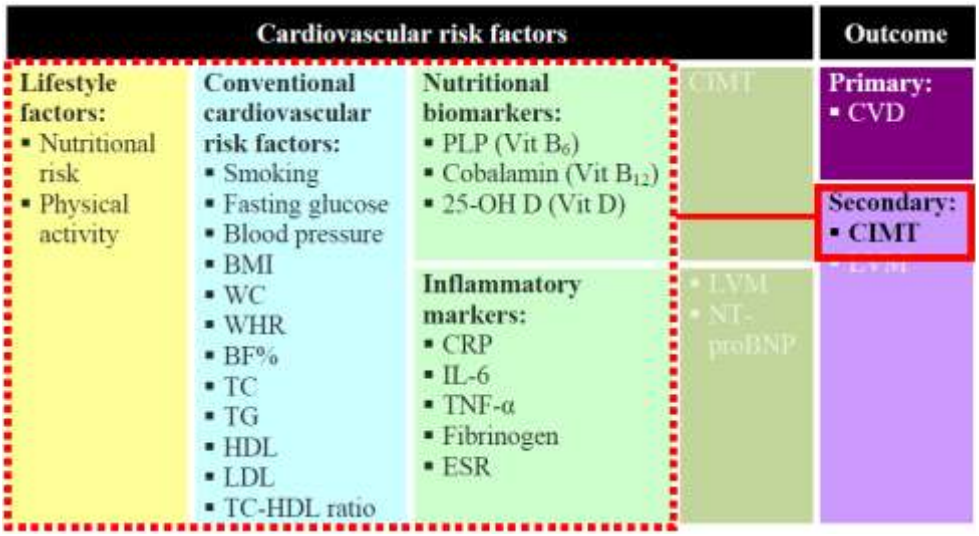
Figure 8-1 Box-plot demonstrating the distribution of CIMT levels for those with and those without CVD

The association between CIMT and CVD was examined using a logistic regression model controlling for sex, age-ethnicity and smoking status. To determine if age-ethnicity has an effect on the relationship between CIMT and CVD, the interaction term (age-ethnicity × CIMT) was included into the regression model. There was no association between the interaction term and CVD (p=0.772). This implies the association between CIMT and CVD was the same for all ages. Therefore, analysis was combined for both age-ethnic groups. Since lipid-lowering medication and blood-pressure-lowering medication has been reported to have an impact on the progression rate of

CIMT (378, 381), they were also entered into the regression model. In all models, CIMT was not associated with CVD. (Appendix B: TABLE B-23, page 307). The same analysis was repeated by replacing CVD with atherosclerotic CVD as the dependent variable. Similar patterns were observed, i.e. CIMT was not associated with atherosclerotic CVD. (Appendix B: TABLE B-24, page 307)

8.1.1.1 Associations between CIMT with CV risk factors

This section will present the association between CIMT (the secondary outcome) and lifestyle factors, conventional CV risk factors, nutrition biomarkers, and inflammatory markers.



Univariate analysis was performed to determine the association between CIMT and each of the lifestyle factors, conventional CV risk factors, nutritional biomarkers, and inflammatory markers. TABLE 8-2 shows the list of variables assessed for the association with CIMT. There were no significant correlations between any variables and CIMT; only low levels of correlation were found (r values between 0 and 0.25). These relationships were investigated further using a linear regression model controlling for possible confounding variables.

TABLE 8-2: Correlations between CIMT and lifestyle factors, conventional CV risk factors, nutritional biomarkers, and inflammatory markers

	Variables	Correlation coefficient	P value[#]
Lifestyle factors	SCREEN II Score	-0.048	0.642
	PASE score	-0.071	0.488
Conventional CV risk factors	Fasting serum glucose	0.102	0.354
	Systolic blood pressure (SBP)	0.063	0.535
	Diastolic blood pressure (DBP)	0.038	0.707
	Total cholesterol (TC)	-0.009	0.934
	Triglyceride (TG)	-0.183	0.092
	High-density lipoprotein (HDL)	-0.062	0.568
	Low-density lipoprotein (LDL)	0.026	0.814
	TC-HDL ratio	-0.007	0.947
	Body mass index (BMI)	-0.049	0.633
	Waist circumference (WC)	0.010	0.926
	Waist-to-hip ratio (WHR)	0.007	0.944
	Body fat percentage (BF%)	-0.125	0.234
Nutrition biomarkers	Pyridoxal 5' phosphate (PLP)	0.027	0.810
	Cobalamin	0.020	0.853
	25 hydroxyvitamin D (25-OH D)	-0.121	0.273
Inflammatory markers	C-reactive protein (CRP)	0.057	0.604
	Interleukin-6 (IL-6)	-0.107	0.373
	Tumour necrosis factor-alpha (TNF-α)*	-0.131	0.275
	Fibrinogen	0.025	0.823
	Erythrocyte sedimentation rate (ESR)	-0.093	0.393

[#] P values are from Spearman's correlation test
* Analysed as categorical data, i.e. <1.0 and ≥1.0pg/mL

Multivariate analyses

Linear regression models were constructed to determine the association between CIMT and lifestyle factors, conventional CV risk factors, nutritional biomarkers, and inflammatory markers controlling for sex, age-ethnicity and smoking status. Since CIMT was not normally distributed, it was $\log_{10}$ transformed to improve the distribution; but the distribution of the $\log_{10}$ transformed CIMT data did not differ significantly from the non-transformed data. Nevertheless, the conservative statistical method was adopted, i.e. $\log_{10}$ transformed CIMT was entered as the dependent variable in the linear regression model. A multivariate linear regression model was developed using $p \leq 0.2$ for entry and $p > 0.2$ for removal. Since pharmacology interventions would have an impact on certain variables, the presence of pertinent medication was added to the model. Pharmacology intervention did not alter the association between $\log_{10}$-CIMT and the variable of interest (TABLE 8-3). In each of the 22 individual models, only systolic blood pressure (Model 4a) and IL-6 (Model 19a) were found to have an association with $\log_{10}$-CIMT at $p \leq 0.2$. However, there was an outlier for variable IL-6 (40.4pg/mL). To determine if this outlier may have led to a spurious association, a sensitivity analysis was performed. It was determined that the high IL-6 value does cause a

spurious effect (Model 19b). As this value is likely to be an abnormality due to autoimmune diseases (e.g. rheumatoid arthritis) instead of chronic low-grade inflammation related to risk of CVD, it was not included in the overall analysis. Therefore, SBP was the only variable that had an association with $\log_{10}$-CIMT at $p \leq 0.2$ after controlling for sex, age-ethnicity, smoking status and blood pressure-lowering medication.

TABLE 8-3: Linear regression models examining the association between CIMT ($\log_{10}$-CIMT) and lifestyle factors, conventional CV risk factors, nutritional biomarkers, and inflammatory markers controlling for sex, age-ethnicity and smoking status

	Model	Variables	Regression coefficient (95% CI)	P value
Lifestyle factors	1	SCREEN II Score	-0.001 (-0.004 – 0.003)	0.460
	2	PASE score	-1.2E-005 (0.000 – 0.000)	0.953
Conventional CV risk factors	3	Fasting serum glucose	0.002 (-0.014 – 0.017)	0.846
	3a	+ glucose-lowering med	-0.003 (-0.021 – 0.016)	0.760
	4	SBP	0.001 (0.000 – 0.002)	0.102
	4a	+ BP med	0.001 (0.000 – 0.002)	**0.106**
	5	DBP	0.001 (-0.001 – 0.003)	0.309
	5a	+ BP med	0.001 (-0.001 – 0.003)	0.269
	6	TC	0.007 (-0.015 – 0.029)	0.545
	6a	+ lipid-lowering med	0.005 (-0.017 – 0.028)	0.637
	7	TG	-0.002 (-0.035 – 0.030)	0.891
	7a	+ lipid-lowering med	-0.002 (-0.035 – 0.031)	0.906
	8	HDL	-0.002 (-0.056 – 0.051)	0.930
	8a	+ lipid-lowering med	-0.003 (-0.056 – 0.051)	0.925
	9	LDL	0.010 (-0.015 – 0.034)	0.440
	9a	+ lipid-lowering med	0.008 (-0.018 – 0.034)	0.529
	10	TC-HDL ratio	0.013 (-0.007 – 0.032)	0.201
	10a	+ lipid-lowering med	0.012 (-0.008 – 0.032)	0.237
	11	BMI	-0.001 (-0.004 – 0.003)	0.623
	12	WC	3.12E-005 (-0.002 – 0.002)	0.970
	13	WHR	-0.048 (-0.400 – 0.305)	0.789
	14	BF%	2.71E-005 (-0.003 – 0.003)	0.987
Nutrition biomarkers	15	PLP	9.79E-006 (0.000 – 0.000)	0.879
		+ nutr suppl	-6.7E-006 (0.000 – 0.000)	0.923
	16	Cobalamin	-3.9E-005 (0.000 – 0.000)	0.495
		+ nutr suppl	-4.3E-005 (0.000 – 0.000)	0.453
	17	25-OH D	0.000 (-0.001 – 0.001)	0.510
		+ nutr suppl	0.000 (-0.001 – 0.001)	0.507

TABLE 8-3: continued

Inflammatory markers	18	CRP	0.000 (-0.002 – 0.003)	0.694
	18a	+ lipid-lowering med §	0.000 (-0.002 – 0.002)	0.739
	19	IL-6	-0.003 (-0.006 – 0.001)	0.135
	19a	+ lipid-lowering med §	-0.003 (-0.006 – 0.001)	0.140
	19b	+ lipid-lowering med ‡§	-3.0E-005 (-0.009 – 0.009)	0.995
	20	TNF-α*	-0.036 (-0.098 – 0.026)	0.253
	20a	+ lipid-lowering med §	-0.036 (-0.098 – 0.027)	0.261
	21	Fibrinogen	0.005 (-0.008 – 0.017)	0.465
	21a	+ lipid-lowering med §	0.005 (-0.008 – 0.017)	0.483
	22	ESR	0.000 (-0.002 – 0.001)	0.517
	22a	+ lipid-lowering med §	0.000 (-0.002 – 0.001)	0.513

Abbreviations: **25-OH D:** 25-hydroxyvitamin D; **BMI:** body mass index; **BF%:** percentage of body fat; **BP:** blood pressure; **CRP:** C-reactive protein; **DBP:** diastolic blood pressure; **ESR:** erythrocyte sedimentation rate; **HDL:** high-density lipoprotein; **IL-6:** Interleukin-6; **LDL:** low-density lipoprotein; **med:** medications; **nutr suppl:** nutritional supplements; **PASE:** Physical Activity Scale for the Elderly; **PLP:** Pyridoxal 5' phosphate; **SCREEN II:** Seniors in the Community: Risk Evaluation for Eating and Nutrition, Version II; **SBP:** systolic blood pressure; **TC:** total cholesterol; **TG:** triglyceride; **TNF-α:** tumour necrosis factor-alpha; **WC:** waist circumference; **WHR:** waist-to-hip ratio

Note:

- Each line is a separate regression model controlling for sex, age-ethnicity and smoking status
- Models 'a' and 'b' were further adjusted for the effect of relevant medication in addition to sex, age-ethnicity and smoking status.

§ Replacing lipid-lowering medications with aspirin did not change the direction and strength of association between the respective variables with $\log_{10}$-CIMT

‡ Excluded outlier IL-6 40.4pg/mL

* Entered as categorical data, i.e. <1.0 and ≥1.0pg/mL

8.1.2 N-terminal pro-brain natriuretic peptide

Results for N-terminal pro-brain natriuretic peptide (NT-proBNP) were available for 80 of the 90 (89%) participants who gave a blood sample for analysis. Of the 10 participants without NT-proBNP results, nine of them (from the pilot study) did not have a NT-proBNP analysis completed because of funding constraints, and the result of the other participant was not available. NT-proBNP values were dispersed asymmetrically with the distribution skewed to the right of the median (positively skewed), i.e. the majority of NT-proBNP values were clustered toward the lower end of the distribution scale with few in the upper end of the scale. The median (IQR) was 40.5 (46.0)pmol/L[35]. One outlying value of 549pmol/L was from an 85-year old woman. Although she did not report that she has had CVD, she is on standard pharmacotherapy for heart failure (HF) and her echocardiogram revealed she has preserved left ventricular (LV) systolic function but with LV hypertrophy and significant biatrial dilatation. The patient had a prior hospitalisation for heart

[35] 1 pmol/L = 8.457pg/mL

failure[36]. In addition, she also had hypertension and a BMI of 33.1kg/m^2. The next highest NT-proBNP value was 321pmol/L.

NT-proBNP, participants' characteristics and medical history

NT-proBNP readings were categorised into tertiles: ≤30.0pmol/L (n=27), 30.1–59.0pmol/L (n=27), and >59.0pmol/L (n=26). The participants' characteristics, medications and medical history across tertiles are presented in TABLE 8-4. There was an increased prevalence of CVD and heart disease across NT-proBNP tertiles. There was no difference in the distribution across NT-proBNP tertile in any other of the participants' characteristics, medications, or medical history.

TABLE 8-4: Participants' characteristics, medications and medical history by NT-proBNP tertiles

Variable, n (column %)	NT-proBNP tertile (pmol/L)			
	Low, n=27	Mid, n=27	High, n=26	P value‡
Sex				
- Men	15 (56)	12 (44)	10 (38)	0.447
- Women	12 (44)	15 (56)	16 (62)	
Age-ethnicity				
- 75-79 years old	11 (41)	8 (30)	6 (23)	0.373
- 85-years old	16 (59)	19 (70)	20 (77)	
Smoking status				
- Current	0	1 (4)	4 (15)	0.125†
- Former	9 (35)	14 (52)	11 (42)	
Use aspirin	13 (48)	11 (41)	14 (54)	0.632
Use lipid-lowering medication	9 (33)	7 (26)	6 (23)	0.687
Use vitamin & mineral supplements	12 (46)	14 (52)	11 (44)	0.891
Hypertension	20 (74)	26 (93)	22 (85)	0.067†
Diabetes	6 (22)	4 (15)	3 (12)	0.649†
Clinically manifest CVD	14 (52)	17 (63)	22 (85)	0.038
Heart disease	8 (30)	12 (44)	20 (77)	0.002
LVH	5 (21)	4 (17)	8 (44)	0.063

Abbreviations: **LVH**: left ventricular hypertrophy; **NT-proBNP**: N-terminal pro-brain natriuretic peptide
‡P values are from Pearson chi-square test, unless specified otherwise
†P values are from Fisher's exact test

[36] This female participant had a Mini Mental State Examination (MMSE) score of <23. Therefore, the interview was conducted with a proxy interviewee.

NT-proBNP and medications

Pharmacotherapy for heart failure (HF)[37] is known to have an impact on reducing natriuretic peptides concentrations. (483, 484) This study showed a significantly higher NT-proBNP level among participants on HF pharmacotherapy than those not on the therapies, median (IQR): 57 (54) vs.29 (30), p=0.001, p=0.001. This is not unexpected because participants with a heart condition will have elevated NT-proBNP levels.

Association between NT-proBNP and clinically manifest CVD

Participants with CVD had a significantly higher NT-proBNP level than those without CVD, median (IQR) pmol/L: 54 (54) vs. 31 (38); p=0.007. This association between NT-proBNP and CVD was further examined with logistic regression adjusting for sex, age-ethnicity and smoking status. To determine if sex- and age-ethnicity had an effect on the relationship between NT-proBNP and CVD, the interaction term (sex × NT-proBNP and age-ethnicity × NT-proBNP) was included into the regression model separately. There was no association found between the interaction term (sex × NT-proBNP, p=0.556 and age-ethnicity × NT-proBNP, p=0.934) and CVD. This implies the association between NT-proBNP and CVD was the same for both sexes and all ages. Therefore, analysis was combined for both sex- and age-ethnic groups. Controlling for sex, age-ethnicity and smoking status revealed than an increased NT-proBNP level was associated with CVD, p=0.032. Because of the potential effect of HF pharmacotherapy on natriuretic peptides levels (484), this was also entered into the regression model. Adding HF pharmacotherapy into the model attenuated the association between CVD and NT-proBNP levels, p=0.073. (Appendix B: TABLE B-25, page 308) This perhaps shows the effect of treatment with HF pharmacotherapy.

Since NT-proBNP is secreted from the stressed ventricles, analysis was re-run and included only participants with heart disease (distinct from those with cerebrovascular disease). The definition of heart disease is listed in Table 3.3 (page 92) and includes ischemic heart disease, acute and old MI, HF, hypertensive heart disease, angina pectoris, cardiac arrest, cardiomegaly, abdominal aneurysm, operation/procedures related to the heart, and resection and replacement of the aorta. NT-proBNP levels were higher in participants with heart disease than without heart disease, median (IQR): 60 (77) vs. 31 (33), p<0.001 (Figure 8-2). Controlling for sex, age-ethnicity

[37] The pharmacotherapy for heart failure used by study participants includes organic nitrates, digitalis glycosides, diuretics, beta-blocking agents and agents acting on the renin-angiotensin system.

and smoking status revealed that the positive association between heart disease and increased NT-proBNP level remains statistically significant, p=0.008. When HF pharmacotherapy was added to the model, the association between heart disease and NT-proBNP level was attenuated but remain statistically significant (p=0.021). (Appendix B: TABLE B-26, page 308)

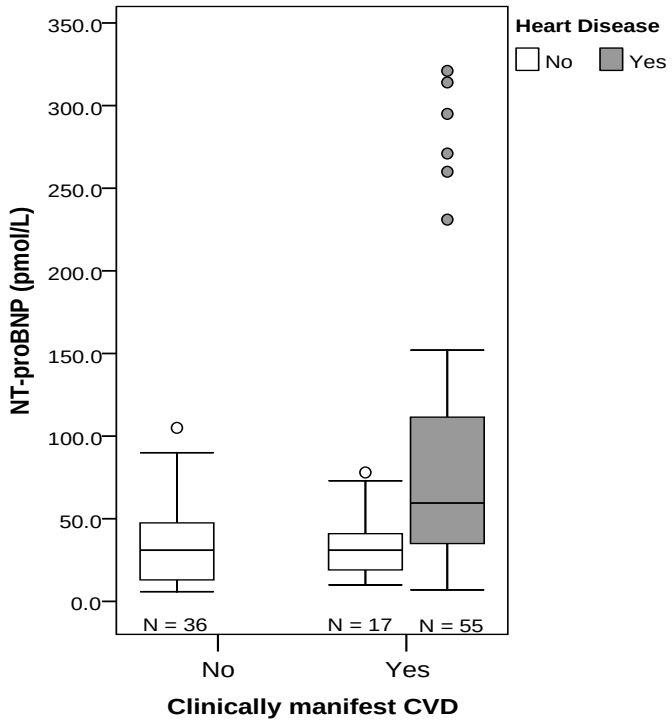


Figure 8-2: Box-plot demonstrating the distribution of NT-proBNP levels between those with and those without heart disease
Note: The NT-proBNP level of 549pmol/L for a participant with CVD was not shown in the box-plot. The Mann-Whitney U test showed a difference in NT-proBNP levels between those with and those without clinically manifest CVD, p=0.007

8.1.3 Echocardiographic measures

One hundred (97%) of the 103 participants who agreed to physical assessments had an echocardiogram; three did not have an echocardiogram due to logistical issues. Among participants who had completed an echocardiogram, ultrasound images were not available for one participant. Therefore, 99 participants had echocardiographic images measured and interpreted by an experienced cardiologist (R.N.D). Not all participants had all the echocardiography variables examined in this study due to the nature of the portable echocardiogram. The images were not satisfactory in some older adults because of the surroundings of the assessment, such as positioning of the bed and electrical interference encountered during home visits. Sixteen echocardiograms were done in the participants' residences, of which three (19%) were found to

have poor views or technical limitations. Similar issues were also experienced in 10 (12%) of the 83 echocardiograms done in local health centres; one of these was specifically attributed to obesity[38].

The echocardiographic parameters evaluated and reported here include structural and functional variables (Figure 8-3).

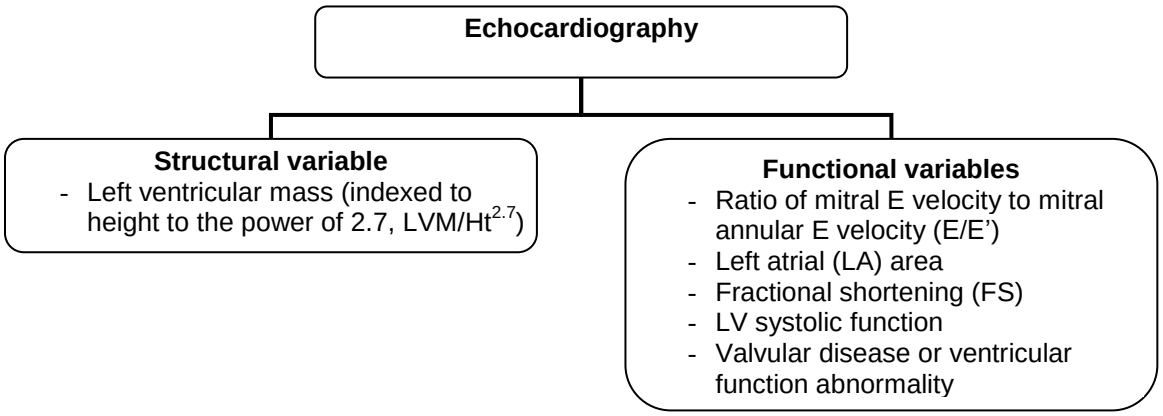


Figure 8-3: Echocardiographic measures examined in the thesis

8.1.3.1 Structural variable

Left ventricular mass

The structural variable examined in this study was left ventricular mass (LVM). Left ventricular mass values were available for 84 of the 99 participants (85%) who had an echocardiogram. $LVM/Ht^{2.7}$ was not distributed normally, i.e. most of the values clustered toward the lower end of the distribution scale with few in the upper end. The overall median (IQR) was 40.1 (28.5)$gm^{-2.7}$. The $LVM/Ht^{2.7}$ median (IQR) for men was 39.2 (28.9)$gm^{-2.7}$; the median (IQR) for women was 40.4 (29.7)$gm^{-2.7}$. The highest value (146.8$gm^{-2.7}$) comes from a 77-year-old woman with hypertension who has had heart failure, myocardial infarction and ischemic heart disease. She is a former smoker and her BMI was 36.5kg/m^2. The next value following 146.8$gm^{-2.7}$ was 92.4$gm^{-2.7}$.

Left ventricular hypertrophy, participants' characteristics, medications and medical history

Left ventricular hypertrophy (LVH) is defined as $LVM/Ht^{2.7}$ ≥48$gm^{-2.7}$ for men and ≥44$gm^{-2.7}$ for women. (444) Thirty-two (38%) participants had LVH, with the majority of these having severely enlarged LVM. (Figure 8-4)

[38] This participant is a 77-year-old woman with a BMI of 65.9kg/m2

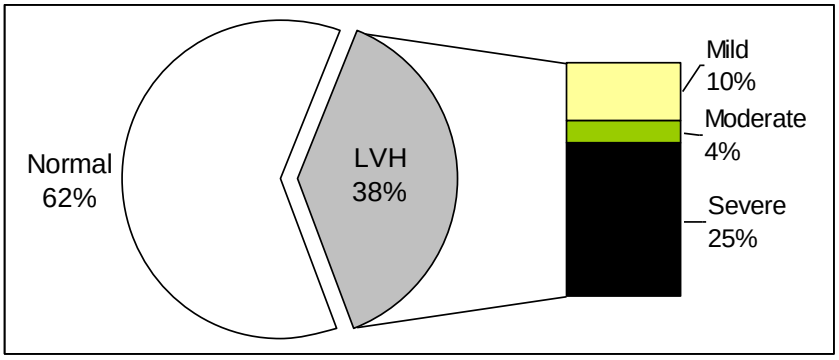


Figure 8-4 Pie-chart showing the distribution of left ventricular mass
Abbreviations: **LVH**: left ventricular hypertrophy
The proportions of LVH add to more than 38% due to rounding
Mild: $LVM/Ht^{2.7}$ ($gm^{-2.7}$) for men=49-55; women=45-51
Moderate: $LVM/Ht^{2.7}$ ($gm^{-2.7}$) for men=56-63; women=52-58
Severe: $LVM/Ht^{2.7}$ ($gm^{-2.7}$) for men≥64; women≥59

The demographic, medications, medical history, and other echocardiographic measures of participants with and without LVH are shown in TABLE 8-5. In this sample, there were differences in the distribution between those with and those without LVH in age-ethnic groups, smoking status, use of vitamin and mineral supplements, and enlarged left atrial area.

As an enlarged LVM may lead to manifestation of heart disease, the relationship between LVH and CVD was reanalysed, limiting to participants with heart disease[39]. Half of the study sample (51%) had heart disease. Among those who had LVM measured, 20 (48%) participants with heart disease had LVH (TABLE 8-5). There was a trend towards heart disease being associated with LVH but this did not reach statistical significance (p=0.072).

[39] Definition of heart disease is listed in TABLE 3-3 (page 87).

TABLE 8-5: Participants' characteristics, medications, medical history, and other echocardiographic measurements between those with and those without LVH

Variable, n (column %)	Left ventricular hypertrophy (LVH)		
	No n=52	Yes n=32	P value‡
Sex			
- Men	24 (4669)	11 (34)	0.288
- Women	28 (54)	21 (66)	
Age-ethnicity			
- 75-79 years old	8 (15)	17 (53)	<0.001
- 85-years old	44 (85)	15 (47)	
Smoking status			
- Current	0	3 (10)	0.046†
- Former	25 (48)	10 (32)	
Use aspirin	26 (50)	12 (38)	0.264
Use lipid-lowering medication	14 (27)	6 (19)	0.393
Heart failure pharmacotherapy	32 (62)	23 (72)	0.333
Use vitamin & mineral supplements	33 (64)	11 (37)	0.019
Hypertension	42 (81)	29 (91)	0.353†
Diabetes	5 (10)	7 (22)	0.197†
NT-proBNP (pmol/L), median (IQR)	34.5 (37.3)	58.0 (86)	0.051§
E/E'#			
- 8 - 15	32 (64)	17 (55)	0.212
- >15	8 (16)	10 (32)	
Enlarged left atrial (LA) area#	27 (53)	26 (90)	0.001
Abnormal factional shortening#	4 (9)	3 (9)	1.000
Clinically manifest CVD	31 (60)	23 (72)	0.255
Heart disease	22 (42)	20 (63)	0.072

Abbreviations: **CVD**: cardiovascular disease; **E/E'**: ratio of mitral E velocity to mitral annular E velocity; **NT-proBNP**: N-terminal pro-brain natriuretic peptide
‡ P values are from Pearson chi-square test, unless specified otherwise
† P values are from Fisher's exact test
§ P value from Mann-Whitney U test
# The percentages within the row were based on the total number of participants who had both the LVM values and the applicable echocardiographic variable

Left ventricular mass and medication

Pharmacotherapy for heart failure and blood pressure has an effect on the left ventricular mass. (483, 592) These include all medications listed in TABLE 5-2 (page 112) except for antithrombotic and lipid-lowering agents. The left ventricular mass for participants who are treated with heart failure and/or blood pressure medications did not differ from those not on these medications, median (IQR)$gm^{-2.7}$: 40.2 (30.9) vs. 39.6 (27.3); p=0.709.

Left ventricular mass and NT-proBNP

BNP, a cardiac hormone, is secreted with increased ventricular stretch and wall tension. (427) At univariate level, NT-proBNP was not associated with LVM (p=0.105). Controlling for sex, age-ethnicity and smoking status revealed that NT-proBNP is positively associated with LVM (standardised ß=0.250, p=0.027). This significant association remains independent of pharmacotherapy for heart failure (standardised ß=0.239, p=0.038).

Association between left ventricular mass and clinically manifest CVD

Fifty-four of the 84 participants (64%) who had LVM measured, had CVD. Participants with CVD did not have a larger LVM than those without CVD, median (IQR)$gm^{-2.7}$: 43.0 (31.2) vs. 36.9 (17.3), p=0.143. The relationship between CVD and LVM was reanalysed comparing LVM in those with and those without heart disease, as defined in Table 3.3 (page 92). Participants with heart disease have a marginally larger LVM than those without heart disease, median (IQR)$gm^{-2.7}$: 45.8 (29.9) vs. 36.9 (16.5), p=0.049. (Figure 8-5)

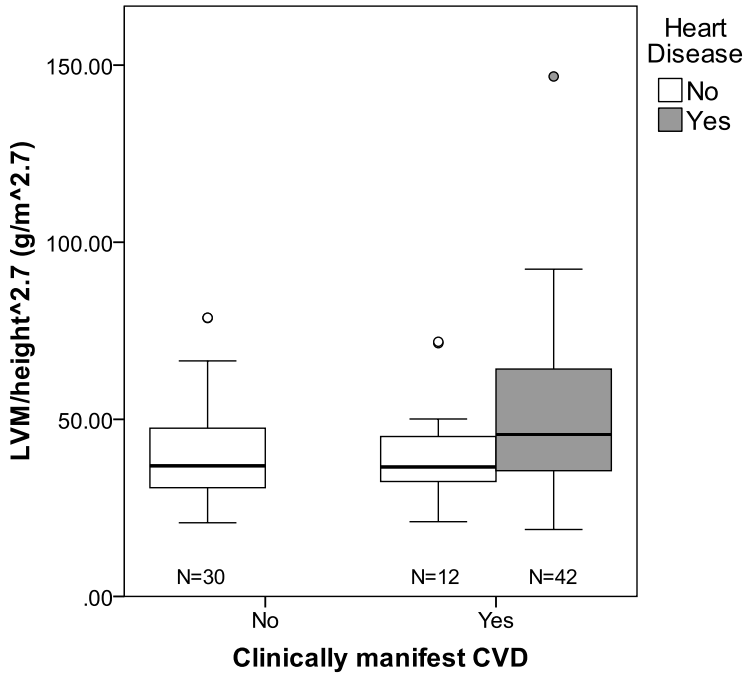


Figure 8-5 Left ventricular mass in those with and those without heart disease

The association between LVM and CVD was further examined using logistic regression controlling for sex, age-ethnicity and smoking status. To determine if age-ethnicity had an effect on the relationship between LVM and CVD, the interaction term (age-ethnicity × LVM) was included into the regression model separately. There was no association between the interaction term and

CVD (p=0.681). This implies the association between LVM and CVD was the same for all ages. Therefore, analysis was combined for both age-ethnic groups. Since pharmacotherapy for heart failure and blood pressure has an effect on the LVM, it was also entered into the regression model. In both models, with and without medications, LVM was not associated with CVD (p=0.124 and p=0.115 respectively). (Appendix B: TABLE B-27, page 308;) The dependent variable (CVD) was then replaced with heart disease, first controlling for sex, age-ethnicity and smoking status, and then including pharmacotherapy for heart failure and blood pressure. In both models, LVM was not statistically associated with heart disease (both models p=0.078). (Appendix B: TABLE B-28, page 309) Although there was no statistically significant association between LVM with CVD or heart disease, the association between LVM with heart disease was stronger than the association between LVM and clinically manifest CVD.

8.1.3.2 Left ventricular functional variables

Ratio of mitral E velocity to mitral annular E velocity

The ratio of mitral E velocity to mitral annular E velocity (E/E') value is a measure of left ventricular (LV) filling pressure. E/E' values were available for 94 participants (95%). E/E' distribution was skewed to the right of the median (positively skewed), i.e. more values clustered at the lower end of the distribution scale with few values in the upper end. The median (IQR) was 11.6 (5.0). Fifteen (16%) participants had normal LV filling pressure (E/E'<8), 19 (20%) had elevated values (E/E'>15), and the majority (64%) had intermediate values (E/E' 8–15) (TABLE 8-6). The participants' characteristics, medications, medical history, and other echocardiographic measures across the three categories of E/E' are presented in TABLE 8-6. There was an increased prevalence of diabetes across E/E' categories (p=0.004). The distribution across the three categories of E/E' was not different in other participants' characteristics, medications, medical history, and other echocardiographic measures.

TABLE 8-6: Participants' characteristics, medications, medical history, and other echocardiographic measurements by three categories of E/E'

Variable, n (column %)	E/E'			
	Normal n=15	Intermediate n=60	Elevated n=19	P value‡
Sex				
- Men	8 (53)	30 (50)	5 (26)	0.159
- Women	7 (47)	30 (50)	14 (74)	
Age-ethnicity				
- 75-79 years old	6 (40)	16 (27)	5 (26)	0.570†
- 85-years old	9 (60)	44 (73)	14 (74)	
Smoking status				
- Current	0	4 (7)	1 (5)	0.834†
- Former	6 (40)	25 (42)	10 (53)	
Use aspirin	5 (33)	29 (48)	8 (42)	0.561
Use lipid-lowering medication	3 (20)	16 (27)	4 (21)	0.831†
Heart failure pharmacotherapy	7 (47)	39 (65)	15 (79)	0.147
Hypertension	14 (93)	50 (83)	18 (95)	0.400†
Diabetes	3 (20)	4 (7)	7 (37)	0.004†
LVH#	4 (29)	17 (35)	10 (56)	0.212
Enlarged LA area#	10 (67)	36 (64)	14 (74)	0.754
Abnormal FS%#	2 (14)	4 (9)	1 (6)	0.737
Clinically manifest CVD	9 (60)	41 (68)	13 (68)	0.773†
Heart disease§	7 (47)	32 (53)	10 (53)	0.898

Abbreviations: **CVD**: cardiovascular disease; **E/E'**: ratio of mitral E velocity to mitral annular E velocity; **FS%**: percentage of fractional shortening; **LA**: left atrial; **LVH**: left ventricular hypertrophy
‡ P values are from Pearson chi-square test, unless specified otherwise
† P values are from Fisher's exact test
# The percentages within the row were based on the total number of participants who had both the E/E' values and LVH; LA area; and FS (%), respectively
§ Definition of heart disease, (page 92)

Left atrial (LA) area

Left atrial (LA) area reflects atrial function and increased LA area is related to LV diastolic dysfunction. LA area was available for 94 of the 99 participants (95%) who had an echocardiogram. Values of LA area were skewed to the right of the median (positively skewed), i.e. the majority of the values were clustered toward the lower end of the distribution scale with few values in the upper end. The median (IQR) was 23(8.6)cm^2. There were two outliers for LA area: 112.0cm^2 from an 85-year-old woman and 59.0cm^2 from a 76-year-old man. Both participants have hypertension but only the man had heart failure, myocardial infarction and ischemic heart disease. He was a current smoker with BMI 33.7kg/m^2, LVM/$Ht^{2.7}$ 64.2 $gm^{-2.7}$ and NT-proBNP 321pmol/L.

Sixty-four (68%) participants have an enlarged left atrial (LA) area (≥20cm^2). The majority of abnormality is with mild severity (Figure 8-6).

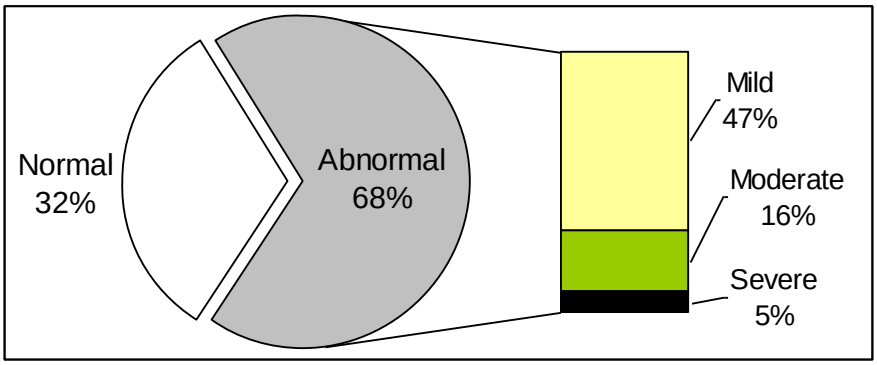


Figure 8-6 Pie-chart for partition of normal and enlarged left atrial (LA) area
Mild: LA area=20-30cm^2; Moderate: LA area=30-40cm^2; Severe: LA area≥40cm^2

The demographic, medications, medical history, and other relevant echocardiographic measurements of participants with normal and enlarged LA area are presented in TABLE 8-7. There was a difference in the distribution between normal and enlarged left atrial area for age-ethnic groups (p=0.004). The prevalence of LVH and CVD was higher among those with enlarged LA area than those with normal LA area (p<0.01). There was no difference in the distribution between those with normal and enlarged LA area in any other participants' characteristics, medications, medical history, and other echocardiographic measures.

TABLE 8-7: Participants' characteristics, medications, medical history, and other echocardiographic measurements for those with and those without enlarged left atrial area

Variable, n (column %)	Left atrial area		
	Normal n=30	Enlarged n=64	P value‡
Sex			
- Men	11 (37)	33 (52)	0.177
- Women	19 (63)	31 (48)	
Age-ethnicity			
- 75-79 years old	3 (10)	25 (39)	0.004
- 85-years old	27 (90)	39 (61)	
Smoking status			
- Current	0	5 (8)	0.171†
- Former	17 (57)	26 (41)	
Use aspirin	13 (43)	28 (44)	0.970
Use lipid-lowering medication	8 (27)	13 (20)	0.491
Heart failure pharmacotherapy	16 (53)	45 (70)	0.108
Hypertension	27 (90)	54 (84)	0.540†
Diabetes	3 (10)	13 (20)	0.215
LVH #	3 (11)	26 (49)	0.001
E/E' #			0.754
- 8 - 15	20 (37)	36 (60)	
- >15	5 (17)	14 (23)	
Abnormal FS% #	4 (16)	3 (6)	0.213
Clinically manifest CVD	13 (43)	49 (77)	0.002
Heart disease §	8 (27)	40 (63)	0.001

Abbreviations: **CVD**: cardiovascular disease; **E/E'**: ratio of mitral E velocity to mitral annular E velocity; **FS%**: percentage of fractional shortening; **LVH**: left ventricular hypertrophy
‡ P values are from Pearson chi-square test, unless specified otherwise
† P values are from Fisher's exact test
# The percentages within the row were based on the total number of participants who had both the LA area values and LVH; E/E'; and FS (%), respectively
§ Definition of heart disease is listed in Table 3.3 (page 92)

Fractional shortening

The percentage of fractional shortening (FS) was used as an index of LV systolic function. In this study sample, FS was calculated for 79 of the 99 participants (79%) who had an echocardiogram. The percentage of fractional shortening was distributed normally, i.e. equal number of values at both ends of the scale. The mean (SD) for FS was 39.3(9.9). According to the American Society of Echocardiography's Guideline (444), seven (9%) participants had an abnormal FS% (men: <25%; women: <27%). Two of these seven participants, a man and a woman, had a severe abnormality (FS≤14% for the man and ≤16% for the woman) and the rest had a mild abnormality. Of the seven participants with abnormal FS%, five were women, four were aged 85 years old, one currently smoked and two were former smokers, five had hypertension, and four had heart disease.

The participants' characteristics, used of medications, medical history, and other relevant echocardiographic measurements of participants with normal and abnormal FS% are presented in TABLE 8-8. There was no difference in the distribution between normal and abnormal FS% in any of the participants' characteristics, medications, medical history, and other echocardiographic measures (TABLE 8-8).

TABLE 8-8: Participants' characteristics, medications, medical history, and other echocardiographic measurements for those with normal and abnormal percentage of fractional shortening

Variable, n (column %)	Percentage of fractional shortening		
	Normal n=72	Abnormal n=7	P value[†]
Sex			
- Men	30 (42)	2 (29)	0.695
- Women	42 (58)	5 (71)	
Age-ethnicity			
- 75-79 years old	22 (31)	3 (43)	0.673
- 85-years old	50 (69)	4 (57)	
Smoking status			
- Current	2 (3)	1 (14)	0.346
- Former	30 (42)	2 (29)	
Use aspirin	31 (43)	2 (29)	0.693
Use lipid lowering medication	15 (21)	2 (29)	0.693
Heart failure pharmacotherapy	45 (63)	5 (71)	1.000
Hypertension	62 (86)	5 (71)	0.287
Diabetes	10 (14)	1 (14)	1.000
LVH [#]	29 (40)	3 (43)	1.000
E/E' [#]			
- 8 - 15	41 (59)	4 (57)	0.737
- >15	16 (23)	1 (14)	
Enlarged left atrial (LA) area [#]	47 (69)	3 (43)	0.213
Clinically manifest CVD	44 (61)	5 (71)	0.703
Heart disease	34 (47)	4 (57)	0.705

Abbreviations: **CVD**: cardiovascular disease; **E/E'**: ratio of mitral E velocity to mitral annular E velocity; **LVH**: left ventricular hypertrophy

[†]Examined with Fisher's exact test because more than 20% of the expected frequencies were less than 5

[#]The percentages within the row were based on the total number of participants who had both the FS(%) and LVH; E/E'; and LA area, respectively

Left ventricular (LV) systolic function

Left ventricular (LV) systolic function was reported as normal, mild, moderate or severe. The majority of the participants (92 of 97 participants) had normal LV systolic function, three participants had mild, one had moderate and one had severe impairment in LV systolic function. Of the five participants with impaired LV systolic function, three were men, three were former smokers, three had hypertension, one had diabetes, and four had heart disease. The 76-year-old man with severe

impairment of the LV systolic function had hypertension, myocardial infarction, angina, heart failure, CABG, a pacemaker implant, and has had an angioplasty. Additionally, he had LVH and an enlarged LA area.

Ventricular function abnormality or valve disease

The presence of ventricular function abnormality or valve disease was able to be established in all 99 participants who completed echocardiography. One-quarter of the participants were found to have a ventricular function abnormality or valve disease. The participants' characteristics, used of medications, medical history, and other relevant echocardiographic measurements of participants with and without ventricular function abnormality or valve disease are presented in TABLE 8-9. There was no difference in the distribution between the two groups in any of the participants' characteristics, medications, medical history, and other echocardiographic measures.

TABLE 8-9: Participants' characteristics, medications, medical history, and other echocardiographic measurements for those with and without ventricular function abnormality or presence of valve disease

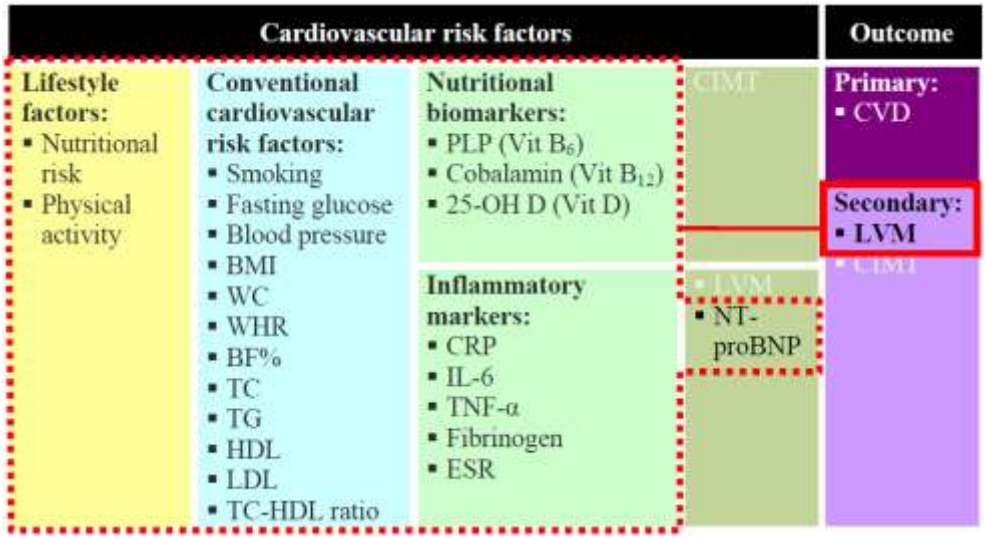
Variable, n (column %)	Ventricular function abnormality/presence of valve disease		
	No n=75	**Yes n=24**	**P value‡**
Sex			
- Men	38 (51)	8 (33)	0.138
- Women	37 (49)	16 (67)	
Age-ethnicity			
- 75-79 years old	22 (29)	7 (29)	0.988
- 85-years old	53 (71)	17 (71)	
Smoking status			
- Current	3 (4)	2 (8)	0.388†
- Former	31 (42)	12 (50)	
Use aspirin	36 (48)	9 (38)	0.369
Use lipid lowering medication	21 (28)	4 (17)	0.266
Heart failure pharmacotherapy	47 (63)	18 (75)	0.516
Hypertension	65 (87)	20 (83)	0.739†
Diabetes	12 (16)	5 (21)	0.551†
LVH #	22 (36)	10 (46)	0.408
E/E' #			
- 8 - 15	48 (66)	12 (57)	0.587†
- >15	13 (18)	6 (29)	
Enlarged left atrial (LA) area #	45 (64)	19 (79)	0.177
Abnormal FS% #	4 (7	3 (14)	0.391†
Clinically manifest CVD	50 (67)	14 (58)	0.472
Heart disease	38 (51)	12 (50)	0.955

Abbreviations: **CVD**: cardiovascular disease; **E/E'**: ratio of mitral E velocity to mitral annular E velocity; **FS%**: percentage of fractional shortening; **LVH**: left ventricular hypertrophy

‡P values are from Pearson chi-square test, unless specified otherwise
†Examined with Fisher's exact test because more than 20% of the expected frequencies were less than 5
#The percentages within the row were based on the total number of participants who had both the ventricular function/valve disease results and LVH; E/E'; LA area; and FS (%), respectively.

8.1.3.3 Associations between left ventricular mass with CV risk factors

This section will present the association between LVM (the secondary outcome, $LVM/Ht^{2.7}$) and behavioural measures, conventional CV risk factors, nutrition biomarkers, and inflammatory markers.



Univariate analysis was performed to determine the association between LVM with each of the lifestyle factors, conventional CV risk factors, nutritional biomarkers, inflammatory markers, NT-proBNP, and CIMT. The correlations between these variables and LVM are shown in TABLE 8-10. There were significant correlations between LVM with PASE score, BMI, waist circumference (WC), and body fat percentage (BF%). These relationships were investigated further using a linear regression model to control for possible confounders.

TABLE 8-10: Correlation between left ventricular mass (LVM/Ht$^{2.7}$) with lifestyle factors, conventional CV risk factors, nutritional biomarkers, inflammatory markers, NT-proBNP and CIMT

	Variables	Correlation coefficient	P value[#]
Lifestyle factors	SCREEN II score	-0.205	0.064
	PASE score	**0.219**	**0.047**
Conventional CV risk factors	Fasting serum glucose	0.163	0.168
	Systolic blood pressure (SBP)	0.104	0.345
	Diastolic blood pressure (DBP)	0.040	0.718
	Total cholesterol (TC)	-0.110	0.351
	Triglyceride (TG)	0.094	0.427
	High-density lipoprotein (HDL)	-0.160	0.174
	Low-density lipoprotein (LDL)	-0.111	0.348
	TC-HDL ratio	0.051	0.667
	Body mass index (BMI)	**0.555**	**<0.001**
	Waist circumference (WC)	**0.391**	**<0.001**
	Waist-to-hip ratio (WHR)	0.134	0.229
	Body fat percentage (BF%)	**0.322**	**0.003**
Nutritional biomarkers	Pyridoxal 5' phosphate (PLP)	0.035	0.773
	Cobalamin	0.145	0.217
	25 hydroxyvitamin D (25-OH D)	0.004	0.977
Inflammatory markers	C-reactive protein (CRP)	0.022	0.853
	Interleukin-6 (IL-6)	0.194	0.131
	Tumour necrosis factor-alpha (TNF-α)*	0	1
	Erythrocyte sedimentation rate (ESR)	-0.036	0.759
	Fibrinogen	-0.005	0.967
N-terminal pro-brain natriuretic peptide (NT-proBNP)		0.203	0.105
CIMT		-0.037	0.741

[#] P values are from Spearman's correlation test

* Analysed as categorical data, i.e. <1.0 and ≥1.0pg/mL

Multivariate analyses

Linear regression models were constructed to determine the association between LVM and lifestyle factors, conventional CV risk factors, nutritional biomarkers, inflammatory markers, NT-proBNP, and CIMT. Since LVM was not normally distributed, it was $\log_{10}$ transformed to improve its distribution. The $\log_{10}$ transformed LVM was entered as the dependent variable in the linear regression model, and the covariates were sex, age-ethnicity and smoking status. And because some pharmacology intervention would have an impact on the variable of interest, the relevant medication was included in the appropriate models. Variables associated with $\log_{10}$-LVM/Ht$^{2.7}$ at $p \leq 0.1$ after controlling for sex, age-ethnicity, smoking status, and relevant medications were entered together into a multivariable model. BMI, WC, WHR, BF% were entered separately into the model due to collinearity. Variables that did not contribute to the overall fit of the model were manually removed.

The results of the above-planned multivariate analyses are as follows. Controlling for sex, age-ethnicity and smoking status revealed that BMI, WC and BF% remained significantly associated with LVM (log_{10}-LVM/$Ht^{2.7}$). PASE score, which was correlated with LVM at the univariate level, was no longer associated with LVM. Relevant pharmacotherapy having an impact on blood pressure, lipid profile, inflammatory markers and NT-proBNP level was added to the relevant regression model (TABLE 8-11). Controlling for relevant medications revealed that TG, LDL, CRP, NT-proBNP and SCREEN II score were associated with log_{10}-LVM/$Ht^{2.7}$ at $p \leq 0.1$. As there were extreme outliers in these variables, sensitivity analyses were performed. One outlying value caused a spurious effect in the CRP model (Model 18b). This value was not included in the multivariable analysis as it probably reflects presence of autoimmune diseases e.g. rheumatoid arthritis. The outliers from TG and NT-proBNP were not excluded from the analysis because they are probable values related to CVD[40]. To establish the final model, SCREEN II score, TG, LDL, and NT-proBNP were all entered into a model, with BMI, WC, WHR and BF% entered separately.

TABLE 8-11: Linear regression models examining the association between left ventricular mass (log_{10}-LVM/$Ht^{2.7}$) and lifestyle factors, conventional CV risk factors, nutritional biomarkers, inflammatory markers, NT-proBNP and CIMT

	Model	Variables	Regression coefficient (95% CI)	P value
Lifestyle factors	1	SCREEN II Score	-0.006 (-0.012 – 0.000)	**0.055**
	2	PASE score	5.02E-005 (-0.001 – 0.001)	0.876
Conventional CV risk factors	3	Fasting serum glucose	0.020 (-0.020 – 0.059)	0.323
	3a	+ glucose-lowering med	0.016 (-0.026 – 0.058)	0.442
	4	SBP	0.001 (0.000 – 0.003)	0.115
	4a	+ BP med	0.001 (0.000 – 0.003)	0.117
	5	DBP	0.001 (-0.002 – 0.004)	0.622
	5a	+ BP med	0.001 (-0.002 – 0.004)	0.608
	6	TC	-0.019 (-0.054 – 0.016)	0.282
	6a	+ lipid-lowering med	-0.025 (-0.061 – 0.010)	0.162
	7	TG	0.057 (0.004 – 0.110)	0.035
	7a	+ lipid-lowering med	0.059 (0.006 – 0.111)	**0.029**

[40] Sensitivity analyses were done for these variables. The outlying values of TG (4.0 & 4.8mmol/L) contribute to the significant association with log10-LVM/Ht2.7 (from p=0.088 to p=0.029). The outlying value from BNP (549pmol/L) did not change the significance level with log10-LVM/Ht2.7.

TABLE 8-11 continued

Conventional CV risk factors	8	HDL	-0.031 (-0.119 – 0.056)	0.477
	8a	+ lipid-lowering med	-0.035 (-0.122 – 0.053)	0.433
	9	LDL	-0.033 (-0.072 – 0.007)	0.104
	9a	+ lipid-lowering med	-0.041 (-0.081 – -0.001)	**0.046**
	10	TC-HDL ratio	0.002 (-0.036 – 0.040)	0.922
	10a	+ lipid-lowering med	-0.001 (-0.040 – 0.037)	0.942
	11	BMI	0.014 (0.003 – 0.008)	**<0.001**
	12	WC	0.005 (0.003 – 0.008)	**<0.001**
	13	WHR	0.574 (0.034 – 1.114)	**0.037**
	14	BF%	0.007 (0.003 – 0.012)	**0.003**
Nutrition biomarkers	15	PLP	0.000 (0.000 – 0.000)	0.158
		+ nutr suppl	0.000 (0.000 – 0.000)	0.289
	16	Cobalamin	-5.0E-006 (0.000 – 0.000)	0.956
		+ nutr suppl	2.74E-006 (0.000 – 0.000)	0.975
	17	25-OH D	0.001 (-0.001 – 0.003)	0.191
		+ nutr suppl	0.001 (-0.001 – 0.003)	0.239
Inflammatory markers	18	CRP	-0.002 (-0.006 – 0.001)	0.139
	18a	+ lipid-lowering med [§]	-0.003 (-0.006 – 0.001)	0.102
	18b	+ lipid-lowering med [‡]	-0.002 (-0.012 – 0.008)	0.673
	19	IL-6	-0.002 (-0.009 – 0.005)	0.596
	19a	+ lipid-lowering med [§]	-0.002 (-0.010 – 0.005)	0.518
	20	TNF-α*	0.023 (-0.110 – 0.156)	0.733
	20a	+ lipid-lowering med [§]	0.020 (-0.113 – 0.153)	0.762
	21	Fibrinogen	-0.014 (-0.034 – 0.006)	0.174
	21a	+ lipid-lowering med [§]	0.146 (0.035 – 0.005)	0.146
	21b	+ lipid-lowering med [‡§]	0.019 (-0.033 – 0.072)	0.462
	22	ESR	-9.1E-005 (-0.002 – 0.002)	0.936
	22a	+ lipid-lowering med [§]	-2.7E-005 (-0.002 – 0.002)	0.981
	23	NT-proBNP	0.000 (0.000 – 0.001)	0.021
	23a	+ med for HF	0.000 (0.000 – 0.001)	**0.025**
	24	CIMT	0.022 (-0.105 – 0.149)	0.730
	24a	+ BP med	0.019 (-0.110 – 0.147)	0.774

Abbreviations: **25-OH D:** 25-hydroxyvitamin D; **BMI:** body mass index; **BF%:** percentage of body fat; **BP:** blood pressure; **CIMT:** carotid intima-media thickness; **CRP:** C-reactive protein; **DBP:** diastolic blood pressure; **ESR:** erythrocyte sedimentation rate; **HDL:** high-density lipoprotein; **HF:** heart failure; **IL-6:** Interleukin-6; **LDL:** low-density lipoprotein; **med:** medications; **NT-proBNP**: N-terminal pro-brain natriuretic peptide; **nutr suppl:** nutritional supplements; **PASE:** Physical Activity Scale for the Elderly; **PLP:** Pyridoxal 5' phosphate; **SCREEN II:** Seniors in the Community: Risk Evaluation for Eating and Nutrition, Version II; **SBP:** systolic blood pressure; **TC:** total cholesterol; **TG:** triglyceride; **TNF-α:** tumour necrosis factor-alpha; **WC:** waist circumference; **WHR:** waist-to-hip ratio

Note:

- Each line is a separate regression model controlling for sex, age-ethnicity and smoking status

- Models 'a' and 'b' were further adjusted for the effect of relevant medication in addition to sex, age-ethnicity and smoking status.

§ Replacing lipid-lowering medications with aspirin did not change the direction and strength of the association between the respective variables with $\log_{10}$-LVM/$Ht^{2.7}$

‡ Excluded outlier CRP 97mg/L

* Entered as categorical data, i.e. <1.0 and ≥1.0pg/mL

ɔ Excluded outlier fibrinogen >18g/L

Variables included in the full models, in addition to sex, age-ethnicity, smoking status, and lipid-lowering medications, were lifestyle factor (SCREEN II score), conventional CV risk factors (TG, LDL, and anthropometric measures) and NT-proBNP. Among the four anthropometric measures, BMI and WC contributed significantly to the fit of the models (Model 1 and Model 2, TABLE 8-12). Between TG and LDL, LDL contributed more to the models than TG. Thus, TG was removed from the models (Model 1a and Model 2a). Between Model 1a (Model with BMI) and 2a (Model with WC), the former model explained 42% of the variance of LVM whereas the latter explained 40% of the variance. An interesting result from the models was a significant inverse association between LDL and LVM. It is not sure if this relationship is expected in those living to advanced age.

TABLE 8-12: Multivariate regression models for $\log_{10}$- LVM/$Ht^{2.7}$

	Model 1 R^2 = 0.407 **Regression coefficient (95% CI)**	**P value**	**Model 1a** R^2 = 0.418 **Regression coefficient (95% CI)**	**P value**
SCREEN II score	-0.003 (-0.009 – 0.003)	0.264	-0.003 (-0.009 – 0.002)	0.247
TG	0.000 (-0.051 – 0.052)	0.988		
LDL	-0.035 (-0.070 – 0.000)	0.048	-0.035 (-0.069 – -0.001)	0.046
NT-proBNP	0.000 (0.000 – 0.001)	0.239	0.000 (0.000 – 0.001)	0.227
BMI	0.012 (0.006 – 0.018)	<0.001	0.012 (0.006 – 0.018)	<0.001
	Model 2 R^2 = 0.392 **Regression coefficient (95% CI)**	**P value**	**Model 2a** R^2 = 0.404 **Regression coefficient (95% CI)**	**P value**
SCREEN II score	-0.001 (-0.008 – 0.005)	0.662	-0.001 (-0.008 – 0.005)	0.625
TG	0.004 (-0.048 – 0.056)	0.868		
LDL	-0.046 (-0.082 – -0.010)	0.014	-0.046 (-0.081 – -0.010)	0.013
NT-proBNP	0.000 (0.000 – 0.001)	0.139	0.000 (0.000 – 0.001)	0.136
WC	0.005 (0.002 – 0.008)	0.001	0.005 (0.002 – 0.007)	<0.001

Abbreviations: **BMI**: body mass index; **LDL**: low-density lipoprotein; **NT-proBNP**: N-terminal pro-brain natriuretic peptide; **SCREEN II**: Seniors in the Community: Risk Evaluation for Eating and Nutrition, Version II; **TG**: triglyceride; **WC**: waist circumference

All models were controlled for sex, age-ethnicity, smoking status, and lipid- lowering medications.

8.1.3.4 Summary of echocardiography measures

In summary, 64 (65%) participants with echocardiography abnormalities had CVD. The number of echocardiography abnormalities examined in this study ranges between zero and five; median was two. The proportions of participants with clinical evidence of CVD increased with the number of echocardiography abnormalities. Among participants without CVD, 94% of this group had at least one abnormal echocardiographic measure and only 6% of them had normal echocardiography measures. (Figure 8-7)

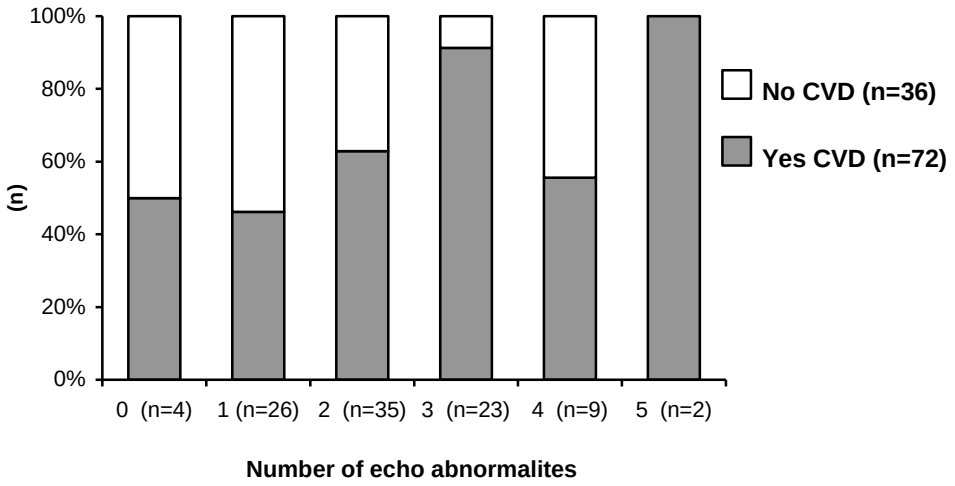


Figure 8-7: Number of echocardiography abnormalities in participants with and participants without heart disease or cardiovascular disease
Abbreviations: **CVD**: cardiovascular disease; **HD**: heart disease
Note: The numbers in the chart will not add up to the total number of CVD in the entire study sample

The most common abnormal echocardiographic measure found in this sample was an enlarged LA area (n=64, 68%), attributed to long term LV diastolic dysfunction. This was followed by LVH (n=32, 38%), abnormal ventricle function/presence of valve disease (n=24, 24%), and elevated LV filling pressure (n=19, 20%). LV systolic dysfunction, determined by percentage of fractional shortening and clinical evaluation by an experienced cardiologist, was found in five participants (5%). The details of echocardiographic measures between those with and those without heart disease/clinically manifest CVD are show in Figure 8-8.

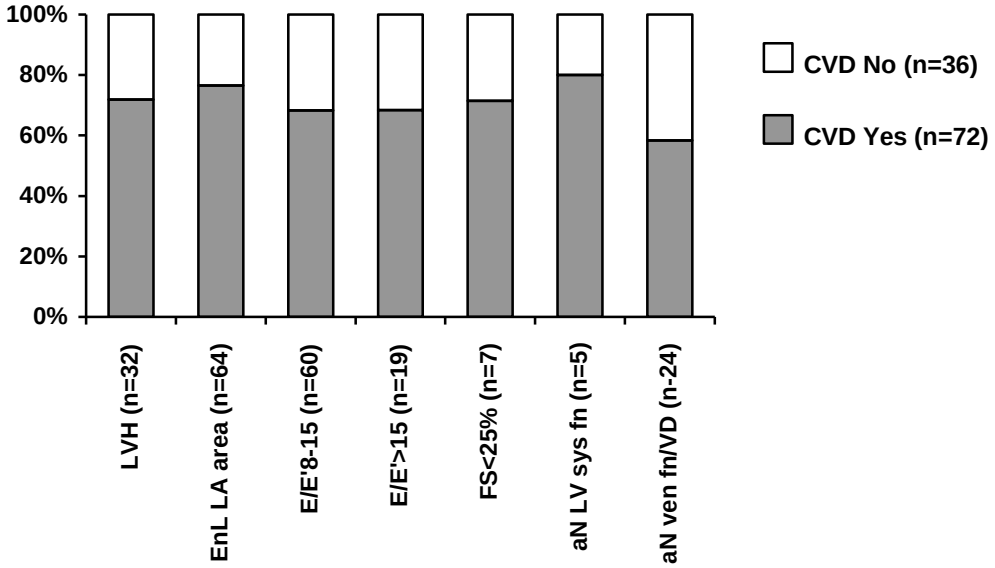


Figure 8-8: Specific echocardiographic measures between those with and those without CVD
Abbreviations: **aN LV sys fn**: abnormal left ventricular systolic function; **aN ven fn/VD**: abnormal ventricular function/valve disease; **CVD**: cardiovascular disease; **EnL LA area**: enlarged left atrial area; **HD**: heart disease; **LVH**: left ventricular hypertrophy
Note: The numbers in the chart will not add up to the total number of CVD in the entire study sample

8.2 Discussion

8.2.1 Carotid intima-media thickness

In this study, there were many participants having normal to moderately increased CIMT and few having markedly increased CIMT, a distribution pattern similar to the Atherosclerosis Risk in Communities (ARIC) study. (389) To the candidate's knowledge, this is the first study reporting CIMT values in people of advanced age. The CIMT median for this sample of those living to advanced age was 1.07mm. Based on the reference range established by the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC), more than half of the participants were categorised as having increased IMT. This proportion is expected for those in advanced age, as CIMT increases by 0.01mm per year in the general population. (389, 390) The 75th percentile of the CIMT value for this sample was 1.206mm and above. The 75th percentile of the CIMT has been considered to be an indication of early atherosclerosis. (480) Of the 24 participants with CIMT above the 75th percentile, one-third did not have clinically manifest CVD. If increased CIMT is considered sub-clinical CVD then this study demonstrates that sub-clinical CVD is common among those of advanced age.

In the Rotterdam Study, the risk of stroke increased for those with CIMT greater than 0.75mm and the risk of first myocardial infarction increased if the baseline CIMT was 0.822mm or greater. (397) In the Multi-Ethnic Study of Atherosclerosis (MESA) which enrolled participants aged between 45 and 84 years, the risk of a CVD event increased with a baseline CIMT of 0.79mm or greater. (395) The current study did not find an association between CIMT and CVD, even after adjusting for age, which is considered a major confounder for increased CIMT. (389) This finding is unexpected considering studies with younger populations found CIMT was associated with cardiovascular events. (379) However, in one community-based prospective cohort study of men aged between 73 and 94 years old (mean age 79 years), CIMT was not predictive of all cause- and CVD mortality. (28) To date, the precise predictive value of CIMT for CVD risk is still not conclusively established. This may be because of the multiple measurement sites for CIMT. There was a segment-specific CIMT association with cardiovascular risk factors (593) and coronary disease. (594) The common CIMT has a stronger relation to conventional CV risk factors than the bifurcation or internal CIMT (593), whereas the internal CIMT has a stronger relationship with CHD and clinically manifest atherosclerotic disease than the common CIMT. (382) In view of this, a composite endpoint of carotid intima-media thickening consisting both right and left bifurcation, internal and/or common carotid may be a more reliable index of atherosclerosis. (479)

Alternatively, the predictive value of CIMT is likely to be CVD-specific because of the pathophysiology of the disease and disease progression. In this study, when the analysis examining the association between CVD and CIMT was narrowed to atherosclerotic CVD, the result remained similar, i.e. no association between CIMT and atherosclerotic CVD. In the MESA study, CIMT was a better predictor for stroke than for CHD. (395) Furthermore, the burden of the systemic atherosclerotic disease profile probably overcame the single risk factor effect (i.e. that of the carotid artery alone). Therefore, disaggregating the associations according to specific outcomes may be more meaningful. This will be a challenge in the advanced-age population due to the heterogeneity of the group. The sample size of a subpopulation would limit the power of the study to detect any associations between the variables of interest.

Furthermore, the study participants' successful vascular adaptations to chronic changes may have nullified the association between CIMT and CVD. Studies have shown that shear stress is associated with atherosclerosis and is inversely related to increase CIMT. (595) Although reduced

blood flow enhanced intima proliferation, the endothelium remained viable. (596) The association between CIMT and atherosclerosis is possibly due to increased collagen density in the medial layer with a stable or reduced amount of elastin leading to arterial stiffening. (597) Additionally, the increased thickness of the intima may restrict the access of nitric oxide (NO), a potent vasodilator factor, to the media. (598) But this arterial vasodilation impairment is possibly compensated for by an increased expression of endothelial NO synthase as seen in some experimental studies in rat aorta. (597) Linking up these evidences, it is reasonable to assume there may be an operating threshold in place for these robust adaptive/compensatory mechanisms before the development of pathological conditions occurs. Genetic components may have a role to play in this adaptive/compensatory mechanism. CIMT is highly heritable (599) but lifestyle factors have a major role in predisposition to a genetically related disease. This study could have recruited survivors among the elderly population, possibly resulting from a genetic endowment coupled with a healthy lifestyle. Future studies exploring the gene-environment interactions may provide valuable insights enabling development of appropriate lifestyle interventions.

Additionally, there could be measurement error in measuring CIMT. Nevertheless, this is not likely as every precautionary step had been observed to ensure the accuracy of the CIMT measurement. Carotid IMT images were obtained by qualified and experienced sonographers, and off-line measurements was undertaken by one trained person using an automated edge detection programme. A random sample of 10 CIMT images was visually re-assessed and verified by an experienced trainer cum researcher in CIMT. The visually re-assessment between the raters were to the satisfaction of the trainer.

Lastly, although every possible confounding factor has been considered while examining the relationship between CIMT and CVD, it is possible there are unknown confounding factors which could mask the association between CIMT and CVD. Increased blood pressure is a well established CV risk factor contributing to an increased CIMT. (391) Anti-hypertensive medication has been reported to regress CIMT. (378, 381) In this study, there was no association between CIMT and systolic blood pressure after adjustment for sex, age-ethnicity, smoking status and blood pressure-lowering medications. This, again, can probably be explained by the segment-specific relationship of the carotid artery to blood pressure. It has been reported that hypertension and systolic blood pressure account for changes in the internal carotid arteries but not the bifurcation

and common carotid arteries (391). This emphasises the need to have a composite of CIMT measurements for assessment of carotid atherosclerosis in advanced age. The insignificant association between systolic blood pressure and CIMT in this study is probably a type II error attributed to the small sample size. Nevertheless, there seems to be a trend towards a positive association between systolic blood pressure and CIMT. A prospective longitudinal study examining the association between the proportional changes in CIMT in relation to changes in blood pressure over time would provide a better understanding of the contributory effect of blood pressure to CIMT. The effect of blood pressure-lowering medications in reversing CIMT observed in younger hypertensive adults (378) has yet to be determined in the elderly population. But the oldest adults (80 years and above) treated for hypertension had similar clinical benefits to those observed in younger populations, i.e. substantial reduction in risk of CVD events and mortality. (202) This favourable outcome could be through the CIMT pathway but this needs to be confirmed in future studies.

The predictive value of CIMT for CVD is still in an exploratory phase. A standardised protocol addressing the heterogeneity of study participants and recommendations on the CIMT segment for clinical end-point would facilitate examination of CIMT as a potential contribution in assessment of CVD risk. As for now, CIMT values should not be viewed as the sole indicator of increased CVD risk in those of advanced age. The American Society of Echocardiography carotid intima-media thickness taskforce recommends the reporting of CIMT values with other clinically relevant findings. (600)

8.2.2 The left ventricular structure and function

In this study of those living to advanced age, abnormal echocardiographic measures were common; 96% of participants had at least one abnormality.

Left ventricular mass

According to the American Society of Echocardiography and European Society of Echocardiography definition of left ventricular hypertrophy (LVH), one-third of this study sample had LVH. The prevalence of LVH in this study was higher in Māori participants, i.e. two-thirds of Māori had LVH compared to one-quarter among non-Māori. It has been reported that Māori had higher cardiovascular risk factors, and thus a poorer cardiovascular health profile, compared to the NZ

European population, independent of age. (42, 469, 470) In two population-based studies in Germany, Kooperative Gesundheitsforschungim Raum Augsburg (KORA) and Study of Health in Pomerania (SHIP), the prevalence of LVH for men and women aged between 65 and 74 years range between 43% and 59% for men, and 55% and 68% for women. (601) In a subgroup of patients from the EPICARDIAN study (EPIdemiología CARDIovascular en los ANcianos en España), the prevalence of LVH for adults above 75 years old was 47% (the average age and age range for this subgroup was not reported). (602) The disparity in the prevalence of LVH across study populations is due to different criteria adopted.

Following on the discussion on the criteria for normalities and abnormalities of echocardiographic measures, we should be reminded that the existing criteria are derived from younger population. It is uncertain if the criteria for LVH are applicable for people of advanced age. The longitudinal Framingham Study showed LVM increased with age. (434) This is perhaps the increasing LVM with ageing is part of the compensatory mechanism, in conjunction with increase blood pressure, to overcome arterial stiffness. Therefore, LVH, which has an adverse impact on cardiovascular health in younger population (436), may deem 'normal' for people of advanced age. The effect of structural changes in those living to advanced age need to be investigated further. A normal reference ranges for echocardiographic measures in the advanced age need to be established. In the absent of these reference ranges, existing criteria for LVH is adopted.

This study found a positive association between smoking status and LVH. All three current smokers and 29% of the former smokers had LVH. Conversely, 71% of the former smokers had normal LVM. In healthy young men, cigarette smoking was associated with greater LVM and there was a dose-dependent effect according to the duration of smoking. (603) A similar relationship was also found in older middle-aged adults. (434) It has been shown that smoking cessation reduces the risk of CVD by up to one-third within two years of quitting and about two-thirds within five years, and after more than 20 cigarette-free years, the risk of coronary artery disease is the same as in an individual who never smoked. (526) This reduced cardiovascular risk was associated with an improved cardiovascular risk profile. (604) Will smoking cessation reverse/normalise LVM? This study was not able to demonstrate the association between smoking cessation and changes (reversal) in the LVM. Re-examining data from existing longitudinal studies with baseline measures

of left ventricular structure and function may elucidate the benefit of smoking cessation beyond the improved cardiovascular risk profile.

A significantly higher proportion of participants who used nutritional supplements had normal LVM compared to those with LVH. This observation has two probable explanations. First, use of vitamin supplements is related to health behaviour (508), and those with 'healthier' behaviours may be less likely to have LVH. Secondly, those with heart conditions were told by doctors not to use nutritional supplements. There has been conflicting evidence supporting the use of vitamin supplements for CVD risk reduction. (605) This is largely attributed to the type and dose of antioxidant/vitamin cocktail administered, and the diverse populations studied. Nonetheless, there has been promising experimental evidence about the effect of a specific antioxidant on LV remodelling and myocardial failure. (606) Kinugawa and colleagues found that in vivo administration of dimethylthiourea, an effective antioxidant in scavenging hydrogen peroxide (a reactive oxygen species that causes myocardial contractile dysfunction and structural damage), significantly improved LV contractile function and showed a smaller increase in LV chamber size and hypertrophy when compared to MI (myocardial infarct) mice not treated with dimethylthiourea. The basis of the association between nutritional supplements and normal LVM observed in this study are most likely confounded by lifestyle factors.

High blood pressure is associated with LVM. (545, 607) This study did not find an association between LVM and blood pressure in both the unadjusted and adjusted model. This lack of association is possibly due to the fact that two-thirds of the study participants were on blood pressure-lowering medication. Blood pressure-lowering medication was found to maintain and even reduce LVM in hypertensive patients. (592, 608) In a meta-analysis of the effect of blood pressure-lowering treatment on LVM, angiotensin II receptor antagonists, calcium antagonists, and ACE inhibitors reduced LVM by about 10% to 13%, whereas the reduction with beta-blocker and diuretics was from 6% to 8%. (592) Hence, blood pressure-lowering treatment may have attenuated the association between LVM and blood pressure in those of advanced age. But when blood pressure-lowering treatments were taken into account, similar results were produced. This lack of association may be a type II error caused by the small sample size. A prospective study is able to determine if LVM changes (i.e. increases, decreases or is maintained) over time in advanced age,

and if the changes are proportionate to blood pressure modification through antihypertensive therapy.

BNP is released under the condition of increased LV wall stress. In this study, NT-proBNP level was positively associated with LVM, as in previous studies. (409, 609) Pharmacotherapy for heart failure has been shown to reduce natriuretic peptides production. (483, 484) Participants in this study who are on pharmacological treatment for heart failure had higher NT-proBNP levels. Elevated NT-proBNP is a biomarker for diagnosis of heart failure prior to initiation of pharmacotherapy. It is reasonable to speculate that if this group of participants were not treated, their NT-proBNP level would be higher still. Albeit the effectiveness of medications in reducing natriuretic peptides level, a patient with heart failure will not have a natriuretic peptides level similar to the general population. (427) Thus, the positive association between NT-proBNP level and LVM found in this study is expected.

In the univariate analysis, LVM was positively associated with physical activity. Studies showed that physical activity is positively associated with LVM in young, healthy, athletic adults (545, 603); and this physiological growth is not associated with increased wall stress, hence natriuretic peptides level is not increased. In contrary, blood pressure-induced LVM is related to the BNP level. (610) The association between LVM and physical activity observed in this study at the univariate level was likely to be confounded by age because, after adjustment for age-ethnicity, LVM was not associated with the PASE score. Therefore, age-related blood pressure level may be associated with the NT-proBNP–LVM relationship in this sample of people in advanced age.

An interesting association found in the study is that LVM was inversely associated with LDL level. This is contrary to expectations and the recommendation of lowering LDL level to reduce CVD risk. (469, 570) This inverse association is probably confounded by existing risk factors, pharmacotherapy, and time elapsed. Advancing age, higher blood pressure, higher BMI, smoking, and diabetes are risk factors for increased LVM. (434) On the other hand, BMI and total and LDL cholesterol, increased up to the age of 65 years and declined thereafter. (24-27, 243, 261, 460) Blood pressure-lowering medications have been reported to reduce LVM (483, 592) and statin is known to be effective in reducing LDL cholesterol. Therefore, assuming the effect of age and pharmacotherapy on LVM is nullified, whilst ageing and lipid-lowering medication concurrently reducing LDL levels might possibly explain the inversed association between LVM and LDL levels in

this study. There are probably other physiological and pathological factors confounding the relationship which are yet to be identified. More investigations are needed to determine if this inverse association between LVM and LDL levels is clinically meaningful or is contributed to by a type I error.

Overall, LVM was not statistically associated with CVD, even when the definition is narrowed to heart disease (p=0.078). This small p value suggests the possibility of a type II error attributable to the small study sample size.

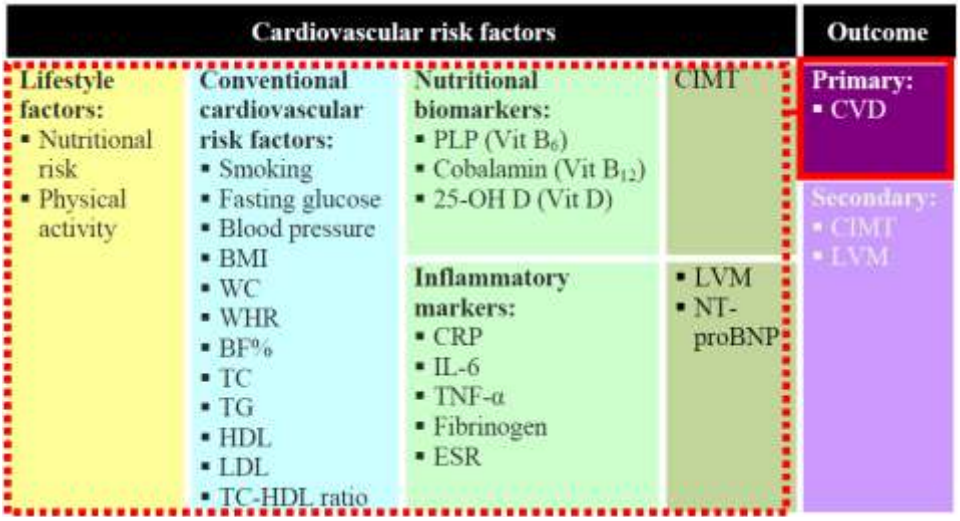
Left ventricular function

In this study, the proportion of people with an abnormal LV function was twice that of people with an abnormal LV structure in this study. Two-thirds had an enlarged left atrial (LA) area, and more than four-fifths did not have a normal LV filling pressure (one-fifth had elevated LV filling pressure, and three-fifths had an intermediate E/E' value). These findings are in line with previous studies. (442, 446) The left atrial (LA) area is enlarged when the pump function of the atrium is impaired due to atrial fibrillation (611) and the inability of the stiff left ventricle to relax, leading to increased LV filling pressure. (612) An enlarged LA area with increased filling pressure is part of the criteria for a diagnosis of diastolic heart failure. (499) (The other conditions to be simultaneously satisfied are presence of signs and symptoms of heart failure and presence of normal or slightly reduced LV ejection fraction (EF>50%). (499) The development of diastolic dysfunction probably precedes symptomatic heart failure but there is little data to support this. Identifying diastolic heart failure and providing appropriate treatment is important as it is associated with high morbidity in elderly patients. (499) The high prevalence of diastolic dysfunction compare to systolic dysfunction in the current study underlines the importance of this disorder in those of advanced age. The burden of diastolic dysfunction and intervention for diastolic heart failure in advanced age warrants further investigation.

In this study sample, 36 (33%) of participants did not have clinically manifest CVD. In this group of participants without CVD, 92% have either abnormal LV structure or function, suggesting subclinical CVD is common in people of advanced age. Extended study following this group of participants would enable the identification of risk factors associated with the first CV event in those of advanced age.

CHAPTER NINE: ASSOCIATIONS BETWEEN CVD AND CARDIOVASCULAR RISK FACTORS, CIMT, AND LVM

This chapter aims to examine the independence of risk factors most relevant to the manifestation of clinical CVD in those of advanced age, utilising regression modelling. This is completed by careful consideration of regression models constructed in previous chapters to select variables to include in a multivariable model, incorporating cardiovascular risk factors. The second section of this chapter will discuss findings from the regression model.



9.1 Results

A regression model was constructed to examine risk factors most relevant to clinically manifest CVD, controlling for sex, age-ethnicity, and smoking status. The model was constructed based on regressions from Chapters Six (Nutritional risk and physical activity), Seven (Cardiovascular risk factors), and Eight (Carotid intima-media thickness and echocardiographic measures). Results of the 25 separate regression models are presented in TABLE 9-1. Interaction terms between age-ethnicity and study variables were not associated with CVD, which implies the association between study variables and CVD was the same for both age-ethnic groups. The effect of medication on variables of interest was controlled for in the analyses. Of the regression models from previous chapters, variables associated with CVD at $p \leq 0.2$ levels were the PASE score, fasting serum glucose, HDL, BMI, WC, NT-proBNP, and LVM. (TABLE 9-1)

TABLE 9-1: Separate logistic regression models examining the association between CVD and cardiovascular risk factors, NT-proBNP, CIMT, and LVM.
Each model (1 to 25) is controlled for sex, age-ethnic groups and smoking status

	Model	Variables	Odds ratio (95% CI)	P value	R^2
Lifestyle factors	1	SCREEN II Score	0.960 (0.890 – 1.036)	0.298	0.049
	2	PASE score	0.990 (0.982 – 0.999)	**0.025**	0.103
Conventional cardiovascular risk factors	3	Fasting serum glucose	0.884 (0.645 – 1.211)	0.442	0.071
		+ glucose-lowering med	0.642 (0.405 – 1.018)	**0.060**	0.156
	4	SBP	0.991 (0.971 – 1.011)	0.394	0.041
		+ med affect BP	0.991 (0.970 – 1.012)	0.386	0.110
	5	DBP	0.978 (0.944 – 1.013)	0.220	0.052
		+ med affect BP	0.982 (0.948 – 1.018)	0.328	0.113
	6	TC	0.736 (0.468 – 1.160)	0.187	0.074
		+ lipid-lowering med	0.786 (0.488 – 1.266)	0.322	0.085
	7	TG	1.316 (0.645 – 2.685)	0.451	0.057
		+ lipid-lowering med	1.300 (0.648 – 2.605)	0.460	0.079
	8	HDL	0.306 (0.097 – 0.965)	0.043	0.110
		+ lipid-lowering med	0.316 (0.100 – 1.000)	**0.050**	0.129
	9	LDL	0.807 (0.486 – 1.339)	0.406	0.058
		+ lipid-lowering med	0.888 (0.519 – 1.520)	0.665	0.074
	10	TC-HDL ratio	1.192 (0.773 – 1.839)	0.427	0.057
		+ lipid-lowering med	1.275 (0.817 – 1.988)	0.284	0.088
	11	BMI	1.083 (0.985 – 1.190)	**0.098**	0.074
	12	WC	1.027 (0.992 – 1.063)	**0.131**	0.063
	13	WHR [#]	1.007 (0.942 – 1.077)	0.835	0.030
	14	BF%	1.003 (0.943 – 1.067)	0.912	0.047
Nutrition biomarkers	15	PLP	1.001 (0.998 – 1.004)	0.701	0.050
		+ nutrition suppl	1.000 (0.997 – 1.004)	0.809	0.074
	16	Cobalamin	1.001 (0.998 – 1.003)	0.510	0.054
		+ nutrition suppl	1.001 (0.998 – 1.003)	0.569	0.070
	17	25-OH D	1.007 (0.985 – 1.029)	0.538	0.054
		+ nutrition suppl	1.005 (0.983 – 1.027)	0.665	0.067
Inflammatory markers	18	CRP	0.965 (0.897 – 1.037)	0.329	0.073
		+ lipid-lowering med	0.969 (0.905 – 1.037)	0.366	0.091
		+ aspirin	0.968 (0.896 – 1.045)	0.403	0.183
	19	IL-6	1.017 (0.913 – 1.134)	0.754	0.020
		+ lipid-lowering med	1.029 (0.918 – 1.153)	0.625	0.086
		+ aspirin	1.019 (0.883 – 1.175)	0.797	0.182
	20	TNF-α *	3.216 (0.357 – 28.987)	0.298	0.043
		+ lipid-lowering med	3.885 (0.418 – 36.092)	0.233	0.113
		+ aspirin	2.614 (0.254 – 26.942)	0.419	0.193
	21	Fibrinogen	1.132 (0.746 – 1.718)	0.560	0.050
		+ lipid-lowering med	1.142 (0.751 – 1.737)	0.534	0.071
		+ aspirin	1.124 (0.784 – 1.611)	0.524	0.174
	22	ESR	1.007 (0.978 – 1.037)	0.617	0.051
		+ lipid-lowering med	1.009 (0.978 – 1.041)	0.570	0.076
		+ aspirin	1.004 (0.973 – 1.036)	0.807	0.166
	23	NT-proBNP	1.022 (1.002 – 1.042)	0.032	0.200
		+ med for HF	1.017 (0.998 – 1.035)	**0.073**	0.281
	24	CIMT	0.547 (0.107 – 2.798)	0.468	0.056
		+ med affect BP	0.376 (0.064 – 2.188)	0.276	0.147
	25	$LVM/Ht^{2.7}$	1.026 (0.994 – 1.059)	0.115	0.112
		+ med affect LVM	1.027 (0.993 – 1.062)	**0.124**	0.240

Abbreviations: **25-OH D:** 25-hydroxyvitamin D; **BF%:** percentage of body fat; **BMI:** body mass index; **CIMT**: carotid intima-media thickness; **CRP:** C-reactive protein; **DBP:** diastolic blood pressure; **ESR:** erythrocyte sedimentation rate; **HDL:** high-density lipoprotein; **Ht:** height; **IL-6:** Interleukin-6; **LDL:** low-density lipoprotein; **LVM**: left ventricular mass; **med:** medication; **NT-proBNP**: N-terminal pro-brain natriuretic peptide; **PLP:** Pyridoxal 5' phosphate; **SBP:** systolic blood

pressure; **TC:** total cholesterol; **TG:** triglyceride; **TNF-α:** tumour necrosis factor-alpha; **WC:** waist circumference; **WHR:** waist-to-hip ratio
Note:
[#] The odds ratio for WHR is an increased of 0.01 unit
* Entered as categorical data, i.e. <1.0 and ≥1.0pg/mL

Relevant variables associated with CVD at p≤0.2 (PASE score, fasting serum glucose, HDL, BMI, WC, NT-proBNP, and LVM) were considered for inclusion in the overall regression model. BNP is released from the cardiac ventricles when in conditions of increased wall stress, and as such is generally considered to be elevated in certain stages of cardiovascular disease such as heart failure, rather than being a risk factor for the development of CVD in those living to advanced age. Thus, NT-proBNP was not included in the current modelling. Concerning fasting serum glucose (Model 3 in TABLE 9-1), adding glucose-lowering medications to the model caused the model to become unstable due to the small sample size (Chapter Seven, Section 7.1.8). Hence, glucose-lowering medication was removed from the model. When the effect of glucose-lowering medications on fasting serum glucose was not considered, fasting serum glucose was not associated with CVD (p=0.442). As a result, fasting serum glucose was not included in the regression model. Lipid-lowering medication was not included in the model because it did not have an apparent association with HDL levels (Model 8 in TABLE 9-1); which is not unexpected because lipid-lowering medications are generally indicated for treatment of increased total and LDL cholesterol concentrations. Similarly, pharmacotherapy for heart failure and blood pressure did not have an apparent confounding effect on altering the association between LVM and CVD (see Model 25 in TABLE 9-1). Therefore, lipid-lowering medication, heart failure and blood pressure-lowering medication were not entered in the model. Since BMI and WC were highly correlated (r=0.832, p<0.001), two models were constructed to examine these separately. TABLE 9-2 shows the regression model which includes relevant variables associated with CVD at p≤0.2: PASE score, HDL, LVM, and BMI including sex, age-ethnicity and smoking status (because the latter three variables are main risk factors for CVD) (Model 1). Model 2 has a similar covariate list, but replaces BMI with WC. Between Models 1 and 2 in TABLE 9-2, Model 1 appears to have a better fit than to Model 2.

As there was collinearity between HDL, BMI and WC, a backward stepwise method was performed by first removing HDL from Model 1 and Model 2, and then re-enter HDL and removing BMI and WC (TABLE 9-2). Without HDL in the models (Model 3 and Model 4), the fit of the model

decreased slightly and the association between variables of interest and CVD did not change except for the association between PASE score and CVD was strengthen [Model 3, OR (95% CI): 0.987 (0.977–0.997), p=0.014]; [Model 4, OR (95% CI): 0.988 (0.978–0.998), p=0.017]. In the second step, i.e. re-entering HDL and removing BMI and WC (Model 5), the fit of the Model 5 was better than Model 3 and 4 (TABLE 9-2). This indicates HDL was a better variable for the model than BMI or WC. Therefore, the parsimonious Model 5 was the most relevant model in determining the variance of having CVD in this study sample. In Model 5, controlling for other variables, women have a lower odds of having CVD [OR (95% CI) 0.22 (0.06-0.78), p=0.019); and controlling for other variables, the PASE score (physical activity) was inversely associated with CVD [OR (95% CI) 0.99 (0.98-1.0), p=0.036). For a 10-unit change in PASE score, the odds ratio (95% CI) is 0.88 (0.79-0.99)

TABLE 9-2: Logistic regression model examining the association between CVD and study variables

	Model 1		Model 2		Model 3		Model 4		Model 5	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Sex (ref: men)	0.250 (0.069–0.909)	0.035	0.294 (0.067–1.295)	0.105	0.299 (0.094–0.948)	0.040	0.356 (0.098–1.295)	0.117	0.221 (0.063–0.780)	0.019
Age-ethnic (ref: NZ European)	1.425 (0.274–7.405)	0.674	1.585 (0.311–8.073)	0.579	1.493 (0.328–6.795)	0.604	1.670 (0.387–7.204)	0.492	2.032 (0.420–9.840)	0.378
Smoking (ref: never)		0.660		0.752		0.839		0.906		0.594
Current	0.230 (0.004–13.83)	0.482	0.233 (0.004–14.28)	0.488	0.524 (0.030–9.139)	0.658	0.560 (0.031–10.28)	0.696	0.169 (0.004–6.912)	0.348
Former	1.364 (0.427–4.354)	0.604	1.160 (0.363–3.702)	0.802	1.216 (0.417–3.544)	0.720	1.107 (0.377–3.247)	0.853	1.209 (0.389–3.754)	0.743
PASE score	0.988 (0.976–1.000)	0.041	0.989 (0.978–1.000)	0.055	0.987 (0.977–0.997)	0.014	0.988 (0.978–0.998)	0.017	0.988 (0.977–0.999)	0.036
PASE score (change of 10-unit)	*0.884 (0.787–0.992)*	*0.036*	*0.893 (0.797–1.000)*	*0.050*	*0.879 (0.795–0.974)*	*0.013*	*0.884 (0.799–0.977)*	*0.015*	*0.884 (0.790–0.990)*	*0.033*
HDL	0.550 (0.135–2.246)	0.405	0.455 (0.111–1.860)	0.273					0.506 (0.127–2.020)	0.335
$LVM/Ht^{2.7}$	1.001 (0.971–1.053)	0.581	1.017 (0.977–1.058)	0.411	1.023 (0.985–1.062)	0.234	1.024 (0.988–1.063)	0.197	1.024 (0.985–1.064)	0.226
BMI	1.109 (0.966–1.274)	0.142			1.074 (0.949–1.216)	0.260				
WC			1.019 (0.971–1.069)	0.453			1.021 (0.976–1.067)	0.368		
Nagelkerke R^2	0.297		0.272		0.234		0.225		0.261	

Abbreviations: **BMI:** Body mass index; **CI:** confidence interval; **CVD**: cardiovascular disease; **HDL:** high-density lipoprotein; **LVM**: left ventricular mass; **OR:** odds ratio; **ref**: reference; **WC:** waist circumference

Model 5 was tested for interactions between medication (≤5 and >5) and the PASE score. The interaction term (PASE score × medication ≤5 and >5) was associated with CVD (p=0.041) in Model 5. Therefore, a separate analysis was completed for participants who used ≤5 and >5 prescribed medications. Nevertheless, the model for those who used >5 prescribed medications became unstable, evidenced by wide confidence intervals observed in sex, age-ethnic groups, and smoking status. The instability of the regression can be attributed to the small sample size. As a result, the analysis was done on the complete group.

Concerning blood pressure, although both SBP and DBP were not associated with CVD at p≤0.2 but it is known to be important variables related to CVD risk, they were added separately to the Model 5 (TABLE 9-2). Controlling for sex, age-ethnicity, smoking, HDL, LVM, and SBP, PASE remains to be associated with CVD [OR (95% CI): 0.987 (0.976–0.0.999), p=0.034]. Replacing SBP with DBP, the association between PASE and CVD remains similar [OR (95% CI): 0.988 (0.977–0.999), p=0.041].

Since the PASE score is made up of three different types of physical activities (i.e. leisure-time, housework-related, and work-related physical activity), scores for each of these components were examined. Of the three types of physical activities, housework-related activity was significantly associated with CVD, p=0.022 (Model 2 in TABLE 9-3); no association was found between leisure-time and work-related physical activity, and CVD.

TABLE 9-3: Logistic regression model examining the association between CVD (dependent variables) and physical activity (independent variable)

Model		Odds ratio (95% CI)	P value	R^2
1	Leisure-time physical activity	0.991 (0.969 – 1.013)	0.404	0.182
2	Household-related physical activity	0.979 (0.962 – 0.997)	0.022	0.276
3	Work-related physical activity	0.984 (0.953 – 1.016)	0.327	0.198

All models were adjusted for sex, age-ethnicity, smoking status, HDL, and $LVM/Ht^{2.7}$

Comparing Model 3 in TABLE 7-24 (page 168) and Model 5 of TABLE 9-2, the addition of the PASE score and $LVM/Ht^{2.7}$ in Model 5 of TABLE 9-2 yielded a significant difference in -2 log likelihood values and an increased in the R^2 value by 0.151. This indicates that the PASE score and $LVM/Ht^{2.7}$ add a substantial explanatory effect to the model.

Assumptions in the model

The ratio of outcome events-to-independent variables for Model 5 was 12.2, which is within the criterion of 10:1 ratio. (485) Interactions among independent variables and age-ethnic groups were tested, but were not significant. Therefore, it was assumed that the association between variable of interest and CVD was the same for both age-ethnic groups. The interaction term [variable of interest × sex] was not tested; hence the model cannot assume the association between variable of interest and CVD was the same for both sexes. Multicollinearity was addressed in construction of the model, hence type I error is minimised. From the residual plots, there do not appear to have any outliers which affect the results significantly. The effect of relevant variable (SBP) in the regression model was assessed even though SBP does not meet the entry criterion of $p \leq 0.2$, this is because SBP has been reported to be important CV risk factor.

9.2 Discussion

9.2.1 Sex and CVD in advanced age

In this study, controlling for age-ethnicity, smoking status, physical activity, HDL, and left ventricular mass, it was revealed that women were less likely to have clinically manifest CVD. In middle ages, women have a lower coronary heart disease risk compared to men, but the risk equalises with increasing age and subsequently women tend to have a higher risk than men in older ages. (155, 156) The finding from the current study, that women of advanced age are less likely to already have CVD, could perhaps in part be explained by the observation that they have higher sub-clinical CVD and the CVD may not have yet become clinically evident. In the Framingham study with more than 4,200 adults (mean age 45 years), followed-up for 16 years, women had a steeper increase in LVM over time, relative to men. (434) Increased LVM was associated with an increased CVD risk factor burden. (434) The prevalence of LV diastolic dysfunction may or may not be more prevalent in women. There is conflicting evidence with reports of a higher prevalence of LV diastolic dysfunction in older women (442); older men (441); and similar prevalence in both genders. (446) LV diastolic dysfunction does not usually present with recognised CVD symptoms. (445, 446) In this study, 94% (n=33) of participants without clinically manifest CVD had abnormal echocardiographic measures, mainly abnormal ventricular function or presence of valvular disease (42%) followed by increased LV filling pressure (36%). Nonetheless, due to the small sample size

in this study, the prevalence of these abnormalities did not appear to differ between the sexes. Studies with more participants are needed in order to have sufficient power to detect associations between echocardiographic measures and CVD in advanced old age, and to consider the moderating effect of sex. Such studies may have implication for the management of coronary heart disease in men and women of advanced age.

9.2.2 Physical activity and CVD in advanced age

This study found an inverse association between physical activity and CVD, independent of sex, age-ethnicity, smoking status, HDL, and LVM. When the type of physical activity was determined, housework-related activity, not leisure-time or work-related activity, was associated with CVD. The cause-effect relationship between physical activity and CVD cannot be determined in this study. Epidemiological studies have showed those who have been more physically active over time may have less CVD because of the protective effect of activity. (518, 613, 614) However, reverse causality is also plausible i.e. the presence of clinically manifest CVD may affect physical activity level. Adverse CV health outcomes such as heart failure and stroke constrain physical function and cause disability. (72-75) Comorbidities, of which CVD is by far the leading condition, are common among older adults. (615) Comorbidities are reported as the main factor restricting physical function leading to subsequent functional decline in older adults. (615) This study is unable to tell which comes first.

The benefit of exercise program has been noted in adults above 70 years with coronary disease. (616) In adults with an average age of 75 years, the significant benefit of physical activity on the cardiovascular system through reduce inflammatory markers is already observed with light physical activity. (349) Therefore, it is likely people of advanced age may attain more absolute benefit because of they have higher absolute CV risk. Nevertheless, in a randomised controlled trial with 59 adults aged 60 and older with heart failure, the 16-week supervised exercise training program failed to produce consistent benefits in term of exercise performance, LV function, neuroendocrine activation and health-related quality of life. (617) Although the benefit was not evident with improvement in peak exercise oxygen consumption, the effect of exercise in ameliorating heart failure-associated-depressive symptoms may be present. By and large, physical activity likely to benefit the cardiovascular health and well-being of those living to advanced age.

In brief, the association between physical activity level and CVD is robust and independent and was expected. The absolute benefit of physical activity will differ between individuals because those living to advanced age are a heterogeneous group. Prospective studies are needed to elucidate the benefit-and-harmful effect (e.g. falls, cardiac arrest) of physical activity in those living to advanced age. The moderating effect of gender should be considered, as the type and intensity of physical activity differs between men and women. (117, 127, 136)

9.2.3 Cardiovascular risk factors, LVM and CVD in advanced age

More than one-fourth of the variance of having CVD in this sample of those living to advanced age can be explained by sex, age-ethnicity, smoking status, physical activity, HDL, and LVM. Adding glucose-lowering medication and fasting serum glucose into the model would have increased the R^2 (Section 7.1.8), but this does not imply glucose-lowering medication has a substantial explanatory effect on the model because of the rarity of participants receiving glucose-lowering medications (n=9, i.e. 8% of the study sample), causing the model to become unstable.

Diabetes and CVD in advanced age

Diabetes is significantly associated with macrovascular complications (e.g. ischemic heart disease, stroke and peripheral vascular disease) leading to premature mortality. (173, 618) It is therefore reasonable to assume there are fewer adults with diabetes living to advanced old age. In this study, one-fifth (n=22) of the study participants had diabetes. A larger sample size may be able to examine the association between fasting serum glucose and CVD in people of advanced age, controlling for glucose lowering medications and other CV risk factors.

Elevated blood pressure and CVD in advanced age

More than four-fifths of this sample has hypertension. Epidemiological data with younger populations showed that blood pressure is linearly related to CVD risk. (199) With age, diastolic blood pressure ceased to increase after the age of 50 years but systolic blood pressure continues increasing until the eight decade of life (198) and appears to remain an important CV risk factor. (212) It is interesting that this study found no association between systolic blood pressure and CVD. Two-thirds of the current study sample was on medications that have an effect on the blood pressure level. The pharmacotherapy could have controlled blood pressure, hence, alleviating the

impact of systolic blood pressure on CVD risk. On the other hand, the linear relationship between blood pressure and CVD observed in younger population could have altered with ageing. In the very elderly, a non-linear relationship between blood pressure and all-cause mortality has been observed. (619, 620) In the recently published results from the INVEST (INternational VErapamil SR-Trandolapril STudy) substudy (mean age 84 years; n=2180), the relationship between SBP and adverse outcomes (i.e. all-cause mortality, non-fatal MI or non-fatal stroke) was a shape of a J-curve; with the lowest hazard ratio for adverse outcomes observed at SBP 140 mmHg. (621) In the Umeå 85+ Study (n=348), SBP value associated with the lowest mortality was 164.2 mmHg. (622) The Tempere Study which recruited 561 older adults (83% of the sample were 85 years and above) found all cause mortality was the lowest in participants with SBP 160 mmHg or above. (623) These studies unanimously demonstrate that a higher SBP, compared to the recommended SBP of less than 140mmHg (203), may be associated with increases survival in those of advanced age. Thus, the body of evidence may suggest that the optimum blood pressure level for people of advanced age may be higher than the current recommendation. It is also possible that those with low blood pressures represent a group that has low cardiac output and is at a greater mortality risk because of their cardiac disease. The very old population is heterogeneous with respect to cardiovascular status. Larger cohort studies are needed to determine the relationship between blood pressure, CVD and chances of survival in those living to advanced age.

Anthropometry measures and CVD in advanced age

The association between anthropometry measures and CVD in adults of advanced age is probably more complex. BMI, a measure of general obesity deemed detrimental to CV health in the younger adults, may be a protective factor for people of advanced age. Prospective studies found that adults above 70 years old with a higher BMI (ranging between 27–31kg/m^2) have a lower risk of 15-year mortality. (236, 237) A factor favouring higher BMI in older adults is positive energy reserves (83, 552) important for recovery from a CV event. Energy sufficiency is closely related to nutritional status. Adequate nutritional status is important for maintenance of CV health, as a balanced diet will provide a range of vitamin antioxidants (84-87, 91-98, 404) and dietary essential fatty acids (21, 99, 100) which have been observed to reduce cardiovascular morbidity and mortality. Waist circumference, on the other hand, as a measure of abdominal adiposity, may continue to be an important CV risk factor in those living to advanced age. Visceral adipose tissue

is one of the major sources of production of proinflammatory cytokines and is strongly related to increased levels of inflammatory markers (239-241), which are associated with increased CVD risk. Therefore, anthropometry measures are likely to carry a specific predictive value for CV risk in people of advanced age. This assumption needs to be confirmed in larger studies.

Lipid profile and CVD in advanced age

The significant association between HDL and CVD controlling for sex, age-ethnicity and smoking status observed in Chapter Seven was attenuated when the model was further controlled for physical activity level and LVM. The association between HDL and CVD may be masked by the presence of physical activity and LVM evidenced by substantial increase in explanatory effect of the expanded model. Additionally, physical activity is likely to mediate the relationship between HDL and CVD. Studies have shown that participation in physical activity increased HDL levels in both young and older adults. (107, 111, 259) The absolute effect of physical activity on HDL level in people of advanced age could be greater as the Leiden 85+ study observed HDL level increase from age 85 to 90 years. (624) Prospective studies are needed to determine the effect of physical activity on HDL level in those living to advanced age.

This study, with other prospective studies (24, 565), suggests that the significance of HDL level in the association with CVD risk in people of advanced age may be more significant compared to other lipid parameters. This is different from the current evidence suggesting that total cholesterol to HDL ratio is the best predictor of CV outcomes in both treated and untreated adults. (625) One of the possible explanations as to why HDL is more important than other lipid parameters in advanced age is that the relationship between cholesterol levels and nutritional status differs in advanced age. In older patients (mean age 68 years) with stable mild to moderate chronic heart failure, cholesterol levels are positively correlated with pre-albumin levels, suggesting that cholesterol levels are an indicator of nutritional status. (626) This current study, with support of other studies, found nutritional risk is prevalent among older adults. Additionally, longitudinal studies showed that total cholesterol declines after age 65 years. (24-27) The impact of ageing- and nutritional status–associated decline in total cholesterol level may suggest the predictive value of total cholesterol to HDL ratio observed in younger adults is not as good a predictor of CVD risk in older ages. HDL level may be more useful. The relationships between lipid profile, nutritional risk and CVD risk in people of advanced age requires further investigation.

The relationship between HDL level and LVM is uncertain. The Framingham study showed change in LVM was associated with increased burden of CV risk factors, i.e. individuals with more CV risk factors had greater baseline LVM and a steeper increase in LVM over time. (434) Greater LVM is associated with increased risk of CVD. (435) Therefore, the 'proximal' relationship between LVM and CVD may have masked the 'distal' relationship between HDL and CVD. In other words, HDL level may be part of the mechanism contributing to changes in LV structure and function which is associated with CVD risk. Larger studies are needed to accurately examine pathophysiological pathways of CVD in advanced age.

LVM and CVD in advanced age

This study did not find an association between LVM and CVD, which is quite surprising. In the Cardiovascular Health Study with participants' average age of 76 years, an increase in LVM was related to an increase in heart failure risk (435) and LV hypertrophy was associated with increased stroke risk. (436) In this study, there are at least two reasons why we did not find the association between LVM and CVD when it may be present. First, there are small numbers of participants with heart failure and stroke; hence, subgroup analyses were not possible. The small sample size contributes to a potential type II error.

Secondly, there may be some participants with concentric remodelling of the left ventricle not identified as having LVH; this may confound the association between heart size and CVD. Furthermore, this study defined LVH according to the American Society of Echocardiography and European Association of Echocardiography. (444) This guideline was developed based on data from younger populations. Hence, it is uncertain if the existing LVM cut-off range in defining LVH is relevant to people of advanced age. The heart is a dynamic organ undergoing remodelling in response to environmental demands and is induced by a variety of stimuli to grow or shrink. (627) Although the growth of the heart plateaus in the face of persistent stress, the remodelling process continues. (627, 628) To date, there is a lack of evidence in relation to the proportion of CV mortality and morbidity attributable to cardiac remodelling. (628) Greater attention to defining concentric remodelling in advanced age and its relationship with CVD may be needed.

Inflammatory markers and CVD in advanced age

Finding of no association between inflammatory markers and CVD in this group of very old adults was not expected. This lack of association is probably due to the small sample size. Most of the studies reporting linear association between inflammatory markers and CVD were large. (TABLE 9-4) Additionally, as discussed in Chapter Seven (Section 7.2.6), analysis of IL-6 and TNF-α in this study was completed using two different lots of assay kits, resulting in different inter- and intra- assay variability. Although such variability is unlikely to affect IL-6 and TNF-α results (at least not in a clinical setting), for research purposes, it is better to have the analysis done in a single batch to minimise variability due to sample handling and measurements of serum concentrations. As inflammation is involved in multiple pathophysiological pathways of CVD, inflammatory markers could be important CV risk factors in adults of advanced age. Studies have shown that inflammatory markers increase with age. (31, 32, 343, 466) Other studies have shown that the association between inflammatory markers and CVD persists into old age. (33-36, 326) Total cholesterol and LDL, on the other hand, were reported to not to have an association with CVD beyond the seventh decade of life. (246, 262) Larger prospective studies are needed to determine the relationship between inflammatory markers and CVD in adults of advanced age. Findings from this study are unable to demonstrate inflammatory markers are important CV risk factor in advanced age.

TABLE 9-4: Prospective studies reporting a linear relationship between inflammatory markers and CVD risk
(Listed according to increasing age)

Study	Sample size	Mean age (years)	Ref
The Framingham Offspring Study	2,632	55	(326)
The Physician Health Study	404	59	(296)
The Rotterdam Study	6,437	69	(33)
The Cardiovascular Health Study	5,888	73	(34)
The Three-City Study	1,004	74	(287)
The Health ABC study	2,610	74	(316)
The Framingham Heart Study	732	78	(35)
The Leiden 85-Plus study	245	90	(36)

Summary for the section

In brief, more than one-quarter of the variance of having CVD in this sample of those living to advanced age can be explained by sex, age-ethnicity, smoking status, physical activity, HDL, and

LVM. The contribution of other CV risk factors and their relationship with CVD in those living to advanced age needs further investigation. As for now, it is possible that the remaining two-quarters of the variation of CVD status in this sample are explained by a combination of genetic endowment, socioeconomic factors and other unmeasured variables. Although, the thesis objectives did not include hereditary and socioeconomic aspects in relation to CVD, their relevance to cardiovascular health in those living to advanced age is discussed briefly in the following section.

9.2.4 Other factors related to CVD not measured in this thesis

Familiality and CVD in advanced age

Twin studies have estimated that familiality accounts for about 30% of average life expectancy. (629) In other words, the remaining 70% is attributable to environmental and behavioural components. According to Thomas Perls and Dellara Terry, genetic factors may play a larger role in ageing than environmental factors. (629) They explained siblings of centenarians are likely to share similar socioeconomic status, lifestyle and region of residence up to adulthood; but as they grow older, their socio- and environmental factors are likely to diverge. In spite of the divergence, they continue to have an increased relative survival probability compared with the U.S. 1900 Birth Cohort. (629) Survival probability is the cumulative experience of death up to that moment in a cohort's life history; in other words, a constant advantage from moment to moment translates into increasing survival advantage over a lifetime. (629) In the New England Centenarian Study, offspring of centenarians had a reduced relative prevalence of heart disease (56%), coronary artery disease (64%), prior MI (63%), and arrhythmias (36%). (630) Additionally, centenarians' offspring also had a reduced relative prevalence of hypertension (66%) and diabetes (59%). (630) Recently, studies showed telomere length (telomere is a region at the end of chromosomes which protects the chromosomes from destruction) was inversely related to CV risk factors (diabetes, fasting insulin, diastolic blood pressure, CIMT, ankle-brachial index, IL-6, and CRP; positive correlation with HDL levels). (433, 631, 632) Furthermore, in the very elderly, decreased telomere length was significantly associated with reduced LV systolic function. (432) Therefore, attrition of telomere length may be related to a predisposition to CVD. These few studies, among an abundance of other aspects of ageing, suggest that genetic factors have a considerable role in CV health in people of very old age. Genetic testing was beyond the scope of the current study.

Socioeconomic factors and CVD in advanced age

Environmental factors including, but not limited to, socioeconomic and physical environment aspects are closely linked to the CV health of older adults. From the dietary perspective, socio interaction and financial situation are related to the quality and quantity of dietary intake. Restrictive accessibility and availability of safe and nutritious foods, which can be attributed to financial situation and debilitating illness (such as CVD), are likely to affect the quality and quantity of dietary intake. (77) Social interaction and eating with others enhances dietary variety and nutrient intake. (77) Therefore, older adults with socioeconomic hardship may be at risk of undernutrition. The possible consequence of a prolonged period of undernutrition is deterioration of CV health through deficiency of vitamin antioxidants and essential fatty acids. Physical environment such as close proximity to shops (e.g. food outlets), safety, and safe sidewalks encourages physical activity. (633) For community living older adults, the choice of physical environment may be determined by socioeconomic status. In brief, the socioeconomic factors are interlinked and are closely related to physical environment. Together they synergistically play a part in impacting on the CV health of those living to advanced age. Therefore, future studies examining the relationship between nutritional risk, physical activity, and CVD in those of advanced age should consider socioeconomic factors and physical environment.

9.3 Study limitations and strengths

One of the limitations in this study is the study sample size. The small sample size has restricted sub-group analyses for the number of prescribed medications, which were found to moderate the relationship between physical activity and CVD. The small sample size also limits the ability of the study to control for comorbidities as a confounder in the multivariable analyses. The considerable number of variables examine in this study likely leads to multicollinearity, which if not address will affect the reliability of the model. This multicollinearity issue was carefully dealt with by first analyses of variable within a specific domain, then variables are selected from each domain using a predefine entry criterion for inclusion into the model. These steps would have minimised type I error. The small sample size could have also contributed to type II error (an effect being present but not detected) in examining the relationship between inflammatory markers and CVD in this sample. This study acknowledged that seasonal variation and use of different assay kits in the analysis of IL-6 and TNF-α may have a contributory role towards error in the result. Nevertheless,

these issues have been carefully considered and adjusted for in the analyses, hence, its' impact on the analyses is likely to be minimised. This study, a cross-sectional design, was not able to determine the cause-effect relationship between physical activity, CV risk factor, and CVD. Larger prospective studies will be able to address these issues. Since the focus of this study is on the biomedical component, the effect of socioeconomic factors and physical environment on cardiovascular health of those living to advanced age was not determined. Genetic factor, which also has an important role in CV health of older adults, was not determined for this sample due to limited resources.

Despite of the small sample size, this study has focused on a group of people living to advanced age who likely have been exposed to similar life events (e.g. the Great Depression and World-War II) which may have influenced their lifestyle behaviour. Additionally, the study acknowledged Māori and non-Māori older adults of similar chronological age likely to have different CV health profiles, and therefore this study recruited people of advanced age with seemingly comparable biological ages. The study has collected a wide array of clinical, subclinical and laboratory measures, and has precise verification of CVD and CV risk factors. This has provided a glimpse of the CV health of those living to advanced age. Data from this study will lead to generation of hypotheses for future investigations of cardiovascular health in advanced age.

Due to the small sample size, findings on the relationships between CV risk factors and CVD from this thesis need to be interpreted cautiously. Larger prospective studies are needed to confirm findings from this thesis, taking into account potential confounders and moderating variables. Findings from this study have added to the limited body of evidence pertaining to CV health of those living to advanced age.

9.4 Summary

In summary, women of advanced age and physically more active participants were less likely to have clinically manifest CVD after adjusting for other CV risk factors. Larger prospective cohort studies are needed to explore these relationships and, ideally, the sector of the population without CVD could be followed to establish risk factors for development of CVD over time. Variables that potentially moderate the relationship between physical activity and CVD (such as number of prescribed medications and the sex of the participant) should be considered in future studies.

CHAPTER TEN: CONCLUSIONS

This chapter aims to present the key findings of the thesis and states the implications from the study findings in concluding remarks.

10.1 Key findings

Chapter 1 and 2

The oldest elderly (85+) is the fastest growing segment of the ageing population. Cardiovascular risk increases with age and is the main cause of morbidity and mortality in older adults. Various risk factors contributing to CVD have been identified. The relationships between cardiovascular risk factors and CVD are well researched in middle-aged and older adults. Epidemiological evidence shows that the relationship between conventional risk factors and CVD behaves in a non-linear manner among individuals over 75 years. (243, 246, 262, 461, 462) Inflammatory markers, on the other hand, seem to demonstrate a positive linear relationship with CVD risk well into advanced age. (33-36) A systematic review of the evidence indicates that there is limited information concerning cardiovascular health and its risk factors in those of advanced age.

Chapter 3 and 4

With this background, this thesis was conducted to determine the cardiovascular health and examine the relationships between cardiovascular risk factors and presence of clinically manifest CVD in people of advanced age. A purposive sample was recruited, Māori 75-79 years and all ethnic groups who turned 85 years of age within a defined time period in three areas in the North Island, New Zealand: Rotorua, Whakatane and Opotiki. A younger age group for Māori participants than non-Māori participants was selected to attain a comparable group with respect to longevity.

A pilot study was carried out to determine the feasibility of the pre-defined recruitment and data collection procedures in a small group of those living to advanced age. The pilot study found the questionnaire, physical assessment, echocardiography measurement, and blood analyses were feasible in those of advanced age. The data collection procedures were replicated and the study began recruitment in January 2008.

Chapter 5

A total of 186 people in advanced age were invited to participate in the study and 112 participated: response rate was 60%. In this study sample, 67% of the study participants had clinically manifest CVD, with angina pectoris being the most common manifestation. Eighty-five percent of participants had dyslipidemia, 84% had hypertension, 27% had a BMI>30kg/m^2, 20% had type 2 diabetes, and 8% of the participants were cigarette smokers.

Chapter 6

Half of the study participants were at risk of undernutrition. This study did not find a significant association between nutritional risk and CVD but found BMI may have a mediating effect on the relationship between nutritional risk and CVD. (514) Most of the study participants performed some level of physical activity, of which 74% constituted housework-related activity with a minimal level of leisure-time activity. Physical activity was associated with CVD, independent of sex, age-ethnicity and smoking status. This may indicate that the benefit of physical activity continues into advanced old age. This study found an association between physical activity and CVD and that this may be moderated by co-morbidities. Larger cohort studies are needed to further examine this finding.

Chapter 7

Among conventional cardiovascular risk factors examined, only the HDL level was inversely associated with CVD, independent of other risk factors. This finding is in line with studies involving adults over 75 years of age, which showed a low HDL level was associated with increased risk of cardiovascular morbidity and mortality; whereas the strong and graded association between total and LDL cholesterol with CVD loses its significance with advancing age. (24, 565) Therefore, there may be a need to re-examine the management of dyslipidemia in adults of advanced age. Instead of lowering total and LDL cholesterol, intervention to increase the HDL level may be a more useful strategy to improve the cardiovascular profile in those of advanced age. To date, intervention to improve HDL levels remains in the exploratory phase. There is a need to understand the cardio-protective role of HDL in older adults.

This study found that both systolic and diastolic blood pressures were not associated with CVD. The null association between diastolic blood pressure and CVD was within expectation as a longitudinal study has shown diastolic blood pressure increases up to 50 years of age and

decreases thereafter. (198) Nevertheless, the null association between systolic blood pressure and CVD is unexpected. This is probably a type II error attributable to the small sample size. Larger cohort studies are needed to determine the relationship between systolic blood pressure and CVD in those living to advanced age.

In this study, of the four anthropometric measures, only waist circumference was marginally higher in those with CVD than those without CVD. Nonetheless, this association was attenuated after controlling for sex, age-ethnicity and smoking status. BMI may have a mediating role in the relationship between nutritional risk and CVD. Therefore, BMI and WC may have specific predictive values for CV risk in people of advanced age. This assumption needs to be confirmed in larger studies.

Concerning inflammatory markers, this study found no associations between inflammatory markers and CVD, but found inflammatory markers were associated with conventional risk factors which also have been observed in younger adults. With advancing age, significant physiological changes have taken place. The inflammatory response, part of the homeostatic process, is inevitably involved in these changes. Epidemiological studies show that inflammatory markers increase with age. In large studies, inflammatory markers are linearly associated with CVD risk and mortality. The small sample size of this study may have contributed to a type II error. Variability in IL-6 and TNF-α assay could also be a factor contributing to this observation. The relationship between inflammatory markers and CVD in advanced age warrants further investigation.

Chapter 7 has addressed the first four study rationale outlined for this thesis.

Chapter 8

To the candidate's knowledge, this thesis is the first study reporting the right common carotid intima-media thickness (CIMT) in people of advanced age. The CIMT median (interquartile range, IQR) was 1.07(0.27)mm; the 75th percentile was 1.206mm. This study did not find an association between CIMT, cardiovascular risk factors, and CVD. It has been suggested that a composite endpoint of carotid intima-media thickening, including both right and left bifurcation, internal and/or common carotid may, be a more reliable index of atherosclerosis. (479) This, however, was not feasible in this study due to resource constraint and participant burden of the approximately 1¼-

hour physical assessment session. The predictive value of CIMT for CVD is still in an exploratory phase. This study adds to the literature of CIMT values and their association with cardiovascular risk and CVD in those of advanced age.

In this sample of people of advanced age, the left ventricular mass (LVM) assessed by adjusting for height ($LVM/Ht^{2.7}$) [median (IQR)] for men was 39.2 (28.9)gm^{-2} and for women was 40.4 (29.7)gm^{-2}. Left ventricular (LV) hypertrophy was evident in 38% of the participants. This study did not find a statistically significant association between LVM and CVD, controlling for sex, age-ethnicity and smoking status. The small sample size may have contributed to a type II error. With regards to LV function, 68% of the study participants had an enlarged left atrial area and 20% had elevated LV filling pressure. Both of these abnormalities are related to LV diastolic dysfunction. Five percent of participants had abnormal LV systolic function. These findings extend evidence from epidemiological studies, that is, in the older population LV diastolic dysfunction is more prevalent than systolic dysfunction. In the Newcastle 85+ study (n=89), 57% of study participants had evidence of at least mild diastolic dysfunction compared to 14% who had systolic dysfunction (ejection fraction <50%). (432) Among participants in this study with no clinically manifest CVD, only 6% had normal echocardiography measures. This suggests that sub-clinical CVD is prevalent in those of advanced age. The clinical significance of these abnormalities in those without CVD needs to be determined in longitudinal studies.

Chapter 8 has addressed the final study rationale outlined for this thesis.

Chapter 9

This study found women in advanced age have a lower likelihood of having clinically manifest CVD. It is not certain whether they have a better cardiovascular health profile but it is likely that men and women have different pathophysiological pathways leading to clinical manifestation of CVD. Of all the variables examined in this study, controlling for other factors, physical activity was inversely associated with clinically manifest CVD. The potential cause-and-effect relationship between physical activity and CVD was unable to be determined in this cross-sectional study. Prospective intervention studies will inform the effect of physical activity on cardiovascular health in those living to advanced age.

The significant association between HDL level and CVD independent of other risk factors observed in Chapter Seven was attenuated when physical activity and LVM were added to the model. This suggests physical activity could be the mediator in the relationship between HDL and CVD, and the 'proximal' relationship between LVM and CVD could have masked the 'distal' relationship between HDL and CVD. The mechanistic role of HDL in cardiovascular health of those living to advanced age requires further investigation.

10.2 Implications

Future research

Nutritional risk

This study found a high prevalence of nutritional risk in this sample, suggesting screening for nutritional risk in people of advanced age is warranted. In view of this, an accurate nutritional assessment is needed. An assessment tool that is sensitive and specific enables timely intervention to prevent malnutrition in people of advanced age. We know preventive strategies are more cost-effective than most pharmacological intervention. Thus, further studies are needed to develop a reliable nutritional assessment tool and to determine an appropriate dietary intervention for people of advanced age identified to be at risk of undernutrition. Furthermore, the mediating role of BMI in the relationship between nutritional risk and CVD observed in this study needs to be confirmed in larger prospective studies.

Physical activity

The independent positive association observed between physical activity and CVD in this study indicates that physical activity is associated with cardiovascular health in advanced age. Nevertheless, the cause-effect relationship is yet to be determined. Epidemiological studies have shown that a more active lifetime physical activity pattern is associated with lower CVD risk. (518, 634, 635) On the other hand, physical activity level in advanced age may be impacted by CVD status and co-morbidities profile. Variation of the type of physical activity between men and women observed in other studies (117, 127, 136) was also observed in this study. The sex-specific physical activity patterns over time and the relationship between change of physical activity level

and cardiovascular health in people of advanced age can only be determined in prospective observational cohort studies. Future observational studies may inform development of randomised controlled trials to assess the benefit of increasing physical activity in those living to advanced age.

HDL levels

The inverse relationship between HDL levels and CVD found in this study suggests that HDL may be more important than total cholesterol, LDL cholesterol levels and TC:HDL ratio in determining CVD risk in advanced age. This, however, needs to be confirmed by larger cohort studies. The mechanistic role of HDL in cardiovascular health is related to the metabolism of HDL (the rate of synthesis and catabolism by the liver) and also properties of the lipoprotein (apoprotein subfractions) which determine the anti-atherogenic, anti-oxidant, anti-inflammatory, and anti-thrombotic function of HDL. (112, 566, 636-638) The question of whether the metabolism and properties of HDL change with ageing needs further investigation. It has been found that HDL particles can exhibit proinflammatory and proatherogenic characteristics when the primary protein in HDL (apolipoprotein A-I) is modified by the enzyme myeloperoxidase. Myeloperoxidase is abundant in macrophages in the inflammatory reaction of the artery wall. (639) Clearly, more research is needed to understand the dynamic of HDL concentration and its properties in relation to CVD risk.

Testing of pharmacological therapy aiming to raise HDL levels is under way. Randomised controlled trials determining the effectiveness of pharmacological interventions on CVD risk should include a representative sample of those living to advanced age. Implementation of the identified interventions (both lifestyle changes and pharmacological) among people of advanced age is likely to be worthwhile. This is because the survival chance of those living to advanced age for another year remains well above 80% up to the age of 92 and 93 years for men and women respectively. (640-Period Life Table 2005-07) Furthermore, the significance of HDL levels on CVD risk in advanced age will inform the management of lipid profile in younger adults.

Blood pressure

The relationship between blood pressure and CVD risk in people of advanced age merits further investigation. To date, among the very elderly, a J-curve relationship has been observed between

blood pressure and all-cause mortality. (621-623) It has yet to be established if there is a J-curve relationship between blood pressure and CV events in the very elderly. Larger cohort studies with a representative sample of those living to advanced age are needed to determine the optimum blood pressure level for CVD risk and the chance of survival.

Inflammatory markers

Although this study found inflammatory markers were not associated with CVD in advanced age, future studies are needed to confirm this finding. As inflammatory markers were found to be more strongly related to risk of fatal vascular events than non-fatal vascular events in younger elderly (591), a similar methodical analysis should be replicated in people of advanced age. A collaborative re-examination of the limited existing data will enhance the study power in determining the relationships between inflammatory markers and specific CVDs in people of advanced age.

Echocardiography

There is no identified "normal range" defined by population studies for those in advanced age. This study found one-third of the study participants did not have clinically manifest CVD but nearly all had "abnormal" echocardiographic measures. One interpretation of this is that it may indicate that subclinical CVD is very prevalent in advanced age. Another interpretation is that these echocardiograms are not necessarily abnormal for this age group. Careful clinical interpretation is needed as most (94%) of those with no evidence of CVD and no symptoms of heart failure had some abnormality on echocardiogram.

What are the appropriate reference ranges for echocardiographic parameters in those living to advanced age? The clinical significance of cardiac abnormalities among people of advanced age needs to be determined in longitudinal cohort studies.

Brain natriuretic peptides

BNP and NT-proBNP can accurately diagnose heart failure. (420, 427) However, the Framingham Study found the diagnostic performance of BNP for LV dysfunction and elevated LV mass in the community was suboptimal. (641) NT-proBNP, a biomarker with a wider reference range, on the other hand, was found to have a better prognostic performance for asymptomatic

structural or functional cardiac abnormalities than BNP. (406, 410, 418, 426) In frail elderly (mean age 84 years), NT-proBNP values are able to discriminate the presence and absence of LV systolic and/or diastolic dysfunction. (642) In a population-based sample of nonagenarians, NT-proBNP was found to be a good predictor for CV and non-CV mortality in participants with and without specific cardiac diagnoses. (643) Considering the increasing atherosclerotic burden and remodelling of the heart with ageing, the prognostic performance of NT-proBNP and its ability to predict cardiac failure in people of advanced age warrants further investigation.

In brief, there is limited data assessing the cardiovascular health status and its relationship with conventional and emerging CV risk factors in advanced age. Concrete CV health data is needed to assist with the development and implementation of a health policy for older people, extending to the very elderly. This can be achieved through prospective cohort studies endeavouring to include a representative sample of octo- and nonagenarians.

Policy

Policy development to improve the well-being of those living to advanced age through better nutrition requires understanding of the current nutritional status. Adequate dietary intakes ensure availability of essential nutrients for proper bodily function. Timely dietary intervention for those at risk of undernutrition is a cost-effective strategy to prevent malnutrition and potentially prevent deterioration of cardiovascular health. Similarly, establishing recommendations of physical activity for people of advanced age should take into account the potential impact of physical activity on cardiovascular health. The risks and benefits of the type and intensity of physical activity need systematic assessment. In short, this study will assist in extension of the current nutritional policy and physical activity recommendations and/or guidelines for people of advanced age.

Practice

To date, clinical decisions in management of CVD in people of advanced age are mostly extrapolated from studies of the younger population. Concerning treatment for dyslipidemia, it remains an open debate as to the utility of cholesterol-lowering in old age. (563) In anticipation of future clinical trials involving people of advanced age, current evidence suggests clinicians should not be overly aggressive in controlling BP based on the present recommendation of SBP/DBP <140/90mmHg. (203) This is because overly low blood pressure may be harmful for people of

advanced age. Studies are ongoing in determining mechanisms of heart failure, and pharmacological interventions – particularly for diastolic heart failure – are being explored.

Echocardiography may be useful in making treatment decisions. Since the mechanism of LV systolic dysfunction and LV diastolic dysfunction is not the same (644, 645), different treatment approaches are needed. Heart failure with LV systolic dysfunction (low ejection fraction) is now well characterised and treatment with pharmacotherapy and device-based therapies is well established from large-scale clinical trials. However, heart failure with preserved LV ejection fraction, or "diastolic heart failure", is less well characterised, yet is a more common form of heart failure in the elderly. Treatment for these patients with heart failure remains uncertain as the current trials of pharmacotherapy with agents such as angiotensin II receptor antagonists have not demonstrated benefit. (644, 646, 647) Clinical assessment of LV systolic and diastolic function requires cardiac imaging, usually with echocardiography, to accurately differentiate these two main types of heart failure. However, access to echocardiography is relatively limited in many areas in New Zealand, an issue that may be important for elderly patients presenting with suspected heart failure in primary care.

Until further concrete findings emerge, the general treatment approach for systolic and diastolic heart failure is to target symptom relief and treatment of the underlying pathological disease (e.g. hypertension and coronary heart disease). (644) More data is needed to define effective clinical management of CVD in those living to advanced age.

10.3 Recent publications in relation to study findings

In finalising this thesis, several feature articles on HDL function, physical activity and the relationship between left ventricular geometry and function were published. One of the known cardioprotective roles of HDL is its ability to reverse cholesterol transport, also termed 'cholesterol efflux capacity'. (89, 648) In a cross-sectional analysis of a healthy cohort and a case-control cohort, Khera *et al.* (2011) (648) found that in healthy adults (mean age 51 years), HDL level was not associated with CIMT in unadjusted and adjusted models. Conversely, cholesterol efflux capacity was significantly inversely associated with CIMT controlling for age, sex, SBP, glycated

haemoglobin, LDL, and apolipoprotein A-1. In the case-control cohort[41], increased cholesterol efflux capacity was associated with a decreased risk of CAD adjusted for age, sex and traditional CV risk factors. The inverse relationship between cholesterol efflux capacity and CAD risk remained robust after the addition of HDL level to the logistic regression model. Findings from this study add to current evidence that HDL quality (i.e. cholesterol efflux capacity), not merely quantity, is reflective of the role of HDL in atheroprotection. Is the significant positive correlation between HDL levels and cholesterol efflux capacity observed in younger population (648) similar in advanced age?

Physical activity increases HDL levels in mid-age and older adults. (111, 520) The recently published ARIC study (a prospective population-based cohort study of more than 2,700 adults aged 60 and above) found that, in adults aged 75 years and above, compared to those who remained sedentary, increasing leisure-time physical activity over a 2-year period was associated with 62% lower mortality in the following 6 years [Hazard ratio (95% CI) 0.52 (0.38–0.70, $p<0.01$][42]; being continually active was associated with 55% lower mortality for the same duration [Hazard ratio (95% CI) 0.45 (0.33–0.62), $p<0.01$]. (649) The exact mechanism exhibited by physical activity in lowering mortality risk is unclear. However, improved HDL levels through physical activity provide a probable reason for the greater longevity. In the current study, physical activity was inversely associated with CVD. The follow-up period in the ARIC study was 6 years and the data analyses excluded participants with diabetes and those on lipid-lowering medication. (520) The long term benefit (beyond 6 years) of physical activity and the generalisability of these findings to those with diabetes and on lipid-lowering medication require further evaluation. Prospective studies are needed to examine the relationship between physical activity and HDL (and other cardiovascular biomarkers) in advanced age.

Remodelling of the left ventricle occurs with ageing. In the Cardiovascular Health Study, Desai *et al*. (2011) (650) reported that 18% (343 of the 1,871) of older adults (mean age 73 years) without heart failure had concentric LV geometry: 284 had concentric remodelling and 59 had concentric hypertrophy. The CHS data showed that remodelling of the LV concentric geometry was dynamic

[41] Cases are patients with luminal stenosis of more than 50% in a major coronary vessel and control are patients with no evidence of angiographic coronary disease and no history of MI

[42] The Cox regression models were adjusted for sex, age, educational level, smoking status, alcohol consumption, coronary disease, cancer, diabetes, hip fracture, SF-36 physical summary, Mini-Mental State Examination, BMI, waist circumference, limitation in mobility, limitation in agility, and limitation in instrumental activities of daily living.

in nature. Of those with LV concentric remodelling, after 7 years, 63% had a normalised LV geometry, 31% remained unchanged, 3% progressed to concentric hypertrophy and 4% progressed to eccentric hypertrophy. Of those with concentric hypertrophy, after 7 years, 29% had a normalised LV geometry, 24% regressed to concentric remodelling, 22% remained unchanged, and 25% progressed to eccentric hypertrophy. The reason for the high rate of regression from a concentric to normal LV geometry in this group of older adults is unclear. The authors speculate that it may be attributed to the use of antihypertensive drugs but a post hoc analysis showed similar results among those with hypertension regardless of the use of antihypertensive drugs. Explanation for these intriguing findings remains to be uncovered. Findings from the CHS study may be biased with a survivor cohort effect, i.e. participants had to be alive during the 7 years of follow-up for evaluation of LV geometry, resulting in a low rate of transition to eccentric geometry. Nevertheless, in a retrospective study of an echocardiographic report database with more than 9,700 patients with average age of 76 years, concentric remodelling was the most prevalent LV geometric pattern in adults age 70 years and above; this group had a 35% higher mortality rate than that of patients with normal geometry, 13% higher than that of patients with eccentric hypertrophy and a similar mortality rate to those with concentric hypertrophy. (651) The poorer outcome of older adults with concentric remodelling may be associated with impaired diastolic function, as observed in healthy (652) and hypertensive adults (653). In the current study, 84% of the study sample had hypertension and 68% had an enlarged left atrial area (which is related to LV diastolic dysfunction); LV geometry was not determined. Longitudinal studies are needed to examine the clinical relevance of LV geometry and its relationship to LV function in advanced age. The latest evidence has provided invaluable insight into examining the pathophysiology of CVD, particularly heart failure, in advanced age.

10.4 Summary

In summary, the pathophysiological pathways for CVD and those living to advanced age may differ from the younger population. HDL emerges as being the only conventional CV risk factor associated with CVD, independent of sex, age-ethnicity, smoking status, and waist circumference. The benefit of physical activity observed in younger adults seems to persist into advanced age. Although one-third of the study sample did not have clinically manifest CVD, nearly all of them had abnormal echocardiographic measures, suggesting sub-clinical CVD is common in those of advanced age. Follow-up is needed to establish the significance of abnormal echocardiographic

measures in this age group. Findings from this study add to the limited body of evidence in those living to advanced age.

Longitudinal studies are needed to understand the pathways leading to adverse cardiovascular health outcomes in the very old. Findings from this study and other studies of people in advanced age (Leiden 85+ and Newcastle 85+) signify the beginning of a journey unravelling factors which influence CV health in those living to advanced age. Conducting research in those of advanced age will be a challenge due to the heterogeneity of the population and the declining number in the cohort with time. Nevertheless, carefully planned research appreciating the inter-relationships between medical and non-medical components will provide valuable evidence. Such evidence will assist the development of appropriate intervention strategies and policy aiming to improve CV health and well-being in advanced age.

As the baby boomers enter old age, it is projected that by the year 2051, 6.4% of the New Zealand population will be 85 years and above, an increase of 507% compared to 2004. (3) CVD will continue to be the leading cause of mortality and morbidity in New Zealand, particularly in Māori. (452, 654, 655) Better understanding of the pathophysiological pathways and interaction between medical and non-medical components are needed to formulate preventative strategies and interventions to prepare for the tsunami of soon-to-be septuagenarians and octogenarians. This thesis contributes to these understandings.

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APPENDICES

APPENDIX A

Figure A-1 Multi-Region Ethics Committee approval letter
(2 pages)

Health and Disability Ethics Committees

Multi-Region Ethics Committee
Ministry of Health
Level 2, 1-3 The Terrace
PO Box 5013
Wellington
Phone (04) 470 0655
(04) 470 0646
Fax (04) 496 2191

1 June 2007

Dr Ngaire Kerse
Department of General Practice & Primary Health Care
The University of Auckland
Private Bag 92019
AUCKLAND

Dear Ngaire

Living to advanced age -feasibility for a cohort study
Lead Investigator: Dr Ngaire Kerse
Co-Investigators: Dr Lorna Dyall, Prof. Martin Connolly, A/Prof Tim Wilkinson, Assoc. Prof Robert Scragg, Mrs Joanna Broad, Prof. Alastair Scott, Ms Valerie Wright-St Clair
Approved Sites: Rotorua General Practice Group, University of Auckland
MEC/06/10/135

The above study has been given ethical approval by the **Multi-Region** Ethics Committee. A list of members of this committee is attached.

Approved Documents

- Information sheet for Participants in Qualitative Interviews – Korero with Older Maori ISKM Version 2-1, dated 9 May 2007
- Consent Form for Participants in the Korero part of the Cohort study CKFM Version 2-2, dated 9 May 2007
- Consent Form for Participants in the Interview and Assessment part of the Cohort study CFPA Version 2-2, dated 10 May 2007
- Information sheet for Participants, their whanau, relatives and friends ISPA Version 2-1, dated 3 November 2006
- Information sheet for Family, Whanau and Friends of Participants and Consent form ISKM Version 2-1, dated 3 November 2006
- Letter of Invitation
- Letter of Invitation from Iwi
- Draft Understanding Reaching Advanced Age: Interview and Assessment Questionnaire Version 2, dated 31 August 2006

Please provide a copy of the quantitative questionnaire so this can also be approved.

Certification
The Committee is satisfied that this study is not being conducted principally for the benefit of the manufacturer or distributor of the medicine or item in respect of which the trial is being carried out.

Accreditation
The Committee involved in the approval of this study is accredited by the Health Research Council and is constituted and operates in accordance with the Operational Standard for Ethics Committees, April 2006.

Progress Reports
The study is approved until **June 2009**. The Committee will review the approved application annually and notify the Lead Investigator if it withdraws approval. It is the Lead Investigator's responsibility to forward a progress report covering all sites prior to ethical review of the project in **31 May 2008**. The report form is available on http://www.newhealth.govt.nz/ethicscommittees. Please note that failure to provide a progress report may result in the withdrawal of ethical approval. A final report is also required at the conclusion of the study.

Requirements for SAE Reporting
The Lead Investigator will inform the Committee as soon as possible of the following:

- Any related study in another country that has stopped due to serious or unexpected adverse events
- withdrawal from the market for any reason
- all serious adverse events occurring during the study in New Zealand which result in the investigator or sponsor breaking the blinding code at the time of the SAE or which result in hospitalisation or death.
- all serious adverse events occurring during the study worldwide which are considered related to the study medicine. Where there is a data safety monitoring board in place, serious adverse events occurring outside New Zealand may be reported quarterly.

All SAE reports must be signed by the Lead Investigator and include a comment on whether he/she considers there are any ethical issues relating to this study continuing due to this adverse event. If the adverse event is local and does not have the sponsor's report attached, an opinion on whether the event is thought to be related to the study should be given along with any other pertinent information. It is assumed by signing the report, the Lead Investigator has undertaken to ensure that all New Zealand investigators are made aware of the event.

Amendments
All amendments to the study must be advised to the Committee prior to their implementation, except in the case where immediate implementation is required for reasons of safety. In such cases the Committee must be notified as soon as possible of the change.

Please quote the above ethics committee reference number in all correspondence.

The Lead Investigator is responsible for advising any other study sites of approvals and all other correspondence with the Ethics Committee.

It should be noted that Ethics Committee approval does not imply any resource commitment or administrative facilitation by any healthcare provider within whose facility the research is to be carried out. Where applicable, authority for this must be obtained separately from the appropriate manager within the organisation.

Yours sincerely

Rebecca Graham
Multi-region Administrator
Email: rebecca_graham@moh.govt.nz

TABLE A-1: Biomarkers analyses method

Test	Methods
PLP	High performance liquid chromatography, with fluorometric detection
Cobalamin	Competitive assay, electrochemiluminescence reading and processed on the E module of the Roche Modular analyser.
25-OH D	Competitive assay, electrochemiluminescence reading and processed on the E module of the Roche Modular analyser.
Serum glucose	GOD-PAP method
TC	Enzymatic colorimetric test, processed on Hitachi Analyser 911, Roche
TG	Enzymatic colorimetric test, processed on Hitachi Analyser 911, Roche
HDL-C	Homogenous Enzymatic colorimetric test, processed on Hitachi Analyser 911, Roche
LDL-C	Friedewald formula:
	LDL-C (mmol/L) = Total cholesterol - HDL - (triglycerides x 0.456)
High-sensitive CRP	Antigen-antibody method, immunoturbidimetric reading and processed on the P module of the Roche Modular analyser
IL-6	Immunology assay using ELISA kits from Bender Med Systems
ESR	Westergren manual method
TNF-α	Immunology assay using ELISA kits from Bender Med Systems
Fibrinogen	von Clauss method, Stago StaR Evolution coagulation analyser, Roche-Diagnostics.
NT-proBNP	Sandwich principle, electrochemilluminescence reading and processed on the E module of the Roche Modular analyser

Abbreviations: **25-OH D:** 25-hydroxyvitamin D; **CRP:** C-reactive protein; **ESR:** erythrocyte sedimentation rate; **HDL:** high-density lipoprotein; **IL-6:** Interleukin-6; **LDL:** low-density lipoprotein; **NT-proBNP**: N-terminal pro-brain natriuretic peptide; **PLP:** Pyridoxal 5' phosphate; **TC:** total cholesterol; **TG:** triglyceride; **TNF-α:** tumour necrosis factor-alpha

APPENDIX B

TABLE B-1: Correlation between SCREEN II score with conventional CV risk factors, nutrition biomarkers, and inflammatory markers using Spearman's correlation test

	Variables	Correlation coefficient	P value
Conventional CV risk factors	Fasting serum glucose	-0.003	0.981
	Systolic blood pressure (SBP)	-0.017	0.868
	Diastolic blood pressure (DBP)	0.141	0.160
	Total cholesterol (TC)	-0.104	0.335
	Triglyceride (TG)	-0.114	0.292
	High-density lipoprotein (HDL)	-0.048	0.654
	Low-density lipoprotein (LDL)	-0.062	0.567
	TC-HDL ratio	-0.001	0.996
	Body mass index (BMI)	-0.098	0.330
	Waist circumference (WC)	-0.035	0.727
	Waist-to-hip ratio (WHR)	0.091	0.373
	Body fat percentage (BF%)	-0.361**	**0.000**
Nutrition biomarkers	Pyridoxal 5' phosphate (PLP)	-0.138	0.206
	Cobalamin	0.060	0.576
	25 hydroxyvitamin D (25-OH D)	0.019	0.862
Inflammatory markers	C-reactive protein (CRP)	-0.100	0.352
	Interleukin-6 (IL-6)	-0.002	0.990
	Tumour necrosis factor-alpha (TNF-α)*	-0.027	0.823
	Erythrocyte sedimentation rate (ESR)	-0.129	0.231
	Fibrinogen	-0.068	0.545

TABLE B-2: Correlation between PASE score with conventional CV risk factors, nutrition biomarkers, and inflammatory markers using Spearman's correlation test

	Variables	Correlation coefficient	P value
Conventional CV risk factors	Fasting serum glucose	-0.097	0.369
	Systolic blood pressure (SBP)	-0.011	0.914
	Diastolic blood pressure (DBP)	0.157	0.115
	Total cholesterol (TC)	-0.057	0.594
	Triglyceride (TG)	-0.130	0.224
	High-density lipoprotein (HDL)	0.089	0.407
	Low-density lipoprotein (LDL)	-0.077	0.473
	TC-HDL ratio	-0.144	0.178
	Body mass index (BMI)	0.196	**0.048**
	Waist circumference (WC)	0.136	0.174
	Waist-to-hip ratio (WHR)	0.039	0.697
	Body fat percentage (BF%)	-0.043	0.677
Nutrition biomarkers	Pyridoxal 5' phosphate (PLP)	0.069	0.524
	Cobalamin	0.095	0.374
	25 hydroxyvitamin D (25-OH D)	0.188	0.080
Inflammatory markers	C-reactive protein (CRP)	-0.134	0.211
	Interleukin-6 (IL-6)	0.100	0.399
	Tumour necrosis factor-alpha (TNF-α)*	-0.005	0.964
	Erythrocyte sedimentation rate (ESR)	-0.160	0.134
	Fibrinogen	-0.243	**0.027**
	• Sensitivity analysis [a]	-0.215	0.052

* Entered as categorical data, i.e. <1.0 and ≥1.0pg/mL
[a] Excluded the high fibrinogen value

Figure B-1: Total PASE score and its components across BMI categories according to sex and age-ethnic groups

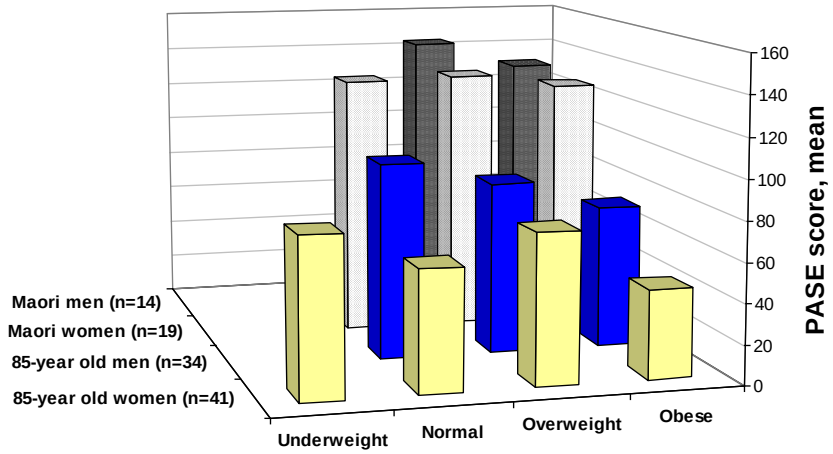


Figure B-1a:
PASE score for Māori and non-Māori, men and women across BMI categories

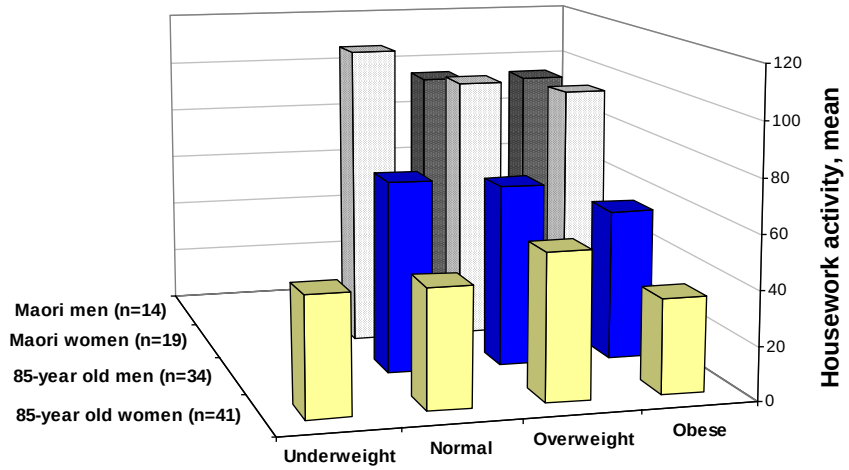


Figure B-1b:
Housework related activity for Māori and non-Māori, men and women across BMI categories

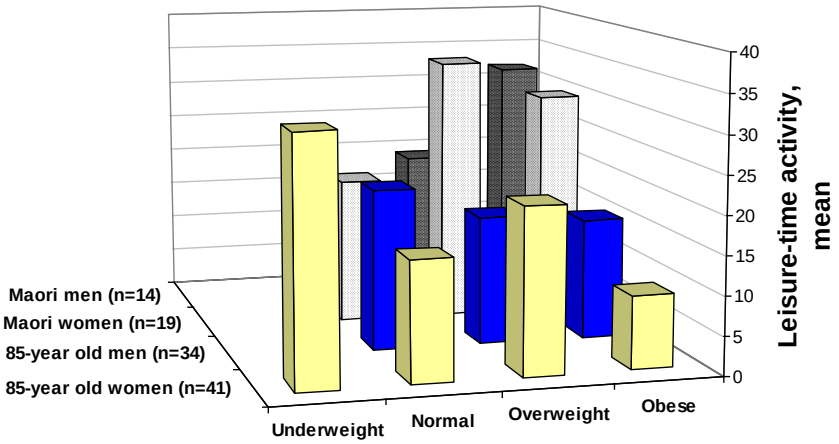
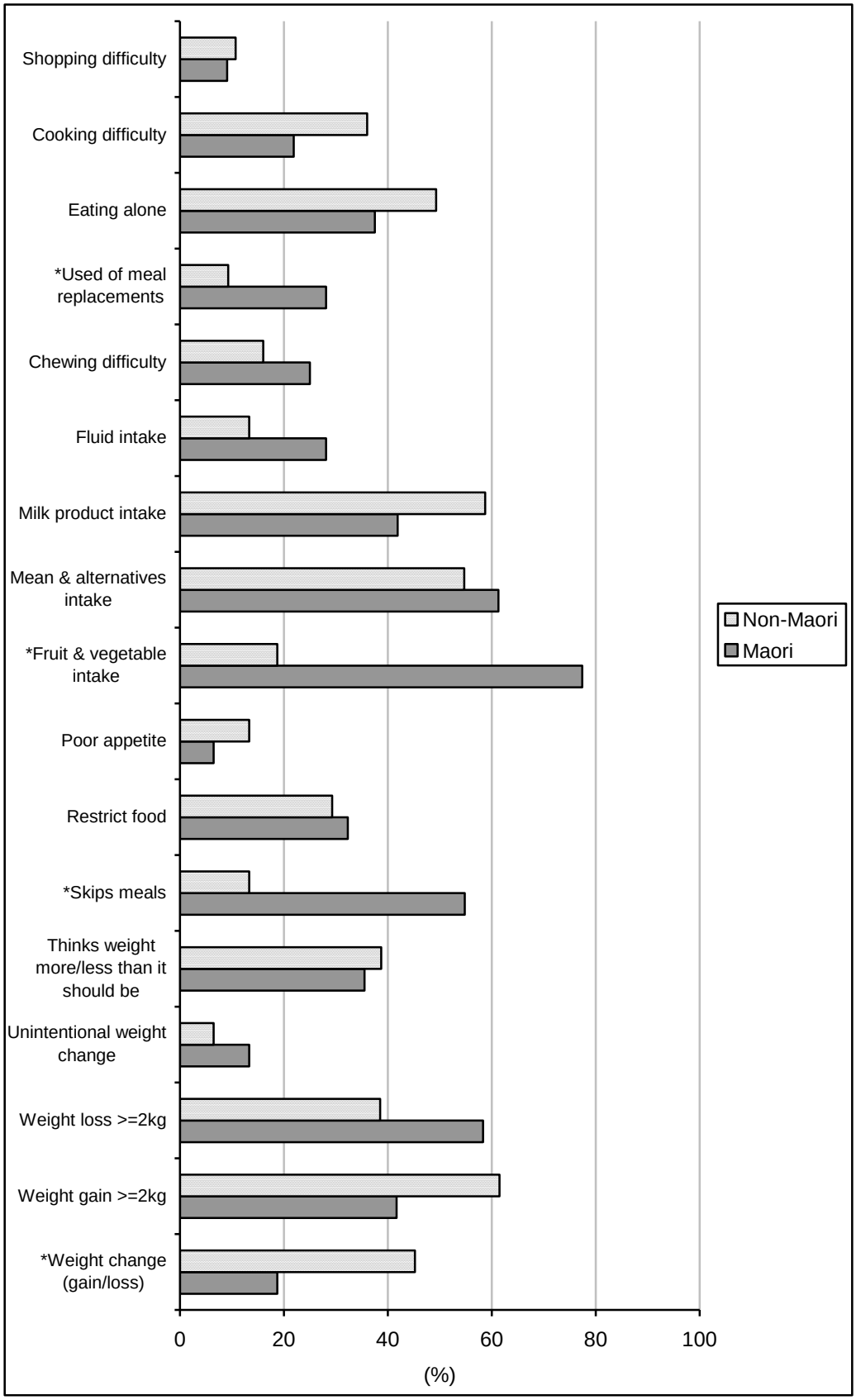


Figure B-1c:
Leisure-time activity for Māori and non-Māori, men and women across BMI categories

Figure B-2: The proportion of SCREEN II item scoring ≤2† between Māori and non-Māori



† SCREEN II items with scores ≤2 out of a maximum score of four, potentially lead to 'nutritional risk'

TABLE B-3: Logistic regression models between CVD (dependent variable) and fasting serum glucose (independent variable)

Variables	Model 1		Model 2	
	OR (95% CI)	P value	OR (95% CI)	P value
Sex (ref: men)	0.439 (0.167–1.154)	0.095	0.322 (0.105–0.988)	0.048
Age-ethnicity (ref: NZ European)	1.479 (0.496–4.410)	0.482	1.427 (0.387–5.262)	0.593
Smoking, (ref: never)		0.876		0.869
Current	0.686 (0.089–5.306)	0.718	0.594 (0.063–5.614)	0.649
Former	1.155 (0.438–3.050)	0.771	0.813 (0.270–2.449)	0.713
Glucose-lowering med (ref: no)			17.191 (0.386–766.125)	0.142
Fasting serum glucose	0.884 (0.645–1.211)	0.442	0.642 (0.405–1.018)	0.060
Nagelkerke R^2	0.071		0.156	

Abbreviations: **med**: medications; **OR:** odds ratio; **ref**: reference

TABLE B-4: Logistic regression models between CVD (dependent variable) and systolic blood pressure (independent variable)

Variables	Model 1		Model 2		Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Sex (ref: men)	0.606 (0.250–1.467)	0.267	0.607 (0.249–1.480)	0.272	0.468 (0.181–1.214)	0.119
Age-ethnicity (ref: NZ European)	1.433 (0.537–3.820)	0.472	1.432 (0.536–3.822)	0.474	1.747 (0.616–4.952)	0.294
Smoking (ref: never)		0.858		0.859		0.708
Current	0.806 (0.122–5.337)	0.823	0.807 (0.122–5.352)	0.824	0.539 (0.075–3.863)	0.539
Former	1.232 (0.500–3.031)	0.650	1.231 (0.500–3.030)	0.651	1.228 (0.485–3.107)	0.665
Systolic BP	0.991 (0.971–1.011)	0.394	0.991 (0.971–1.012)	0.409	0.991 (0.970–1.012)	0.386
Med for hypertension (ref: no)			0.987 (0.385–2.469)	0.978		
Med affect BP (ref: no)					2.926 (1.158–7.398)	0.023
Nagelkerke R^2	0.041		0.041		0.110	

Abbreviations: **BP**: blood pressure; **med**: medications; **OR:** odds ratio; **ref**: reference

TABLE B-5: Logistic regression models between CVD (dependent variable) and diastolic blood pressure (independent variable)

Variables	Model 1		Model 2		Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Sex(ref: men)	0.552 (0.228–1.340)	0.189	0.557 (0.227–1.365)	0.201	0.435 (0.168–1.127)	0.087
Age-ethnicity (ref: NZ European)	1.552 (0.580–4.151)	0.382	1.546 (0.577–4.146)	0.386	1.842 (0.652–5.201)	0.249
Smoking (ref: never)		0.826		0.828		0.680
Current	0.668 (0.097–4.579)	0.681	0.671 (0.098–4.609)	0.685	0.479 (0.065–3.499)	0.468
Former	1.187 (0.484–2.908)	0.708	1.187 (0.484–2.909)	0.708	1.176 (0.468–2.952)	0.730
Diastolic BP	0.978 (0.944–1.013)	0.220	0.978 (0.944–1.014)	0.225	0.982 (0.948–1.018)	0.328
Med for hypertension (ref: no)			0.952 (0.385–2.353)	0.915		
Med affect BP (ref: no)					2.768 (1.092–7.018)	0.032
Nagelkerke R^2	0.052		0.052		0.113	

Abbreviations: **BP**: blood pressure; **med**: medications; **OR:** odds ratio; **ref**: reference

TABLE B-6: Logistic regression model between CVD (dependent variable) and BMI (independent variable)

Variables	Odds ratio (95% CI)	P value
Sex (ref: men)	0.662 (0.270 – 1.620)	0.366
Age-ethnicity (ref: NZ European)	0.842 (0.266 – 2.663)	0.769
Smoking (ref: never)		0.909
Current	0.982 (0.145 – 6.663)	0.985
Former	1.218 (0.492 – 3.012)	0.670
Body mass index	1.083 (0.985 – 1.190)	0.098
Nagelkerke R^2	0.074	

TABLE B-7: Logistic regression models between CVD (dependent variable) and WC (independent variable)

Variables	Odds ratio (95% CI)	P value
Sex (ref: men)	0.818 (0.301 – 2.224)	0.694
Age-ethnicity (ref: NZ European)	1.048 (0.367 – 2.996)	0.930
Smoking (ref: never)		0.948
Current	0.916 (0.133 – 6.320)	0.929
Former	1.145 (0.463 – 2.830)	0.769
Waist circumference	1.027 (0.992 – 1.063)	0.131
Nagelkerke R^2	0.063	

TABLE B-8: Logistic regression models between CVD (dependent variable) and WHR (independent variable)

Variables	Odds ratio (95% CI)	P value
Sex (ref: men)	0.635 (0.202 – 1.995)	0.437
Age-ethnicity (ref: NZ European)	1.404 (0.526 – 3.750)	0.499
Smoking (ref: never)		0.918
Current	0.868 (0.131 – 5.759)	0.883
Former	1.177 (0.477 – 2.905)	0.724
WHR*	1.007 (0.942 – 1.077)	0.835
Nagelkerke R^2	0.030	

* The odds ratio for WHR (waist-to-hip ratio) is an increased of 0.01 unit

TABLE B-9: Logistic regression models between CVD (dependent variable) and percentage of body fat (independent variable)

Variables	Odds ratio (95% CI)	P value
Sex (ref: men)	0.464 (0.161 – 1.340)	0.156
Age-ethnicity (ref: NZ European)	1.448 (0.507 – 4.133)	0.489
Smoking (ref: never)		0.964
Current	0.838 (0.125 – 5.622)	0.856
Former	1.079 (0.428 – 2.718)	0.872
BF%	1.003 (0.943 – 1.067)	0.912
Nagelkerke R^2	0.047	

Abbreviations: **BF%**: percentage of body fat; **ref**: reference

TABLE B-10: Logistic regression models between CVD (dependent variable) and total cholesterol (independent variable)

Variables	Model 1		Model 2	
	OR (95% CI)	P value	OR (95% CI)	P value
Sex (ref: men)	0.646 (0.236–1.774)	0.397	0.603 (0.215–1.686)	0.335
Age-ethnicity (ref: NZ European)	1.167 (0.401–3.398)	0.777	1.154 (0.396–3.365)	0.793
Smoking, (ref: never)		0.887		0.888
Current	0.851 (0.116–6.240)	0.874	0.881 (0.118–6.565)	0.902
Former	1.236 (0.470–3.252)	0.668	1.245 (0.472–3.278)	0.658
Lipid lowering med (ref: no)			1.637 (0.534–5.018)	0.388
Total cholesterol	0.884 (0.645–1.211)	0.187	0.786 (0.488–1.266)	0.322
Nagelkerke R^2	0.074		0.085	

Abbreviations: **med**: medications; **OR:** odds ratio; **ref**: reference

TABLE B-11: Logistic regression models between CVD (dependent variable) and triglycerides (independent variable)

Variables	Model 1		Model 2	
	OR (95% CI)	P value	OR (95% CI)	P value
Sex (ref: men)	0.468 (0.180–1.215)	0.119	0.454 (0.173–1.191)	0.109
Age-ethnicity (ref: NZ European)	1.262 (0.442–3.607)	0.664	1.246 (0.432–3.589)	0.684
Smoking, (ref: never)		0.836		0.846
Current	0.745 (0.100–5.539)	0.774	0.776 (0.104–5.810)	0.805
Former	1.255 (0.482–3.265)	0.641	1.257 (0.480–3.294)	0.641
Lipid lowering med (ref: no)			1.938 (0.662–5.674)	0.227
Triglyceride	1.316 (0.645–2.685)	0.451	1.300 (0.648–2.605)	0.460
Nagelkerke R2	0.057		0.079	

Abbreviations: **med**: medications; **OR:** odds ratio; **ref**: reference

TABLE B-12: Logistic regression models between CVD (dependent variable) and high-density lipoprotein (independent variable)

Variables	Model 1		Model 2	
	OR (95% CI)	P value	OR (95% CI)	P value
Sex (ref: men)	0.584 (0.222–1.535)	0.276	0.567 (0.214–1.501)	0.254
Age-ethnicity (ref: NZ European)	1.015 (0.341–3.026)	0.978	0.987 (0.329–2.962)	0.982
Smoking, (ref: never)		0.664		0.685
Current	0.609 (0.078–4.761)	0.637	0.646 (0.082–5.116)	0.679
Former	1.417 (0.529–3.796)	0.489	1.417 (0.526–3.814)	0.491
Lipid lowering med (ref: no)			1.865 (0.630–5.520)	0.260
HDL	0.306 (0.097–0.965)	0.043	0.316 (0.100–1.000)	0.050
Nagelkerke R2	0.110		0.129	

Abbreviations: **HDL**: high-density lipoprotein; **med**: medications; **OR:** odds ratio; **ref**: reference

TABLE B-13: Logistic regression models between CVD (dependent variable) and low-density lipoprotein (independent variable)

Variables	Model 1		Model 2	
	OR (95% CI)	P value	OR (95% CI)	P value
Sex (ref: men)	0.567 (0.213–1.511)	0.257	0.525 (0.193–1.424)	0.206
Age-ethnicity (ref: NZ European)	1.233 (0.429–3.543)	0.698	1.224 (0.425–3.528)	0.709
Smoking, (ref: never)		0.900		0.883
Current	0.859 (0.117–6.284)	0.881	0.865 (0.116–6.456)	0.887
Former	1.220 (0.465–3.201)	0.686	1.247 (0.473–3.287)	0.655
Lipid lowering med (ref: no)			1.791 (0.577–5.557)	0.313
LDL	0.807 (0.486–1.339)	0.406	0.888 (0.519–1.520)	0.665
Nagelkerke R2	0.058		0.074	

Abbreviations: **med**: medications; **LDL**: low-density lipoprotein; **OR:** odds ratio; **ref**: reference

TABLE B-14: Logistic regression models between CVD (dependent variable) and TC/HDL ratio (independent variable)

Variables	Model 1		Model 2	
	OR (95% CI)	P value	OR (95% CI)	P value
Sex (ref: men)	0.494 (0.193–1.263)	0.141	0.471 (0.181–1.221)	0.121
Age-ethnicity (ref: NZ European)	1.239 (0.434–3.535)	0.689	1.206 (0.417–3.489)	0.729
Smoking, (ref: never)		0.750		0.726
Current	0.664 (0.083–5.285)	0.699	0.646 (0.079–5.285)	0.684
Former	1.332 (0.511–3.472)	0.557	1.356 (0.515–3.566)	0.537
Lipid lowering med (ref: no)			2.210 (0.735–6.647)	0.158
TC/HDL ratio	1.192 (0.773–1.839)	0.427	1.275 (0.817–1.988)	0.284
Nagelkerke R^2	0.057		0.088	

Abbreviations: **med**: medications; **OR:** odds ratio; **ref**: reference; **TC/HDL ratio**: total cholesterol to high-density lipoprotein ratio

TABLE B-15: Logistic regression models between CVD (dependent variable) and CRP (independent variable)

Variables	Model 1		Model 2		Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Sex (ref: men)	0.545 (0.211–1.406)	0.209	0.525 (0.202–1.366)	0.187	0.497 (0.184–1.342)	0.168
Age-ethnicity (ref: NZ European)	1.540 (0.509–4.660)	0.445	1.492 (0.490–4.540)	0.481	2.132 (0.658–6.905)	0.207
Smoking (ref: never)		0.839		0.854		0.619
Current	0.684 (0.091–5.135)	0.712	0.720 (0.094–5.491)	0.752	0.660 (0.085–5.114)	0.691
Former	1.209 (0.462–3.162)	0.699	1.214 (0.461–3.194)	0.694	1.512 (0.546–4.189)	0.426
CRP	0.965 (0.897–1.037)	0.329	0.969 (0.905–1.037)	0.366	0.968 (0.896–1.045)	0.403
Lipid lowering med (ref: no)			1.799 (0.611–5.298)	0.286		
Aspirin (ref: no)					3.977 (1.439–10.997)	0.008
Nagelkerke R^2	0.073		0.091		0.183	

Abbreviations: **CRP:** C-reactive protein; **med**: medications; **OR:** odds ratio; **ref**: reference

TABLE B-16: Logistic regression models between CVD (dependent variable) and IL-6 (independent variable)

Variables	Model 1		Model 2		Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Sex (ref: men)	0.653 (0.228–1.867)	0.427	0.675 (0.232–1.960)	0.469	0.613 (0.204–1.843)	0.384
Age-ethnicity (ref: NZ European)	1.299 (0.384–4.395)	0.674	1.225 (0.355–4.230)	0.748	1.889 (0.504–7.077)	0.345
Smoking (ref: never)		0.977		0.962		0.864
Current	1.308 (0.113–15.193)	0.830	1.391 (0.115–16.782)	0.795	1.195 (0.093–15.339)	0.891
Former	1.010 (0.350–2.915)	0.985	1.079 (0.367–3.168)	0.890	1.368 (0.437–4.285)	0.590
IL-6	1.017 (0.913–1.134)	0.754	1.029 (0.918–1.153)	0.625	1.019 (0.883–1.175)	0.797
Lipid lowering med (ref: no)			3.395 (0.870–13.241)	0.078		
Aspirin (ref: no)					5.355 (1.683–17.042)	0.004
Nagelkerke R^2	0.020		0.086		0.183	

Abbreviations: **IL-6**: Interleukin-6; **med**: medications; **OR:** odds ratio; **ref**: reference

TABLE B-17: Logistic regression models between CVD (dependent variable) and TNF-α (independent variable)

Variables	Model 1		Model 2		Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Sex (ref: men)	0.644 (0.226–1.837)	0.411	0.659 (0.226–1.918)	0.444	0.604 (0.200–1.822)	0.371
Age-ethnicity (ref: NZ European)	1.378 (0.403–4.704)	0.609	1.307 (0.374–4.564)	0.675	2.031 (0.537–7.683)	0.297
Smoking (ref: never)		0.961		0.938		0.871
Current	1.410 (0.121–16.395)	0.783	1.568 (0.129–19.071)	0.724	1.258 (0.099–16.011)	0.860
Former	0.991 (0.342–2.871)	0.987	1.060 (0.362–3.157)	0.904	1.351 (0.431–4.231)	0.606
TNF-α	3.216 (0.357–28.987)	0.298	3.885 (0.418–36.092)	0.233	2.614 (0.254–26.942)	0.419
Lipid lowering med (ref: no)			3.570 (0.909–14.020)	0.068		
Aspirin (ref: no)					5.178 (1.614–16.611)	0.006
Nagelkerke R^2	0.043		0.113		0.193	

Abbreviations: **TNF-α:** Tumour necrosis factor-alpha; **med**: medications; **OR:** odds ratio; **ref**: reference

TABLE B-18: Logistic regression models between CVD (dependent variable) and fibrinogen (independent variable)

Variables	Model 1		Model 2		Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Sex (ref: men)	0.552 (0.208–1.466)	0.233	0.529 (0.197–1.419)	0.206	0.506 (0.182–1.407)	0.192
Age-ethnicity (ref: NZ European)	1.608 (0.503–5.137)	0.423	1.550 (0.482–4.989)	0.462	2.308 (0.664–8.027)	0.189
Smoking (ref: never)		0.846		0.870		0.629
Current	0.599 (0.077–4.631)	0.623	0.640 (0.082–5.018)	0.671	0.611 (0.076–4.906)	0.643
Former	1.111 (0.413–2.991)	0.835	1.119 (0.413–3.030)	0.825	1.485 (0.512–4.300)	0.467
Fibrinogen	1.132 (0.746–1.718)	0.560	1.142 (0.751–1.737)	0.534	1.124 (0.784–1.611)	0.524
Lipid lowering med (ref: no)			1.874 (0.631–5.567)	0.258		
Aspirin (ref: no)					4.300 (1.497–12.353)	0.007
Nagelkerke R^2	0.050		0.071		0.174	

Abbreviations: **med**: medications; **OR:** odds ratio; **ref**: reference

TABLE B-19: Logistic regression models between CVD (dependent variable) and ESR (independent variable)

Variables	Model 1		Model 2		Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Sex (ref: men)	0.475 (0.182–1.241)	0.129	0.454 (0.171–1.204)	0.113	0.453 (0.166–1.240)	0.123
Age-ethnicity (ref: NZ European)	1.227 (0.427–3.523)	0.704	1.201 (0.415–3.476)	0.735	1.778 (0.568–5.566)	0.323
Smoking (ref: never)		0.836		0.844		0.585
Current	0.770 (0.105–5.665)	0.797	0.800 (0.108–5.949)	0.827	0.733 (0.095–5.647)	0.766
Former	1.266 (0.488–3.283)	0.628	1.270 (0.486–3.317)	0.625	1.604 (0.583–4.409)	0.360
ESR	1.007 (0.978–1.037)	0.617	1.009 (0.978–1.041)	0.570	1.004 (0.973–1.036)	0.807
Lipid lowering med (ref: no)			1.990 (0.676–5.859)	0.212		
Aspirin (ref: no)					4.076 (1.473–11.280)	0.007
Nagelkerke R^2	0.051		0.076		0.174	

Abbreviations: **ESR:** Erythrocyte sedimentation rate; **med**: medications; **OR:** odds ratio; **ref**: reference

TABLE B-20: Sensitivity analyses for TABLE 7-22

Variables	Model 1 OR (95% CI)	P value	Model 2 OR (95% CI)	P value
Sex (ref: men)	0.409 (0.119–1.407)	0.156	0.529 (0.127–2.210)	0.383
Age-ethnicity (ref: NZ European)	0.945 (0.184–4.859)	0.946	1.257 (0.265–5.962)	0.774
Smoking, (ref: never)		0.373		0.375
Current	0.145 (0.010–2.153)	0.160	0.142 (0.009–2.180)	0.161
Former	0.890 (0.268–2.952)	0.848	0.866 (0.264–2.846)	0.813
Anti-diabetic med (ref: no)	2.233E9 (0.000–...)	0.999	1.278E9 (0.000–...)	0.999
Serum glucose	0.534 (0.283–1.010)	0.054	0.544 (0.291–1.020)	0.058
HDL	0.287 (0.065–1.259)	0.098	0.257 (0.059–1.115)	0.070
BMI	0.118 (0.973–1.285)	0.117		
WC			1.028 (0.0981–1.078)	0.240
Nagelkerke R^2	0.297		0.271	

Abbreviations: **BMI:** Body mass index; **HDL:** high-density lipoprotein; **med**: medications; **OR:** odds ratio; **ref**: reference; **WC:** waist circumference

TABLE B-21: Seasonal variation of CRP levels

	n	CRP (mg/L), Mean (SD)
Nov 2007–Jan 2008	9	2.04 (1.13)
March–May 2008	55	2.82 (3.38)
June–August 2008	24	7.89 (19.56) [a]
September–October 2008	2	0.75 (2.21)
ANOVA		p=0.219

[a] Excluding the outlier 97mg/L, the mean (SD) value = 4.02 (4.82); there remain no significant difference between the four groups, p=0.358

TABLE B-22: CIMT value between participants who receive and those do not receive lipid-lowering and blood pressure-lowering medication

	Lipid-lowering medication		
	No (n=73)	**Yes (n=25)**	**P value [a]**
Median (IQR)	1.064 (0.268)	1.095 (0.268)	0.906

	Blood pressure-lowering medication		
	No (n=36)	**Yes (n=62)**	**P value [a]**
Median (IQR)	1.071 (0.183)	1.052 (0.304)	0.751

Abbreviation: **CIMT**: Carotid intima-media thickness**; IQR:** interquartile range
[a] P values are from Mann-Whitney U test

TABLE B-23: Logistic regression models between CVD (dependent variable) and CIMT (independent variable)

Variables	Model 1		Model 2		Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Sex (ref: men)	0.465 (0.188–1.152)	0.098	0.464 (0.187–1.150)	0.097	0.316 (0.113–0.881)	0.028
Age-ethnicity (ref: NZ European)	1.457 (0.540–3.932)	0.457	1.425 (0.525–3.867)	0.487	1.798 (0.620–5.211)	0.280
Smoking (ref: never)		0.908		0.938		0.791
Current	0.764 (0.098–5.950)	0.797	0.826 (0.104–6.553)	0.856	0.555 (0.067–4.564)	0.584
Former	1.155 (0.465–2.869)	0.756	1.138 (0.457–2.834)	0.781	1.164 (0.453–2.994)	0.752
CIMT	0.547 (0.107–2.798)	0.468	0.554 (0.108–2.839)	0.478	0.376 (0.064–2.188)	0.276
Lipid lowering med (ref: no)			1.362 (0.485–3.824)	0.557		
Med affect BP (ref: no)					3.596 (1.339–9.659)	0.011
Nagelkerke R^2	0.056		0.061		0.147	

Abbreviation: **BP**: blood pressure; **CIMT**: Carotid intima-media thickness**; OR**: odds ratio; **ref**: reference

TABLE B-24: Logistic regression models between atherosclerotic CVD (dependent variable) and CIMT (independent variable)

Variables	Model 1		Model 2		Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Sex (ref: men)	0.448 (0.186–1.082)	0.074	0.442 (0.182–1.075)	0.072	0.303 (0.112–0.816)	0.018
Age-ethnicity (ref: NZ European)	2.868 (1.070–7.688)	0.036	2.789 (1.033–7.535)	0.043	3.776 (1.287–11.078)	0.016
Smoking (ref: never)		0.644		0.733		0.456
Current	0.387 (0.048–3.091)	0.370	0.439 (0.054–3.578)	0.442	0.275 (0.033–2.273)	0.231
Former	1.062 (0.439–2.57)	0.894	1.027 (0.420–2.507)	0.954	1.085 (0.432–2.727)	0.862
CIMT	0.556 (0.104–2.962)	0.492	0.563 (0.104–3.052)	0.506	0.403 (0.069–2.361)	0.314
Lipid lowering med (ref: no)			1.687 (0.623–4.570)	0.303		
Med affect BP (ref: no)					3.880 (1.446–10.406)	0.007
Nagelkerke R^2	0.108		0.122		0.205	

Abbreviation: **BP**: blood pressure; **CIMT**: Carotid intima-media thickness**; OR**: odds ratio; **ref**: reference

TABLE B-25: Logistic regression models between CVD (dependent variable) and NT-proBNP (independent variable)

Variables	Model 1 OR (95% CI)	P value	Model 2 OR (95% CI)	P value
Sex (ref: men)	0.503 (0.175–1.447)	0.203	0.433 (0.141–1.335)	0.145
Age-ethnicity (ref: NZ European)	1.349 (0.429–4.244)	0.608	1.936 (0.545–6.877)	0.307
Smoking, (ref: never)		0.481		0.272
Current	0.240 (0.023–2.558)	0.237	0.142 (0.012–1.671)	0.121
Former	1.007 (0.335–3.033)	0.990	1.087 (0.338–3.489)	0.889
Medication for HF (ref: no)			3.956 (1.219–2.834)	0.022
NT-proBNP	1.022 (1.002–1.042)	0.032	1.017 (0.998–1.035)	0.073
Nagelkerke R^2	0.200		0.281	

Abbreviation: **NT-proBNP**: N-terminal pro-brain natriuretic peptide**; OR**: odds ratio; **ref**: reference

TABLE B-26: Logistic regression models between heart disease (dependent variable) and NT-proBNP (independent variable)

Variables	Model 1 OR (95% CI)	P value	Model 2 OR (95% CI)	P value
Sex (ref: men)	0.842 (0.299–2.373)	0.745	0.791 (0.269–2.323)	0.670
Age-ethnicity (ref: NZ European)	2.739 (0.846–8.872)	0.093	3.927 (1.058–14.571)	0.041
Smoking, (ref: never)		0.450		0.260
Current	0.371 (0.032–4.280)	0.427	0.239 (0.019–2.978)	0.266
Former	1.603 (0.538–4.777)	0.397	1.867 (0.594–5.872)	0.285
Medication for HF (ref: no)			3.503 (1.055– 11.627)	0.041
NT-proBNP	1.027 (1.007–1.047)	0.008	1.023 (1.003–1.043)	0.021
Nagelkerke R^2	0.313		0.369	

Abbreviation: **NT-proBNP**: N-terminal pro-brain natriuretic peptide**; OR**: odds ratio; **ref**: reference

TABLE B-27: Logistic regression models between CVD (dependent variable) and LVM (independent variable)

Variables	Model 1 OR (95% CI)	P value	Model 2 OR (95% CI)	P value
Sex (ref: men)	0.378 (0.137–1.039)	0.059	0.220 (0.067–0.725)	0.013
Age-ethnicity (ref: NZ European)	0.976 (0.281–3.387)	0.970	0.571 (0.395–6.256)	0.522
Smoking, (ref: never)		0.960		0.803
Current	0.678 (0.046–10.046)	0.777	0.414 (0.027–6.440)	0.529
Former	0.966 (0.356–2.621)	0.946	0.854 (0.298–2.448)	0.769
Medication affect LVM (ref: no)			5.461 (1.656–18.007)	0.005
$LVM/Ht^{2.7}$	1.026 (0.994–1.059)	0.115	1.027 (0.993–1.062)	0.124
Nagelkerke R^2	0.112		0.240	

Abbreviation: **LVM:** left ventricular mass; **$LVM/Ht^{2.7}$**: left ventricular mass indexed to height; **OR**: odds ratio; **ref**: reference

TABLE B-28: Logistic regression models between heart disease (dependent variable) and LVM (independent variable)

Variables	Model 1		Model 2	
	OR (95% CI)	P value	OR (95% CI)	P value
Sex (ref: men)	0.853 (0.339–2.148)	0.736	0.627 (0.231–1.704)	0.360
Age-ethnicity (ref: NZ European)	1.278 (0.405–4.037)	0.676	1.730 (0.497–6.021)	0.389
Smoking, (ref: never)		0.715		0.764
Current	1.169 (0.085–16.055)	0.907	0.976 (0.066–14.511)	0.986
Former	1.487 (0.575–3.845)	0.413	1.439 (0.540–3.836)	0.467
Medication affect LVM (ref: no)			3.855 (1.302–11.416)	0.015
$LVM/Ht^{2.7}$	1.027 (0.997–1.058)	0.078	1.027 (0.997–1.059)	0.078
Nagelkerke R^2	0.096		0.190	

Abbreviation: **LVM:** left ventricular mass; **$LVM/Ht^{2.7}$**: left ventricular mass indexed to height; **OR**: odds ratio; **ref**: reference