The relationship of fatness, fitness, physical activity and sedentary behaviour with vascular health in human populations

by

Huynh Long Quan

BMed

Submitted in fulfilment of the requirements for the Degree of Doctor of Philosophy (Medical Research)

Menzies Research Institute Tasmania

University of Tasmania

January 2014

The research work presented in this thesis was supervised by:

Primary supervisor

Professor Alison Jane Venn, PhD

Menzies Research Institute Tasmania

University of Tasmania

Hobart, Australia

Co-primary supervisor

Associate Professor Christopher Leigh Blizzard, PhD

Menzies Research Institute Tasmania

University of Tasmania

Hobart, Australia

and

Co-supervisor

Associate Professor James Edward Sharman, PhD

Menzies Research Institute Tasmania

University of Tasmania

Hobart, Australia

Declaration of originality

This thesis contains no material which has been accepted for a degree or diploma by the University or any other institution, except by way of background information and duly acknowledged in the thesis, and to the best of my knowledge and belief no material previously published or written by another person except where due acknowledgement is made in the text of the thesis, nor does the thesis contain any material that infringes copyright.

Name: Huynh Long Quan

Signed: …… Date: ……

Statement of authority of access

The publishers of the papers comprising Chapters 3, 4 and 5 hold the copyright for that content, and access to the material should be sought from the respective journals. The remaining unpublished content of this thesis may be made available for loan and limited copying in accordance with the *Copyright Act 1968*.

Name: Huynh Long Quan

Signed: …… Date: ……

Statement of ethical conduct

The research associated with this thesis abides by the international and Australian codes on human and animal experimentation, the guidelines by the Australian Government's Office of the Gene Technology Regulator and the rulings of the Safety, Ethics and Institutional Biosafety Committees of the University.

Name: Huynh Long Quan

Signed: …… Date: ……

Abstract

Background: Impaired arterial structure and stiffness are strong predictors of cardiovascular events and mortality. These subclinical signs of impairment can be used to identify early stages of cardiovascular disease. Improved understanding of their determinants may enable earlier interventions to reduce cardiovascular risk.

Aim: This research aimed to study the associations of fatness, fitness, physical activity and sedentary behaviour with arterial structure and stiffness.

Methods: Data were from four large population-based studies: the Burnie Take Heart (BTH), Can Tho (CT), Childhood Determinants of Adult Health (CDAH), and Cardiovascular Risk in Young Finns (Young Finns) studies. The subjects for BTH (n=832 Australians aged 25–64 years in 1998–99), CT (n=1978 Vietnamese aged 25–64 years in 2005), CDAH (n=2328 Australians aged 7–15 years in 1985 and when aged 26–36 years in 2004–06) and Young Finns (n=2175 Finns aged 30–45 years in 2007) were all drawn from population-based samples. Measurements included anthropometry, blood pressure, resting heart rate (RHR), physical activity and fitness, sedentary behaviours, blood biochemistry, and arterial structure and stiffness assessed using carotid ultrasound.

Results: First, body mass index was positively associated with pulse pressure (an indicator of large artery stiffness) among adult Caucasians, but with both systolic and diastolic pressure among adult Asians. Second, adult carotid artery stiffness was exclusively dependent on adult body size and fatness, whereas adult carotid artery structure (assessed as intima-media thickness) was associated with childhood body size and fatness independently of attained adult values. Cross-sectional data showed that adult carotid artery stiffness was associated thirdly with physical fitness and fourthly with vigorous activity, each independently of current body size/fatness and with each association mediated by RHR. Fifth, carotid artery stiffness was positively associated with sitting time, independently of physical activity and fitness, body size/fatness, RHR, or metabolic syndrome.

Conclusions: For the first time, our findings suggest a different pathophysiology related to obesity-induced hypertension among Caucasians (increased arterial stiffness phenotype) and Asians (essential hypertension phenotype). Adult arterial stiffness was primarily influenced by attained adult body size and fatness, whereas adult arterial structure was influenced by body size and fatness in both childhood and adulthood. Independently of fatness, young adults may reduce stiffening of large arteries by doing vigorous activity and improving their fitness,

and by minimising sedentary behaviours. For the first time, our findings attribute a key intermediary role to RHR in the relationship of arterial stiffness with physical activity and fitness, and identify a positive relationship between arterial stiffness and sitting time independent of measurements of physical activity and fitness. These findings strengthen the case for lifestyle interventions to reduce obesity, encourage participation in vigorous activity and reduce prolonged sitting periods to reduce cardiovascular risk.

Acknowledgements

I wish to express my gratitude and thanks to all my colleagues, friends and family for their support and encouragement not only during the preparation of this thesis, but also during the four years of my PhD candidature. Without them, the work presented in this thesis would not be possible.

First of all, my particular thanks are due to my supervisors, Professor Alison Venn, Associate Professor Leigh Blizzard and Associate Professor James Sharman, for their guidance, encouragement and constant support. They are not only my teachers, but also my dear friends. I have utterly enjoyed every day of the past four years working with them, and am looking forward to many more years to come.

Alison, you are a fabulous mentor! Every conversation with you is so motivating. Whenever "my PhD" became frustrating, talking to you seemed to magically solve the problem. You guided me and taught me how to develop ideas on my own. I also want to thank you for sharing your passion and enthusiasm for epidemiology, and transferring them to me. I honestly believe that I am now enthused with epidemiology (perhaps not as much as you are, but more than enough to make me proud of!).

Leigh, I do not even know where to start! I think I just cannot thank you enough. I would like to express my deepest gratitude for everything you taught me during the past four years. While I do not think I have yet shared your extreme passion for statistics and numbers, I realised how much impact your teachings had on me when I started criticising others' analyses and presentation of data when they do not meet "Leigh's standards". During the last few years, there were many moments that I thought I had a "statistical break-through", but they all ended shortly after I showed you my findings. I always knew that I would never win a statistical discussion with you, but I kept hoping and I still do! Above all, having you and Cheryl at my wedding in Vietnam was the biggest honour ever!

James, thank you for your constant support and for sharing your expertise in physiology! This research would not be possible without your knowledge in the physiological properties of vascular health. I also want to thank you for always dropping what you were doing when I came with silly questions, and for spending hours with me trying to rebut reviewers' comments. With you on my side, I was never worried about having difficult comments in relation to vascular physiology.

I also want to send my biggest thanks to Dr. Thuy Au who made my PhD candidature possible from the very beginning and helped me a lot during my first days in Australia. She is a friend and a big sister to whom I always owe a huge debt of gratitude.

A special thanks to all fellow PhD students in the "cake club" for their support and for keeping me company! Thank you for the laughs during lunch time and for spoiling me with all the yummy cakes! You guys have made Menzies such an enjoyable place to work.

To the CDAH team, thank you all for your support in the past four years and for making me feel like home here. Costan, thank you so much for your help all along and also for being a

really good friend! Petr, thank you for taking your time to answer all my silly statistical questions and to teach me how to use Stata! A big thank you to the team involved in the fieldwork and to all the study participants!

Professor Terry Dwyer, thank you for your contributions to the CDAH study and for your constructive comments for all my drafts of the papers! Professor Olli Raitakari, thank you for your support and for letting me use data from the Young Finns study!

Finally, my love and deepest gratitude to my parents, my brother and particularly Huong, my wife! I could keep going only because of you. Thank you for your unconditional love and support, and for always being there for me no matter what!

Table of contents

List of tables

List of figures

List of abbreviations

BMI – body mass index

BTH – Burnie Take Heart

CD – carotid distensibility

CDAH – Childhood Determinants of Adult Health

cMetS – continuous metabolic syndrome score

CI – confidence interval

CT – Can Tho

CRF – cardiorespiratory fitness

CVD – cardiovascular disease

DALY – disability adjusted life years

DBP – diastolic blood pressure

HDL-C – high density lipoprotein cholesterol

IMT – intima-media thickness

IPAQ – International Physical Activity Questionnaire

LAS – large artery stiffness

LDL-C – low density lipoprotein cholesterol

MAP – mean arterial pressure

PA – physical activity

PP – pulse pressure

PWC_{170} – physical work capacity at a heart rate of 170 beats per min

SBP – systolic blood pressure

SD – standard deviation

SI – stiffness index

VLPA – vigorous leisure-time physical activity

RHR – resting heart rate

YEM – Young's elastic modulus

Statement of authorship

This thesis includes five papers, in which Huynh Long Quan (HLQ) is not the sole author. HLQ took the lead in this research. He designed the studies, performed analyses, interpreted the findings and prepared the manuscripts, with contributions from the co-authors. The contributions of each of the authors are detailed as follows.

The paper presented in Chapter 3

Quan HL, Blizzard CL, Venn AJ, Thuy AB, Luc PH, Sharman JE. Blood pressure and body mass index: a comparison of the associations in the Caucasian and Asian populations. *Hypertension Research*. 2012;35(5):523-30.

The contributions of each author are as follows:

- HLQ contributed to the design of the study, performed data analyses, interpreted the findings, composed the drafts of the manuscript and coordinated revisions of the manuscript.
- CLB contributed to the acquisition of the data and the design of the study, provided statistical expertise and critically revised the manuscript.
- AJV contributed to the design of the study and critically revised the manuscript.
- ABT contributed to the acquisition of the data and critically revised the manuscript.
- PHL contributed to the acquisition of the data and critically revised the manuscript.
- JES contributed to the design of the study and the interpretation of the findings, and critically revised the manuscript.

The paper presented in Chapter 4

Huynh Q, Blizzard L, Sharman J, Magnussen C, Schmidt M, Dwyer T, Venn A. Relative contributions of adiposity in childhood and adulthood to vascular health of young adults. *Atherosclerosis*. 2013;228(1):259-64.

The contributions of each author are as follows:

- HLQ contributed to the design of the study, performed data analyses, interpreted the findings, composed the drafts of the manuscript and coordinated revisions of the manuscript.

- CLB contributed to the design of the study and the interpretation of the findings, provided statistical expertise and critically revised the manuscript.
- JES contributed to the design of the study and critically revised the manuscript.
- CGM contributed to the acquisition of the data and critically revised the manuscript.
- MS contributed to the design of the study and critically revised the manuscript.
- TD contributed to the acquisition of the data and critically revised the manuscript.
- AJV contributed to the design of the study and the acquisition of the data, and critically revised the manuscript.

The paper presented in Chapter 5

Quan HL, Blizzard CL, Sharman JE, Magnussen CG, Dwyer T, Raitakari O, Cheung M, Venn AJ. Resting Heart Rate and the Association of Physical Fitness With Carotid Artery Stiffness. *American Journal of Hypertension*. 2013 Advance published online (doi: 10.1093/ajh/hpt161).

The contributions of each author are as follows:

- HLQ contributed to the design of the study, performed data analyses, interpreted the findings, composed the drafts of the manuscript and coordinated revisions of the manuscript.
- CLB contributed to the design of the study and the interpretation of the findings, provided statistical expertise and critically revised the manuscript.
- JES contributed to the design of the study and the interpretation of the findings, and critically revised the manuscript.
- CGM contributed to the acquisition of the data and critically revised the manuscript.
- TD contributed to the acquisition of the data and critically revised the manuscript.
- OR critically revised the manuscript.
- MC critically revised the manuscript.
- AJV contributed to the design of the study and the acquisition of the data, and critically revised the manuscript.

The paper presented in Chapter 6

Quan HL, Blizzard CL, Raitakari O, Sharman JE, Magnussen CG, Dwyer T, Juonala M, Kähönen M, Venn AJ. Vigorous physical activity and carotid distensibility in young and mid-aged adults. Currently under consideration at the journal *Medicine and Science in Sports and Exercise.* Manuscript submitted in 11/11/2013.

The contributions of each author are as follows:

- HLQ contributed to the design of the study, performed data analyses, interpreted the findings, composed the drafts of the manuscript and coordinated revisions of the manuscript.
- CLB contributed to the design of the study and the interpretation of the findings, provided statistical expertise and critically revised the manuscript.
- OR contributed to the acquisition of the data and critically revised the manuscript.
- JES contributed to the interpretation of the findings and critically revised the manuscript.
- CGM contributed to the acquisition of the data and critically revised the manuscript.
- TD contributed to the acquisition of the data and critically revised the manuscript.
- MJ critically revised the manuscript.
- MK critically revised the manuscript.
- AJV contributed to the design of the study, the acquisition of the data and the interpretation of the findings, and critically revised the manuscript.

The paper presented in Chapter 7

Quan HL, Blizzard CL, Sharman JE, Magnussen CG, Dwyer T, Venn AJ. The association of sitting time with carotid artery stiffness in young adults. Currently under consideration at the journal *BMJ Open.* Revised manuscript submitted in 01/11/2013.

The contributions of each author are as follows:

- HLQ contributed to the design of the study, performed data analyses, interpreted the findings, composed the drafts of the manuscript and coordinated revisions of the manuscript.
- CLB contributed to the design of the study and the interpretation of the findings, provided statistical expertise and critically revised the manuscript.

- JES contributed to the design of the study and critically revised the manuscript.
- CGM contributed to the acquisition of the data and critically revised the manuscript.
- TD contributed to the acquisition of the data and critically revised the manuscript
- AJV contributed to the design of the study, the acquisition of the data and the interpretation of the findings, and critically revised the manuscript.

Signed by primary supervisor, Professor Alison Venn

Signed: …… Date: ……

Chapter 1

Introduction

Chapter 1. Introduction

Epidemiology of cardiovascular disease (CVD)

What is CVD?

The term CVD refers to any disease of the heart or blood vessels. It includes conditions such as coronary heart disease (or ischaemic heart disease), cerebrovascular disease (stroke), heart failure, rheumatic heart disease and other peripheral vascular diseases.

Global burden of CVD and "the epidemiologic transition"

Over the last century, CVD has shifted from a disease with low burden to a disease with very high burden that has replaced infectious disease as the leading cause of death and disability worldwide.[1] It was estimated that 17.3 million people died from CVD in 2008, accounting for 48% of deaths from non-communicable disease and 30% of total deaths.[2] Coronary heart disease and stroke are the two most common causes of CVD deaths and were the two leading causes of death worldwide in 2011, accounting for 7 million and 6.2 million deaths respectively.[3] The top ten leading causes of death worldwide are shown in Figure 1.1. In terms of total burden of disability-adjusted life years (DALY) loss that accounts for years of life lost due to premature death and years lived with disability, coronary heart disease and stroke have increased by 29% and 19% respectively over the last two decades.[4] In 2010, coronary heart disease and stroke were the leading causes of DALY loss worldwide, up from the fourth and fifth leading causes in 1990.[4] According to World Health Organization (WHO) estimates, by 2030 the number of deaths from CVD will have increased to 25 million per annum, and CVD will remain the single leading cause of death not only in high- and middle-income countries, but also in low-income countries.[5]

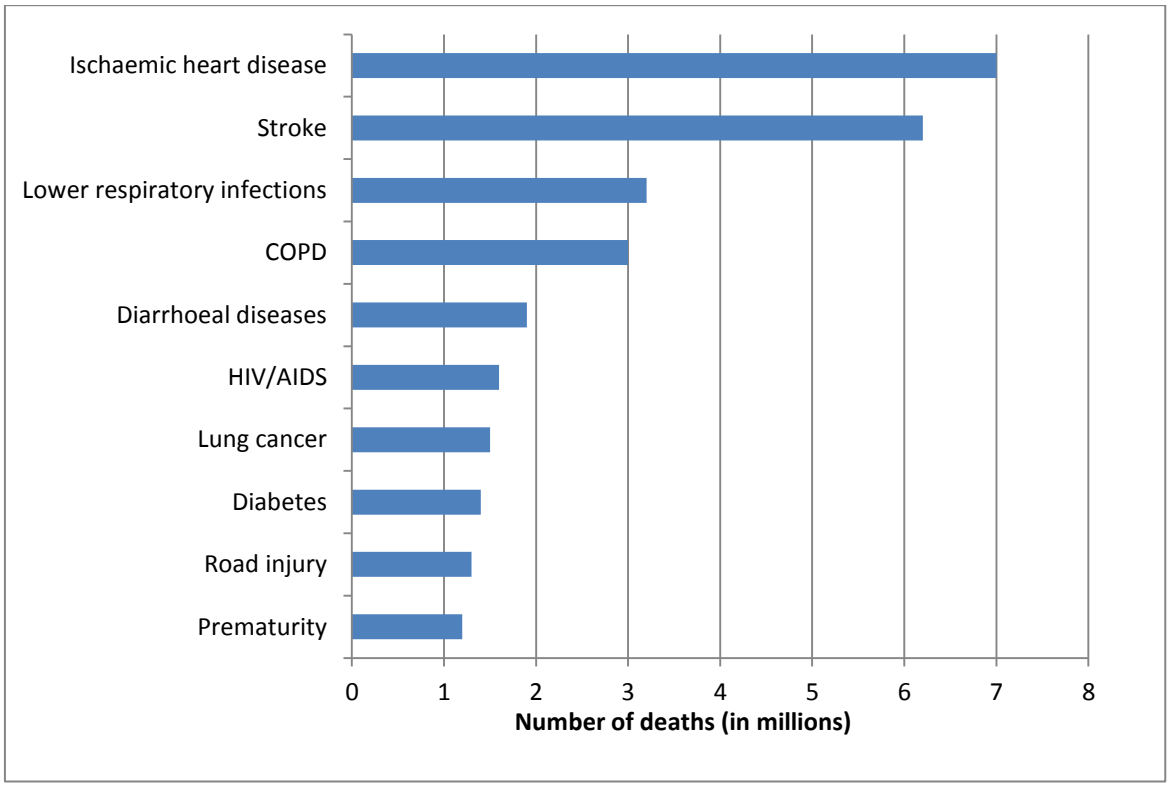


Figure 1.1. The top 10 leading causes of death worldwide in 2011. Figure reproduced from data reported by the WHO[3]

The shift in burden from communicable to non-communicable diseases has been termed "the epidemiologic transition". Omran originally identified three stages in this transition (Age of pestilence and famine, Age of receding pandemics, and Age of degenerative and man-made diseases).[6] A fourth (Age of delayed degenerative diseases) and fifth (Age of health regression and social upheaval) stage were recently added by Olshansky *et al*[7] and Yusuf *et al.*[8] The mortality burden of CVD is lowest in stage 1, increases in stage 2, peaks in stage 3, and tapers off in stage 4. Yusuf *et al* have predicted increases in CVD of infectious aetiology (rheumatic heart disease) in stage 5, together with increases in ischaemic and hypertensive diseases among the young.[8] This transition is characterised by reduced proportions of communicable disease and increased proportions of chronic disease (including CVD) and injuries. One of the major factors driving this change has been the improvements in public health and medical care that have resulted in an increase in average life expectancy. Because CVD is more common in older ages, improved life expectancy increases the proportion of people who survive to older ages when CVD is most prevalent. Another major factor that is attributable to "the epidemiologic transition" is increased prevalence of "lifestyle" CVD risk factors such as smoking, unhealthy (energy-rich) diet and a sedentary lifestyle. At any given

time, countries and regions are going through different stages of the transition. Two examples of this are discussed in the following sections.

Burden of CVD in Australia

Similarly to other countries with established market economies, Australia is likely to be in the fourth stage of the transition (Age of delayed degenerative diseases).[7] In this stage, deaths from CVD have begun to decline after reaching a peak in the third stage (Age of degenerative and man-made diseases) due to public health interventions such as those to reduce smoking, improved treatment, extensive primary and secondary prevention efforts, and major technological advances. Indeed, from 2002 to 2011, the number of CVD deaths in Australia fell by 9.3%.[9] However, as reported by the National Heart Foundation, CVD remains the largest cause of mortality in Australia, accounting for 34% of deaths among males and 39% of deaths among females.[10] Stroke and ischaemic heart disease are the leading causes of CVD burden for Australian men and women of all ages.[10]

Burden of CVD in Vietnam

In this section, Vietnam is highlighted as an example of a developing country because, in Chapter 3, the associations of body size and fatness with blood pressure among Australian adults are compared with those of Vietnamese adults. Developing countries such as Vietnam are likely to be in the second stage of the transition (Age of receding pandemics), in which rising incomes, better nutrition and improved living conditions result in reduced malnutrition and abatement of infectious diseases. This results in lower infant and child mortality rates, and substantially improved life expectancy. However, urbanisation and changing of lifestyles and diet also lead to higher levels of CVD risk factors such as obesity, hypertension, diabetes and hypercholesterolemia. These factors, together with longer lifespans, result in a steep increase of CVD burden in developing countries.[11] In Vietnam, even though infectious diseases still contribute significantly to the total years of life lost, CVD was the leading cause of deaths in 2008, accounting for 24% of deaths among men and 31% among women.[12]

Major risk factors for CVD

There are many risk factors that are associated with CVD including those that are modifiable (such as smoking, obesity, physical inactivity, hypertension, diabetes, and hypercholesterolemia) and those that are non-modifiable (such as increasing age, male sex, race, and family history). Primary and secondary prevention efforts have focused on modifiable risk factors in order to reduce CVD risk. Extensive epidemiological research has attributed significant contribution of these risk factors – particularly hypertension,[13] smoking,[14] diabetes,[15] and hypercholesterolemia[16] – to the development of future cardiovascular events. Intervention studies have shown that treatment or reduction of these four risk factors reduces CVD risk markedly.[14, 17, 18] Thus, smoking, hypertension, diabetes, and hypercholesterolemia are usually referred to as the major or traditional CVD risk factors.[19]

In the past, the prevailing belief was that traditional CVD risk factors were present among at most one-half of people with CVD.[20-23] However, more recent data from major clinical trials and cohort studies have demonstrated that CVD is very uncommon in the absence of traditional CVD risk factors.[24, 25] These studies used data from 14 clinical trials and three large prospective cohorts, and together included more than half a million subjects. The findings showed that 80% to 90% of patients with significant coronary heart disease, and more than 95% of patients with fatal coronary events, had been exposed to at least one major CVD risk factor. Indeed, according to findings from five large cohort studies including over 350,000 men and women aged 18 to 59 years at baseline in the United States, those without any major CVD risk factor had 72% to 85% lower risk of cardiovascular mortality and 40% to 58% lower risk of all-cause mortality than those with at least one major CVD risk factor.[26] In addition, findings from the INTERHEART study – an international, standardised, case-control study with approximately 15,000 cases and 15,000 controls from 52 countries across all geographic regions and ethnic groups of the world – showed that hypertension, smoking, diabetes, abnormal lipids, obesity, physical inactivity, psychosocial factors, lack of consumption of fruit and vegetable, and regular alcohol consumption accounted for 90% (men) and 94% (women) of risk of acute myocardial infarction worldwide.[27] These important results convincingly challenge the theory that at most one-half of CVD events are attributable to the traditional CVD risk factors and more importantly, emphasise the importance of identifying and controlling major CVD risk factors to reduce CVD burden.

Hypertension

The most recent classification of blood pressure (as in Table 1.1) for adults aged 18 years or older was introduced in 2003 by the Joint National Committee in their seventh report.[28] This classification differed from their sixth report by adding a new category (prehypertension), and combining stage 2 and 3 hypertension.

Table 1.1. Classification of blood pressure for adults aged 18 years or older[28]

Blood pressure classification	SBP (mmHg)		DBP (mmHg)
Normal	< 120	and	< 80
Prehypertension	120 - 139	or	80 - 89
Stage 1 hypertension	140 - 159	or	90 - 99
Stage 2 hypertension	≥ 160	or	≥ 100

Abbreviations: SBP (systolic blood pressure); DBP (diastolic blood pressure).

Hypertension is the leading cause of CVD worldwide and contributes to 13% of total deaths.[29] Data from the Framingham Heart Study suggest that normotensive individuals at the age of 55 years have 90% lifetime risk of developing hypertension.[30] For individuals classified as prehypertensive, anti-hypertensive medication is not yet indicated unless co-morbidity such as chronic kidney disease or diabetes is present, but lifestyle modifications are recommended because affected individuals have around two-fold higher risk of developing hypertension,[31] and of developing CVD,[32] than those with normal blood pressure.

Some individuals may develop high systolic pressure (≥ 140mmHg), but have low or normal diastolic pressure. This usually happens in older adults, and results in high pulse pressure that is calculated as the difference between systolic and diastolic pressure.[33] This phenomenon is called isolated systolic hypertension, and it is associated with higher CVD risk.[34, 35] This is possibly because a greater gap between systolic and diastolic pressure (i.e. higher pulse pressure) is usually referred to as an indicator of increased arterial stiffness in older adults (i.e. those aged over 50 years).[33] Increased arterial stiffness predicts cardiovascular events and mortality independently of blood pressure.[36]

To investigate the direct and continuous relationship between blood pressure and CVD risk, a systematic meta-analysis of one million adults without pre-existing vascular disease was performed using data from 61 prospective studies that had not selected participants on a basis of a history of stroke or heart disease.[37] The findings showed that an increment of 20 mmHg

in systolic blood pressure or 10 mmHg in diastolic blood pressure doubled the risk of cardiovascular mortality, even in individuals with blood pressure as low as 115/75 mmHg.[37] In addition, data from randomised controlled trials show that using anti-hypertensive therapies to lower blood pressure reduces the risk of stroke, coronary heart disease, myocardial infarction and mortality among hypertensive patients.[38-40] Collectively, these findings demonstrate the importance of preventing or reducing elevated levels of blood pressure as a means of reducing CVD risk.

Tobacco smoking

Smoking is the second leading cause of CVD worldwide and accounts for 9% of total deaths.[29] It is estimated that there are currently one billion smokers in the world.[29] The causal relationship of smoking or tobacco use with many types of CVD across various racial and ethnic groups, and also with many other diseases, are strongly dose-related and well established[14] in terms of biological plausibility and the other criteria of Bradford Hill.[41]

Smoking has been found to be associated with endothelial dysfunction – broadly defined as an imbalance between vasodilating and vasoconstricting substances produced by (or acting on) endothelial cells[42] – by various mechanisms.[43-45] Atherosclerotic plaques among smokers are more frequently complicated by mural thrombosis on arterial walls than those from non-smokers.[46] This is probably due to disturbance of the coagulation-fibrinolytic system, which may lead to vascular occlusion by thrombotic fragments and sudden cardiac death.[47] Smoking also leads to increased inflammation[48, 49] and an adverse lipid profile.[50] It detrimentally influences cardiac function by: increasing oxygen demand of the myocardium;[51] decreasing oxygen supply by reducing coronary blood flow;[52] and diminishing the capacity of red blood cells to carry oxygen.[53] Acute and episodic increases in blood pressure observed in smokers expose the arterial wall to greater mechanical load.[54] Collectively, these pathways accelerate the adverse progression of atherosclerosis and cardiac events in individuals who smoke tobacco.

In relation to other CVD risk factors, smoking may act synergistically to increase substantially the CVD risk associated with other risk factors.[55] It is estimated that smoking may shift forward the onset of premature coronary heart disease by a decade.[24] The adverse effects of smoking on cardiovascular health appear to be similar for both men and women.[56, 57] Smoking is also a strong risk factor for myocardial infarction even among women less than 50 years of age, for whom the absolute risk of cardiovascular events is very low.[58, 59]

Given the high CVD risk associated with tobacco use, it is encouraging to smokers that their risk due to smoking is substantially decreased within a few years after cessation of smoking, and may return to that of a non-smoker within 15 years of quitting.[60] This beneficial effect can be seen even among those who have been heavy smokers for many years.[60] For individuals who have already developed coronary heart disease, smoking cessation also substantially reduces the risk of recurrent myocardial infarction, stroke or mortality by at least 50%.[61, 62] Given this evidence, there is little doubt that smoking cessation would reduce the risk of CVD for smokers.

Diabetes

Diabetes is a metabolic disease primarily defined by hyperglycaemia resulting from defects in insulin secretion, insulin action or both, and contributing to both microvascular and macrovascular diseases. It is estimated that diabetes affected 246 million people worldwide in 2007, and will affect 380 million in the year 2025.[63] In Australia, it is estimated that one in four adults aged 25 years or older has diabetes or impaired glucose metabolism (consisting of impaired fasting glucose or impaired glucose tolerance).[64] The classification of blood glucose tolerance status based on fasting and/or 2-hour postprandial blood glucose is presented in Table 1.2.

Table 1.2. Classification of blood glucose tolerance status[65]

	Plasma glucose (mmol/L)		
	Fasting		2-hour postprandial
Diabetes	≥ 7.0	or	≥ 11.1
Impaired glucose tolerance	< 7.0	and	7.8 – 11.0
Impaired fasting glucose	6.1 - 6.9	and	< 7.8
Normal	< 6.1	and	< 7.8

Diabetes is strongly related to CVD and regarded as a traditional CVD risk factor.[19] There are two types of diabetes: type 1 diabetes (formerly called insulin-dependent diabetes, in which the pancreas fails to produce insulin) and type 2 diabetes (formerly called noninsulin-dependent diabetes, which is a metabolic disorder characterised by high blood glucose due to insulin resistance and relative insulin deficiency). Both type 1 and type 2 diabetes are associated with greater CVD risk.[66, 67] Indeed, CVD is responsible for at least 50% of deaths in people with diabetes.[63, 68] Diabetes may even be considered as a "cardiovascular disease" because most diabetic patients have coexisting CVD risk factors. Compared with people with

normal blood glucose tolerance, those who have diabetes are much more likely to have hypertension, hypercholesterolemia, and obesity.[64] This may explain why the absolute risk of diabetic patients is usually higher than the Framingham score calculated for hyperglycaemia, and is as high as that of patients with previous myocardial infarction.[69] Diabetic patients are also at higher risk of developing specific CVD such as coronary heart disease, diabetic cardiomyopathy and stroke;[70] once having developed CVD, they have a poor prognosis.[71] This renders diabetic patients a special case in CVD risk assessment and classifies them as high-risk category that requires comprehensive management of all CVD risk factors.[19]

Hypercholesterolemia

Cholesterol is a fat-like substance that is transported in the blood in particles called lipoproteins. There are three major types of lipoproteins, including high density lipoprotein (also called "good" cholesterol), low density lipoprotein (also called "bad" cholesterol), and very low density lipoprotein (a triglyceride-rich lipoprotein). Among these lipoproteins, low density lipoproteins make up 60% to 70% of total blood cholesterol. They are regarded as the major atherogenic lipoprotein and are the primary target for cholesterol lowering therapy.[72] Hypercholesterolemia is defined as having total cholesterol equal to or greater than 6.2 mmol/L (or 240 mg/dL).[72]

The causal relationship of hypercholesterolemia with CVD has been well documented by major population studies including the Framingham Heart Study,[67, 73] the Multiple Risk Factor Intervention Trial,[74] and the Lipid Research Clinics trial.[75, 76] The strong association of hypercholesterolemia with CVD is also clearly demonstrated among individuals with genetic hypercholesterolemia who commonly develop premature coronary heart disease even in the absence of other risk factors.[77] In addition, findings from clinical trials of cholesterol lowering therapies, particularly those using HMG CoA reductase inhibitors (statins), have provided convincing evidence of significant reduction not only in coronary events, but also in cardiovascular and total mortality.[78] The benefits of lowering cholesterol are observed across a wide range of cholesterol levels in different subgroups of patients, among those with or without established CVD, in smokers or non-smokers, and among those with or without hypertension or diabetes.[79, 80]

To estimate by how much and how quickly a given reduction of serum cholesterol concentration may reduce the risk of ischaemic heart disease, an analysis used data from ten large cohort studies (each of which had recorded at least 350 coronary events), three

international studies (for comparison among participants in different communities in 25 countries totally), and 28 randomised controlled trials.[81] The findings showed that interventions to reduce serum cholesterol earlier in life rather than later may result in lower risk of ischaemic heart disease, and that the full effect of reduction in risk is achieved by five years.[81] These findings emphasise the importance of long-term prevention of CVD and the need to understand risk factors in younger people and how they may influence CVD risk later in life.

Obesity

The prevalence of overweight and obesity has been consistently increasing in many countries over several decades, and is a major public health concern because obesity is a major risk factor for many chronic diseases.[82, 83] It is estimated that approximately one in four adult Australians and one in three adult Americans are obese.[82, 83] Overweight or obese individuals have higher risk of cardiovascular events and mortality.[84, 85] In the past, the link between obesity and CVD was usually referred to as an indirect relationship mediated through subsequent increases in other CVD risk factors among obese people. That is, obese people are more likely to develop hypertension, diabetes and hypercholesterolemia,[86] which will increase their risk of developing CVD. However, there is evidence that changes in cardiac structure and function may occur in obese individuals even in the absence of other risk factors,[87] and that the magnitude of these changes may be related to the severity of obesity.[88] In addition, major long-term longitudinal studies have shown that obesity strongly predicts cardiovascular events and mortality independently of other risk factors.[84, 85, 89] For this reason, obesity has now been designated as a major CVD risk factor.[90]

In both clinical and research work, overweight and obesity are often defined using body mass index (BMI), which is calculated by dividing weight in kilograms by height in squared meters. In Australia, the proportion of men and women who are overweight (BMI 25 – 29.9 kg/m^2) or obese (BMI $\geq$ 30 kg/m^2) generally increases with age, and most significantly so for adults from 18-24 years of age to 45-54 years of age.[83] Between 1985 and 2011-12, young Australian adults had the most substantial increases in overweight and obesity, including men aged 25-34 years (increased by 7%), men aged 35-44 years (increased by 8%), women aged 18-24 years (increased by 9%), and women aged 35-44 years (increased by 10%).[83] This trend of increasing overweight and obesity among young adults also exists in other populations,[82] and may be mainly responsible for elevated risk factors observed among young adults in those countries. The Coronary Artery Risk Development in Young Adults Study collected data on

young black and white adults aged 18–30 years at baseline (stratified by age, sex, race and education) and followed-up for 15 years.[91] Findings from this study showed that young adults who maintained stable BMI over 15 years had unchanged levels of metabolic syndrome components, regardless of baseline BMI, whereas those with increased BMI had adverse progression of risk factors and greater incidence of metabolic syndrome.[91] These unfavourable trends of risk factors in younger adults may explain why mortality rates in older adults continues to decline significantly, whilst rates among younger adults have declined minimally or even increased.[92, 93] This adverse trend in mortality experienced for younger adults, despite advanced development of medical and interventional therapies, again underlines the need for long-term studies of CVD risk factors – particularly obesity – among young people and their long-term consequences for health.

Physical activity and fitness

In Australia, physical inactivity causes 7% of total disease burden and is the second leading risk factor contributing to total disease burden, following tobacco use.[94] Similarly, lack of physical activity is the second leading behavioural cause of death in the United States, following tobacco use.[95] It is now widely accepted that physical activity plays a role in both primary and secondary prevention of CVD.[96-98] Indeed, physical inactivity has been reported to independently predict the development of coronary heart disease.[99, 100] Unless otherwise contraindicated, regular physical activity can increase cardiovascular functional capacity (by reducing resting heart rate and increasing maximal cardiac output) and reduce myocardial oxygen demand (by increasing the ability of myocardium to extract and use oxygen delivered by red blood cells) not only among apparently healthy individuals, but also among CVD patients.[96] To maintain these cardio-protective effects, individuals need to undertake exercise training habitually.[96]

The direct causal relationship between physical activity and mortality has been documented in many studies. A systematic review and meta-analysis in 2007 including 33 cohort studies with nearly 900,000 apparently healthy participants who were followed-up for at least three years showed 35% and 33% reduction respectively in cardiovascular and all-cause mortality among those who were physically active.[101] For individuals with established CVD, a Cochrane systematic review in 2011 including 47 randomised controlled trials showed that regular exercise training reduced total mortality among patients by 13% and cardiovascular mortality by 26% across all ages.[102] For these patients, regular exercise also reduced the risk of hospital readmission within 12 months by 31%.[102] In relation to other CVD risk factors, physical

activity also reduces both systolic and diastolic blood pressure, particularly for people with hypertension,[103] reduces triglyceride levels and increases high-density lipoprotein levels,[104] and reduces insulin resistance and glucose intolerance.[105] Based on the evidence of the many beneficial effects that participation in physical activity provides, physical inactivity has now been designated as a major CVD risk factor.[96]

In relation to the role of physical activity in producing weight loss, a systematic review in 2007 including 16 prospective, randomised controlled trials of at least four months in duration demonstrated that substantial weight loss may be achieved by physical activity alone, but requires large amount of exercise to be prescribed and sustained.[106] This is in line with findings from another systematic review of both epidemiological studies and clinical trials that compared the benefits of physical activity at different intensities.[107] These findings showed greater cardioprotective benefits (including reduction in blood pressure and glucose, and increase in aerobic capacity) produced by vigorous physical activity compared with those produced by light-to-moderate physical activity, given that the total energy expenditure from the two types of exercise was held constant.[107] This evidence suggests that participation in vigorous physical activity may provide benefits that are beyond those provided by light-to-moderate physical activity, but the underlying mechanisms are unclear at present.

Cardiorespiratory fitness (CRF) refers to the ability of the circulatory and respiratory systems to supply oxygen to skeletal muscles during sustained physical activity. CRF measures the capacity of an individual to perform physical activity and can be improved by regular exercise training. The American Heart Association has recently recognised CRF as an important cardiovascular health metric and recommends routine assessment in clinical practice.[108] This official statement was based on strong evidence that CRF independently predicts various health outcomes including cardiovascular and all-cause mortality.[109-111] A recent systematic meta-analysis of 33 cohort studies on apparently healthy participants showed that those with low CRF had 47% and 56% greater risk of developing cardiovascular events than those with intermediate and high CRF respectively.[112] This meta-analysis also showed that participants with low CRF had 40% and 70% greater risk of all-cause mortality than those with intermediate and high CRF respectively.[112] More importantly, unfit individuals (with or without chronic diseases) who improve their CRF may reduce their risk of death,[113, 114] regardless of changes in BMI.[115] This evidence not only shows the importance of CRF in prevention of CVD, but also suggests that – regardless of weight loss – individuals who participate in physical activity may improve their CRF, and thereby, reduce CVD risk. This

again implicates the potential importance of vigorous physical activity in prevention of CVD because previous studies have demonstrated that the higher the exercise intensity, the greater the increase in CRF.[107, 116]

Most of the findings on the relationship of physical activity and fitness with CVD are based on data from older adults and thus, less is known for younger adults. This is possibly due to low prevalence of cardiovascular events at younger age. However, given that CVD mortality rates among younger adults do not appear to have declined as they have among older adults,[83, 84] additional research is needed to better understand how these risk factors may influence the early stages of CVD among young people. This is critical for long-term prevention of CVD because it may enable early interventions to reduce CVD risk. As discussed in the preceding text, weight gain appears to be mainly responsible for elevated risk factors observed in young people.[91] Thus, reducing obesity among young people is obviously crucial. However, obesity has many behavioural and genetic components that are not easily addressed. For overweight and obese people who experience difficulties with losing weight, increasing physical activity and improving CRF appears to be a good alternative because they are associated with lower risk of CVD mortality independent of BMI changes.[114, 115] Although some participants as young as 20 years of age were included in the aforementioned studies, these findings were primarily based on data from older adults because death from CVD is rare among young adults. Therefore, the impact of physical activity and greater CRF on the early stages of CVD remains less certain and needs to be examined among young people, which is one of the aims of this research.

Sedentary behaviours

Sedentary behaviours such as sitting, watching television and using a computer are ubiquitous in contemporary society and have become a new focus for research in physical activity and health. They are defined by both their posture (sitting or reclining) and their low levels of energy expenditure (typically in the range of 1.0 to 1.5 multiples of the basal metabolic rate).[117] In the past, it was a common belief that adverse health consequences of being sedentary were due to lack of physical activity. However, recent findings suggest that sedentary behaviours should not be viewed as equivalent to physical inactivity, but as an independent risk factor.[118]

Over the past few years, several studies have reported detrimental relationships of sedentary behaviours – including self-reported sitting time[119, 120] and television viewing time[121-123] –

with cardiovascular and all-cause mortality, after adjustment for physical activity and BMI. Among older men, time spent riding in a car was also reported to be associated with CVD-related mortality.[124] In line with these findings, sedentary behaviours were found to be associated with a number of CVD risk factors, such as obesity, and elevated blood glucose and cholesterol,[125, 126] which may act as possible pathways leading to a higher risk of mortality. Strengthening this evidence, data from accelerometers showed that objectively-measured sedentary time was associated with waist circumference, blood glucose, insulin and lipids.[127, 128] More importantly, these data also demonstrated that individuals who had more "breaks" during sedentary periods (in other words, interrupted their sedentary behaviours more frequently) had better cardiometabolic profile than those who did not, independent of total sedentary time and time spent doing moderate-to-vigorous physical activity. Collectively, these findings suggest a causal relationship between being sedentary and mortality risk.

Despite all the evidence presented above, there has never been a study that examines the relationship between sedentary behaviour and vascular health, an important predictor of cardiovascular events and mortality.[36, 129] Novel information in relation to this relationship may advance our knowledge in the field, and shed some light on the possible mechanisms involved in the relationship of sedentary behaviour with mortality, which still remains poorly understood at present.

Advanced imaging techniques and vascular measures as subclinical markers of CVD

The evidence presented in the preceding text underlines the need to study CVD risk factors among young people and to understand how these risk factors may influence the early stages of developing atherosclerosis (the underlying cause of most CVD). This is essential not only because of the adverse trend in cardiovascular mortality observed among contemporary younger adults,[83, 84] but also because controlling risk factors associated with early stages of atherosclerosis may help prevent, or delay, the clinical manifestations of CVD and thereby, reduce CVD burden. However, because cardiovascular events are rare among the young, studying early stages of CVD or atherosclerosis in the past have relied on either autopsy studies, which was performed by the Bogalusa Heart Study[130] and the PDAY Study,[131] or the use of invasive techniques that leave a great burden on participants and are not feasible for large population studies.

The advancement of novel non-invasive imaging techniques during the 1990s opened a new era for studying subclinical markers of CVD among young and apparently healthy people. These markers are feasible for large population-based studies because they are relatively inexpensive, highly reproducible and can be repeated frequently without incurring risk for participants.[132-134] These markers, including the structure (intima-media thickness – IMT) and stiffness of an artery, provide information regarding health of the arterial vasculature and may reflect early stages of atherosclerosis. IMT is constituted by thickness of the tunica intima and tunica media – the two innermost layers of the arterial wall − and is usually measured in the carotid artery because the carotid artery wall has a very thin smooth muscle layer and carotid atherosclerosis is strongly associated with coronary and peripheral atherosclerosis. In particular, carotid IMT is a strong predictor of future cardiovascular events, including myocardial infarction and stroke.[129] Arterial stiffness is also commonly measured in the carotid artery (and in the aorta) because stiffening of these large arteries independently predicts future cardiovascular events and all-cause mortality.[135-137] Other subclinical markers of CVD that have been used in previous studies include: flow-mediated dilation (an endothelium-dependent process facilitating the relaxation of an artery in response to increased shear stress[138]), pulse wave velocity (a measure of arterial stiffness[139]) and coronary calcification.[140]

Since the reproducibility and prognostic values of the carotid IMT and carotid artery stiffness were established,[36, 141] these subclinical markers of vascular health have been widely used as the main outcomes of interest in many studies that examine the effects of lifestyle risk factors – including fatness, and physical activity and fitness – and the effects of interventions to reduce these risk factors. However, most of these studies have targeted older adults, used small samples, or compared sedentary persons with highly trained athletes. In addition, although the association of physical activity and fitness with vascular health has been examined in several studies, there has never been a study that specifically investigates the possible mechanisms involved in this relationship. Large population-based studies that have measured carotid IMT and/or carotid artery stiffness among young people are summarised in Table 1.3. All of these studies are on-going longitudinal studies and collected anthropometrical measures of participants. Of these studies, only the Childhood Determinants of Adult Health (CDAH) Study and Cardiovascular Risk in Young Finns (Young Finns) Study collected objectively-measured physical activity, together with information on physical activity that were self-reported using a questionnaire. Of these two studies, only the CDAH study has objectively-measured CRF on participants.

Table 1.3. Summary of large population-based longitudinal studies that have measured carotid intima-media thickness (IMT) and/or carotid artery stiffness among young people

Study	Country	Commenced in	Population at baseline	Vascular outcomes measured in adulthood
The Muscatine Study[142]	USA	1971	N=4829, aged 8–18 years	Carotid IMT, measured at 33–42 years of age
The Bogalusa Heart Study[143, 144]	USA	1973	N=3525, aged 5–14 years	Carotid IMT, measured at 20–43 years of age
The Amsterdam Growth and Health Longitudinal Study[145, 146]	Netherlands	1977	N=450, aged 13 years	Carotid IMT and carotid artery stiffness, measured at 36 years of age
The Cardiovascular Risk in Young Finns Study[147, 148]	Finland	1980	N=3596, aged 3–18 years	Carotid IMT and carotid artery stiffness, measured at 24–39 and at 30–45 years of age
The Childhood Determinants of Adult Health Study[149, 150]	Australia	1985	N=8498, aged 7–15 years	Carotid IMT and carotid artery stiffness, measured at 26–36 years of age
The Atherosclerosis Risk in Young Adults Study[151]	Netherlands	1999–2000	N=750, aged 12–16 years	Carotid IMT, measured at 27–30 years of age

Childhood origins of CVD

Although the major manifestations of CVD typically do not present until older ages, the antecedents of CVD (notably atherosclerosis) appear earlier in life.[152] The process of atherosclerosis is slow and involves the development of fatty streaks in blood vessels during childhood, which may accumulate more lipid deposition in subsequent years to form a fibrous plaque. In early stages, there are no symptoms. However, with time, these lesions may enlarge and result in complications such as calcification, haemorrhage, rupture or thrombosis. The natural history of atherosclerosis is illustrated in Figure 1.2, which was reproduced from McGill *et al*.[153] The magnitude of the consequences from lesions depends on which artery is affected. For example, a lesion in the coronary artery or cerebral artery may result in myocardial infarction or stroke, leading to death or severe disability. Conversely, a lesion in a small artery might result in minor consequences.

The first evidence of atherosclerosis beginning in childhood was provided in the late 1950s and early 1960s.[154-156] The authors in these studies demonstrated that fatty streaks were present in aortas of children as young as three years of age and that these fatty streaks progressed to fibrous plaques by young adulthood. As an extension of their work, these authors compared early aortic atherosclerotic lesions among individuals between one and 40 years of age in New Orleans, Guatemala and Costa Rica.[157] A similar pattern of the early development of fatty streaks was found among these individuals, despite their wide racial and environmental differences.[157] However, the progress from fatty streaks to fibrous plagues was different among populations, and these differences were well correlated with the incidence of clinical manifestations of atherosclerosis in these populations.[157] These findings suggest that the origin of atherosclerosis begins very early in childhood, and factors (perhaps during late childhood and early adulthood) that influence the development of atherosclerosis may be important in determining CVD risk at older ages. More recently, autopsy data from the Bogalusa Heart Study[130, 158, 159] and the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Study[131, 160] respectively showed positive associations of antemortem and postmortem CVD risk factors (such as smoking, hypertension, obesity, dyslipidaemia and elevated blood glucose) with the extent and severity of atherosclerosis in aortas and coronary arteries of young individuals (aged two to 39 years) who died principally from trauma and other external causes. Collectively, these findings suggest that control of CVD risk factors early in life may delay the development of atherosclerosis.

Taking benefits from the advancement of novel non-invasive imaging techniques, many cohort studies have now focused on investigating the relationship of CVD risk factors in childhood with subclinical markers of CVD in adulthood. These studies are briefly summarised in Table 1.4. Although several studies have found a positive association of body size and fatness in childhood with carotid IMT and stiffness in adulthood, their findings in relation to whether body size and fatness in childhood may influence adult vascular health independently of adult body size and fatness are inconsistent. In addition, most of these studies relied upon BMI as their sole measure of body size and fatness in childhood. Although BMI is commonly used in research and clinical practice, it is not clear whether BMI is superior to other practical measures of body size and fatness in respect of predicting long-term CVD risk.[161, 162]

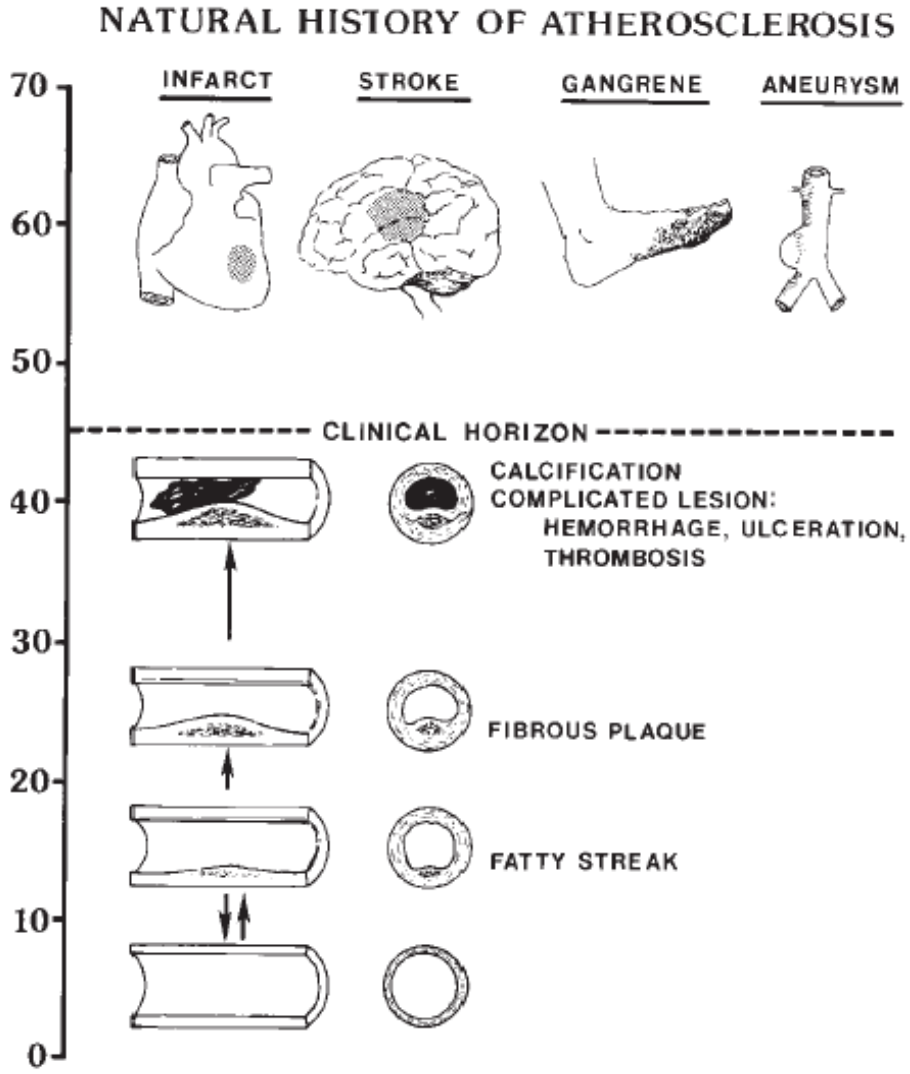


Figure 1.2. Natural history of atherosclerosis by years of age.
Reproduced from McGill *et al*[153]

Table 1.4. Summary of cohort studies investigating the associations of childhood risk factors with vascular health in adulthood

Childhood risk factors	Study	Vascular health in adulthood	Association*
Body size and fatness	BHS[143, 144]	Carotid IMT	(+)
	ARYA[151]	Carotid IMT	(+)
	YFS[147, 148, 163]	Carotid IMT and stiffness	(+)
	TFC[164]	Carotid IMT	Null
	MS[165]	Coronary calcification	(+)
	AGHL[145, 166]	Carotid IMT and stiffness	(+)
Physical activity	AGHL[167]	Carotid stiffness	(−)
	AGHL[168]	Brachial and femoral compliance	(+)
CRF	AGHL[146, 166]	Carotid IMT	Male (−) Female (Null)
		Carotid stiffness	Null
Blood lipids	BHS[169-171]	Carotid IMT	(+)
	MS[142, 165]	Carotid IMT	(+)
	YFS[147, 172, 173]	Carotid IMT and stiffness	(+)
	YFS[173]	Brachial FMD	(−)
	YFS[174]	Coronary calcification	(+)
	AGHL[166]	Carotid stiffness	(+)
	CDAH[175]	Carotid IMT	(+)
Blood pressure	BHS[142, 169]	Carotid IMT	(+)
	BHS[176]	Brachial-ankle PWV	(+)
	YFS[147, 148]	Carotid IMT and stiffness	(+)
	YFS[177]	Brachial FMD	(−)
	YFS[174]	Coronary calcification	(+)
	AGHL[166]	Carotid stiffness	(+)
Active smoking	YFS[147]	Carotid IMT	(+)
		Carotid stiffness, brachial FMD and coronary calcification	Null
	NIYHP[178]	Aorto-iliac PWV	(+)

Passive smoking	YFS, CDAH[179]	Brachial FMD	(+)
Unhealthy diet	YFS[180, 181]	Carotid IMT	(+)
	YFS[182]	Arterial PWV	(+)
	AGHL[183, 184]	Carotid stiffness	(+)

*(+) indicates a positive association, (−) indicates a negative association, and "Null" indicates no association.

Abbreviations: BHS (the Bogalusa Heart study), ARYA (the Atherosclerosis Risk in Young Adults study), YFS (the Cardiovascular Risk in Young Finns study), TFC (Thousand Families cohort study), MS (the Muscatine study), AGHL (the Amsterdam Growth and Health Longitudinal study), CDAH (the Childhood Determinants of Adult Health study), NIYHP (the Northern Ireland Young Hearts Project), CRF (cardiorespiratory fitness), IMT (intima-media thickness), FMD (flow-mediated dilation), and PWV (pulse wave velocity).

Aims of this thesis

This research has been designed to help to fill the evidence gaps and produce novel information to extend our current knowledge in the field. The main aims are to study the relationships of fatness, fitness, physical activity and sedentary behaviour with vascular health among younger adults to better understand how these lifestyle risk factors are associated with early stages of CVD and to investigate the possible mechanisms involved. In order to do that, the novel studies presented in this thesis aim to:

- Compare the associations of body size and fatness with blood pressure using Australian and Vietnamese population-based samples to better understand the relationship between fatness and vascular health.
- Determine whether child fatness predicts adult vascular health, and whether it does so independently of adult fatness.
- Examine the relationship of physical fitness with arterial stiffness, and to investigate the possible mechanisms underlying any association.
- Examine the relationship of different types of physical activity with arterial stiffness, and to investigate the possible mechanisms underlying any association.
- Examine the relationship of sedentary behaviour assessed by sitting time with arterial stiffness, and to investigate the possible mechanisms underlying any association.

Sources of data used in this thesis

To address the aims of this thesis, data from four large population-based studies were used for analyses: the Burnie Take Heart (BTH), Can Tho (CT), CDAH, and Young Finns studies. In an attempt to better understand the associations of body size and fatness with blood pressure (an important component of cardiovascular health), these associations were compared using a sample predominantly containing Caucasians (the BTH study, Australia) and another sample predominantly containing Asians (the CT study, Vietnam), which is presented in Chapter 3 of this thesis. The findings from this chapter provide some insights into cardiovascular health. Thereafter, the associations of fatness, fitness, physical activity and sedentary behaviour with vascular health were examined among younger adults. These studies, which are presented in Chapters 4, 5, 6 and 7 of this thesis, used data from the CDAH study and the Young Finns study, both of which are member cohorts of the International Childhood Cardiovascular Cohort (i3C) Consortium.

Structure of this thesis

Chapter 1: Introduction

Chapter 2: Methods

Chapter 3: Blood pressure and body mass index: a comparison of the associations in Caucasian and Asian populations.

Chapter 4: Relative contributions of adiposity in childhood and adulthood to vascular health in young adults.

Chapter 5: Resting heart rate and the association of physical fitness with carotid artery stiffness.

Chapter 6: Vigorous physical activity and carotid distensibility in young and mid-aged adults.

Chapter 7: The association of sitting time with carotid artery stiffness in young adults.

Chapter 8: Summary, implications, future directions and conclusions

Concluding remarks

This chapter provides an overview of CVD burden and risk factors. The evidence from studies reviewed in the preceding text of this chapter points out that (1) the development of CVD is a long process and has origins from early stages of life, (2) long-term prevention of CVD may contribute to reduce CVD burden, and (3) improving lifestyle risk factors including fatness, fitness, physical activity and sedentary behaviour may reduce CVD risk, but their relationships with early stages of CVD are less clear and need to be examined among younger adults. This research aims to examine the relationships of these lifestyle risk factors with early stages of CVD assessed by subclinical markers of vascular health among younger adults to help to fill the current evidence gaps. The novel findings produced by this research may advance our knowledge in the field.

Postscript

The next chapter will describe the participants and methods of the four population-based samples used in this thesis.

References

1. The Global Burden of Disease: 2004 update. Geneva: World Health Organization; 2008.

2. Global status report on noncommunicable diseases 2010. Geneva: World Health Organization 2011.

3. The top 10 causes of death in 2011 (Fact sheet N°310). Geneva: World Health Organization 2013.

4. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, *et al.* Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2197-223.

5. World Health Statistics 2012. Geneva: World Health Organization; 2012.

6. Omran AR. The epidemiologic transition: a theory of the epidemiology of population change. *Millbank Memorial Fund Q*. 1971;49:509-38.

7. Olshansky SJ, Ault AB. The fourth stage of the epidemiologic transition: the age of delayed degenerative diseases. *Milbank Q*. 1986;64(3):355-91.

8. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. *Circulation*. 2001;104(22):2746-53.

9. Causes of death 2011: Australian Bureau of Statistics. March 2013.

10. The burden of cardiovascular disease in Australia for the year 2003: National Heart Foundation of Australia (Report by Vos T and Begg S, Centre for Burden of Disease and Cost-effectiveness, University of Queensland School of Population Health).2007.

11. Reddy KS, Yusuf S. Emerging epidemic of cardiovascular disease in developing countries. *Circulation*. 1998;97(6):596-601.

12. Viet Nam Burden of Disease and Injury Study 2008. Hanoi: Hanoi School of Public Health.2011.

13. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, *et al.* Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure:

prospective observational studies corrected for the regression dilution bias. *Lancet*. 1990;335(8692):765-74.

14. The Health Consequences of Smoking: A Report of the Surgeon General. Atlanta, Ga: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. 2004.

15. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care*. 1993;16(2):434-44.

16. Verschuren WM, Jacobs DR, Bloemberg BP, Kromhout D, Menotti A, Aravanis C, *et al.* Serum total cholesterol and long-term coronary heart disease mortality in different cultures. Twenty-five-year follow-up of the seven countries study. *JAMA*. 1995;274(2):131-6.

17. Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, *et al.* Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet*. 1990;335(8693):827-38.

18. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ*. 2003;326(7404):1423.

19. Grundy SM, Pasternak R, Greenland P, Smith S, Jr., Fuster V. Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *Circulation*. 1999;100(13):1481-92.

20. Rosenman RH, Friedman M. Neurogenic factors in pathogenesis of coronary heart disease. *Med Clin North Am*. 1974;58(2):269-79.

21. Braunwald E. Shattuck lecture--cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. *N Engl J Med*. 1997;337(19):1360-9.

22. Hennekens CH. Increasing burden of cardiovascular disease: current knowledge and future directions for research on risk factors. *Circulation*. 1998;97(11):1095-102.

23. Futterman LG, Lemberg L. Fifty percent of patients with coronary artery disease do not have any of the conventional risk factors. *Am J Crit Care*. 1998;7(3):240-4.

24. Khot UN, Khot MB, Bajzer CT, Sapp SK, Ohman EM, Brener SJ, *et al.* Prevalence of conventional risk factors in patients with coronary heart disease. *JAMA*. 2003;290(7):898-904.

25. Greenland P, Knoll MD, Stamler J, Neaton JD, Dyer AR, Garside DB, Wilson PW. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. *JAMA*. 2003;290(7):891-7.

26. Stamler J, Stamler R, Neaton JD, Wentworth D, Daviglus ML, Garside D, *et al.* Low risk-factor profile and long-term cardiovascular and noncardiovascular mortality and life expectancy: findings for 5 large cohorts of young adult and middle-aged men and women. *JAMA*. 1999;282(21):2012-8.

27. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, *et al.* Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364(9438):937-52.

28. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr., *et al.* The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289(19):2560-72.

29. Mendis S, Puska P, Norrving B, editors. Global Atlas on Cardiovascular Disease Prevention and Control. Geneva: World Health Organization (in collaboration with the World Heart Federation and World Stroke Organization); 2011.

30. Vasan RS, Beiser A, Seshadri S, Larson MG, Kannel WB, D'Agostino RB, Levy D. Residual lifetime risk for developing hypertension in middle-aged women and men: The Framingham Heart Study. *JAMA*. 2002;287(8):1003-10.

31. Vasan RS, Larson MG, Leip EP, Kannel WB, Levy D. Assessment of frequency of progression to hypertension in non-hypertensive participants in the Framingham Heart Study: a cohort study. *Lancet*. 2001;358(9294):1682-6.

32. Vasan RS, Larson MG, Leip EP, Evans JC, O'Donnell CJ, Kannel WB, Levy D. Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Engl J Med*. 2001;345(18):1291-7.

33. Franklin SS, Gustin Wt, Wong ND, Larson MG, Weber MA, Kannel WB, Levy D. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. *Circulation*. 1997;96(1):308-15.

34. Benetos A, Zureik M, Morcet J, Thomas F, Bean K, Safar M, Ducimetiere P, Guize L. A decrease in diastolic blood pressure combined with an increase in systolic blood pressure is

associated with a higher cardiovascular mortality in men. *J Am Coll Cardiol*. 2000;35(3):673-80.

35. Blacher J, Staessen JA, Girerd X, Gasowski J, Thijs L, Liu L, *et al.* Pulse pressure not mean pressure determines cardiovascular risk in older hypertensive patients. *Arch Intern Med*. 2000;160(8):1085-9.

36. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, *et al.* Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J*. 2006;27(21):2588-605.

37. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360(9349):1903-13.

38. Neal B, MacMahon S, Chapman N. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. Blood Pressure Lowering Treatment Trialists' Collaboration. *Lancet*. 2000;356(9246):1955-64.

39. Wright JM, Musini VM. First-line drugs for hypertension. *Cochrane Database Syst Rev*. 2009;(3):CD001841.

40. Musini VM, Tejani AM, Bassett K, Wright JM. Pharmacotherapy for hypertension in the elderly. *Cochrane Database Syst Rev*. 2009;(4):CD000028.

41. Hill AB. The environment and disease: association or causation? *Proc R Soc Med*. 1965;58:295-300.

42. Deanfield J, Donald A, Ferri C, Giannattasio C, Halcox J, Halligan S, *et al.* Endothelial function and dysfunction. Part I: Methodological issues for assessment in the different vascular beds: a statement by the Working Group on Endothelin and Endothelial Factors of the European Society of Hypertension. *J Hypertens*. 2005;23(1):7-17.

43. Blann AD, Kirkpatrick U, Devine C, Naser S, McCollum CN. The influence of acute smoking on leucocytes, platelets and the endothelium. *Atherosclerosis*. 1998;141(1):133-9.

44. Campisi R, Czernin J, Schoder H, Sayre JW, Schelbert HR. L-Arginine normalizes coronary vasomotion in long-term smokers. *Circulation*. 1999;99(4):491-7.

45. Newby DE, Wright RA, Labinjoh C, Ludlam CA, Fox KA, Boon NA, Webb DJ. Endothelial dysfunction, impaired endogenous fibrinolysis, and cigarette smoking: a

mechanism for arterial thrombosis and myocardial infarction. *Circulation*. 1999;99(11):1411-5.

46. Spagnoli LG, Mauriello A, Palmieri G, Santeusanio G, Amante A, Taurino M. Relationships between risk factors and morphological patterns of human carotid atherosclerotic plaques. A multivariate discriminant analysis. *Atherosclerosis*. 1994;108(1):39-60.

47. Burke AP, Farb A, Malcom GT, Liang YH, Smialek J, Virmani R. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. *N Engl J Med*. 1997;336(18):1276-82.

48. Friedman GD, Siegelaub AB, Seltzer CC, Feldman R, Collen MF. Smoking habits and the leukocyte count. *Arch Environ Health*. 1973;26(3):137-43.

49. Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation*. 2000;101(15):1767-72.

50. Craig WY, Palomaki GE, Haddow JE. Cigarette smoking and serum lipid and lipoprotein concentrations: an analysis of published data. *BMJ*. 1989;298(6676):784-8.

51. Benowitz NL. Drug therapy. Pharmacologic aspects of cigarette smoking and nicotine addition. *N Engl J Med*. 1988;319(20):1318-30.

52. Quillen JE, Rossen JD, Oskarsson HJ, Minor RL, Jr., Lopez AG, Winniford MD. Acute effect of cigarette smoking on the coronary circulation: constriction of epicardial and resistance vessels. *J Am Coll Cardiol*. 1993;22(3):642-7.

53. Rampling MW. Clotting factors and rheology: mechanisms of damage and intervention. In: Poulter N, Sever P, Thom S, editors. Cardiovascular Disease: Risk Factors and Intervention. Oxford: Radcliffe Medical Press; 1993. p. 201–13.

54. Narkiewicz K, van de Borne PJ, Hausberg M, Cooley RL, Winniford MD, Davison DE, Somers VK. Cigarette smoking increases sympathetic outflow in humans. *Circulation*. 1998;98(6):528-34.

55. Keil U, Liese AD, Hense HW, Filipiak B, Doring A, Stieber J, Lowel H. Classical risk factors and their impact on incident non-fatal and fatal myocardial infarction and all-cause mortality in southern Germany. Results from the MONICA Augsburg cohort study 1984-1992. Monitoring Trends and Determinants in Cardiovascular Diseases. *Eur Heart J*. 1998;19(8):1197-207.

56. Willett WC, Green A, Stampfer MJ, Speizer FE, Colditz GA, Rosner B, *et al.* Relative and absolute excess risks of coronary heart disease among women who smoke cigarettes. *N Engl J Med*. 1987;317(21):1303-9.

57. Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary prevention of coronary heart disease in women through diet and lifestyle. *N Engl J Med*. 2000;343(1):16-22.

58. Rosenberg L, Kaufman DW, Helmrich SP, Miller DR, Stolley PD, Shapiro S. Myocardial infarction and cigarette smoking in women younger than 50 years of age. *JAMA*. 1985;253(20):2965-9.

59. Croft P, Hannaford PC. Risk factors for acute myocardial infarction in women: evidence from the Royal College of General Practitioners' oral contraception study. *BMJ*. 1989;298(6667):165-8.

60. U.S. Dept of Health and Human Services. The Health Benefits of Smoking Cessation. A Report of the Surgeon General.: USDHHS, Centers for Disease Control. Office of Smoking and Health. 1990. DHHS Publication (CDC) 90-8416. .

61. Sparrow D, Dawber TR. The influence of cigarette smoking on prognosis after a first myocardial infarction. A report from the Framingham study. *J Chronic Dis*. 1978;31(6-7):425-32.

62. Salonen JT. Stopping smoking and long-term mortality after acute myocardial infarction. *Br Heart J*. 1980;43(4):463-9.

63. Diabetes Atlas, Third Edition. Brussels: International Diabetes Federation. 2006.

64. Dunstan D, Zimmet P, Welborn T, Sicree R, Armstrong T, Atkins R, *et al.* Diabesity & Associated Disorders in Australia - 2000. The Accelerating Epidemic. The Australian Diabetes, Obesity and Lifestyle Study (AusDiab). Melbourne. 2001.

65. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: a report of a WHO/IDF consultation. Geneva: World Health Organization. 2006.

66. Lloyd CE, Kuller LH, Ellis D, Becker DJ, Wing RR, Orchard TJ. Coronary artery disease in IDDM. Gender differences in risk factors but not risk. *Arterioscler Thromb Vasc Biol*. 1996;16(6):720-6.

67. Wilson PW. Diabetes mellitus and coronary heart disease. *Am J Kidney Dis*. 1998;32(5 Suppl 3):S89-100.

68. Geiss LS, Herman WH, Smith PJ. Chapter 11: Mortality in Non-Insulin-Dependent Diabetes. *Diabetes in America, 2nd Edition*. Bethesda, Md: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1995. p. 233–57.

69. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med*. 1998;339(4):229-34.

70. Grundy SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV, *et al.* Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation*. 1999;100(10):1134-46.

71. Stone PH, Muller JE, Hartwell T, York BJ, Rutherford JD, Parker CB, *et al.* The effect of diabetes mellitus on prognosis and serial left ventricular function after acute myocardial infarction: contribution of both coronary disease and diastolic left ventricular dysfunction to the adverse prognosis. The MILIS Study Group. *J Am Coll Cardiol*. 1989;14(1):49-57.

72. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106(25):3143-421.

73. Castelli WP, Anderson K, Wilson PW, Levy D. Lipids and risk of coronary heart disease. The Framingham Study. *Ann Epidemiol*. 1992;2(1-2):23-8.

74. Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA*. 1986;256(20):2823-8.

75. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA*. 1984;251(3):351-64.

76. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *JAMA*. 1984;251(3):365-74.

77. Brown MS, Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis. *Science*. 1986;232(4746):34-47.

78. Gordon DJ. Cholesterol lowering reduces mortality: the statins. In: Grundy SM, editor. Cholesterol-lowering therapy: evaluation of clinical trial evidence. New York: Marcel Dekker Inc.; 2000. p. 299-311.

79. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, *et al.* Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med*. 1999;341(6):410-8.

80. Sacks FM, Tonkin AM, Shepherd J, Braunwald E, Cobbe S, Hawkins CM, *et al.* Effect of pravastatin on coronary disease events in subgroups defined by coronary risk factors: the Prospective Pravastatin Pooling Project. *Circulation*. 2000;102(16):1893-900.

81. Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *BMJ*. 1994;308(6925):367-72.

82. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. *JAMA*. 2006;295(13):1549-55.

83. Australian Health Survey: First Results, 2011-12 (cat. no. 4364.0.55.001): Australian Bureau of Statistics. 2012.

84. Manson JE, Willett WC, Stampfer MJ, Colditz GA, Hunter DJ, Hankinson SE, Hennekens CH, Speizer FE. Body weight and mortality among women. *N Engl J Med*. 1995;333(11):677-85.

85. Wilson PW, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. *Arch Intern Med*. 2002;162(16):1867-72.

86. Van Itallie TB. Health implications of overweight and obesity in the United States. *Ann Intern Med*. 1985;103(6 (Pt 2)):983-8.

87. Alpert MA, Hashimi MW. Obesity and the heart. *Am J Med Sci*. 1993;306(2):117-23.

88. Duflou J, Virmani R, Rabin I, Burke A, Farb A, Smialek J. Sudden death as a result of heart disease in morbid obesity. *Am Heart J*. 1995;130(2):306-13.

89. Rabkin SW, Mathewson FA, Hsu PH. Relation of body weight to development of ischemic heart disease in a cohort of young North American men after a 26 year observation period: the Manitoba Study. *Am J Cardiol*. 1977;39(3):452-8.

90. Eckel RH. Obesity and heart disease: a statement for healthcare professionals from the Nutrition Committee, American Heart Association. *Circulation*. 1997;96(9):3248-50.

91. Lloyd-Jones DM, Liu K, Colangelo LA, Yan LL, Klein L, Loria CM, Lewis CE, Savage P. Consistently stable or decreased body mass index in young adulthood and longitudinal changes in metabolic syndrome components: the Coronary Artery Risk Development in Young Adults Study. *Circulation*. 2007;115(8):1004-11.

92. Ford ES, Capewell S. Coronary heart disease mortality among young adults in the U.S. from 1980 through 2002: concealed leveling of mortality rates. *J Am Coll Cardiol*. 2007;50(22):2128-32.

93. O'Flaherty M, Ford E, Allender S, Scarborough P, Capewell S. Coronary heart disease trends in England and Wales from 1984 to 2004: concealed levelling of mortality rates among young adults. *Heart*. 2008;94(2):178-81.

94. Mathers CD, Vos ET, Stevenson CE, Begg SJ. The Australian Burden of Disease Study: measuring the loss of health from diseases, injuries and risk factors. *Med J Aust*. 2000;172(12):592-6.

95. Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Actual causes of death in the United States, 2000. *JAMA*. 2004;291(10):1238-45.

96. Fletcher GF, Balady G, Blair SN, Blumenthal J, Caspersen C, Chaitman B, *et al.* Statement on exercise: benefits and recommendations for physical activity programs for all Americans. A statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association. *Circulation*. 1996;94(4):857-62.

97. Gordon NF, Gulanick M, Costa F, Fletcher G, Franklin BA, Roth EJ, Shephard T. Physical activity and exercise recommendations for stroke survivors: an American Heart Association scientific statement from the Council on Clinical Cardiology, Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention; the Council on Cardiovascular Nursing; the Council on Nutrition, Physical Activity, and Metabolism; and the Stroke Council. *Stroke*. 2004;35(5):1230-40.

98. Leon AS, Franklin BA, Costa F, Balady GJ, Berra KA, Stewart KJ, *et al.* Cardiac rehabilitation and secondary prevention of coronary heart disease: an American Heart Association scientific statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity), in collaboration with the American association of Cardiovascular and Pulmonary Rehabilitation. *Circulation*. 2005;111(3):369-76.

99. Powell KE, Thompson PD, Caspersen CJ, Kendrick JS. Physical activity and the incidence of coronary heart disease. *Annu Rev Public Health*. 1987;8:253-87.

100. Morris JN, Clayton DG, Everitt MG, Semmence AM, Burgess EH. Exercise in leisure time: coronary attack and death rates. *Br Heart J*. 1990;63(6):325-34.

101. Nocon M, Hiemann T, Muller-Riemenschneider F, Thalau F, Roll S, Willich SN. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. *Eur J Cardiovasc Prev Rehabil*. 2008;15(3):239-46.

102. Heran BS, Chen JM, Ebrahim S, Moxham T, Oldridge N, Rees K, Thompson DR, Taylor RS. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev*. 2011;(7):CD001800.

103. Pescatello LS, Franklin BA, Fagard R, Farquhar WB, Kelley GA, Ray CA. American College of Sports Medicine position stand. Exercise and hypertension. *Med Sci Sports Exerc*. 2004;36(3):533-53.

104. Leon AS, Sanchez OA. Response of blood lipids to exercise training alone or combined with dietary intervention. *Med Sci Sports Exerc*. 2001;33(6 Suppl):S502-15; discussion S28-9.

105. Bauman AE. Updating the evidence that physical activity is good for health: an epidemiological review 2000-2003. *J Sci Med Sport*. 2004;7(1 Suppl):6-19.

106. Catenacci VA, Wyatt HR. The role of physical activity in producing and maintaining weight loss. *Nat Clin Pract Endocrinol Metab*. 2007;3(7):518-29.

107. Swain DP, Franklin BA. Comparison of cardioprotective benefits of vigorous versus moderate intensity aerobic exercise. *Am J Cardiol*. 2006;97(1):141-7.

108. Kaminsky LA, Arena R, Beckie TM, Brubaker PH, Church TS, Forman DE, *et al.* The importance of cardiorespiratory fitness in the United States: the need for a national registry: a policy statement from the american heart association. *Circulation*. 2013;127(5):652-62.

109. Blair SN, Kohl HW, 3rd, Paffenbarger RS, Jr., Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality. A prospective study of healthy men and women. *JAMA*. 1989;262(17):2395-401.

110. Mora S, Redberg RF, Cui Y, Whiteman MK, Flaws JA, Sharrett AR, Blumenthal RS. Ability of exercise testing to predict cardiovascular and all-cause death in asymptomatic women: a 20-year follow-up of the lipid research clinics prevalence study. *JAMA*. 2003;290(12):1600-7.

111. Kokkinos P, Myers J, Kokkinos JP, Pittaras A, Narayan P, Manolis A, *et al*. Exercise capacity and mortality in black and white men. *Circulation*. 2008;117(5):614-22.

112. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, *et al*. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA*. 2009;301(19):2024-35.

113. Blair SN, Kohl HW, 3rd, Barlow CE, Paffenbarger RS, Jr., Gibbons LW, Macera CA. Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men. *JAMA*. 1995;273(14):1093-8.

114. Gregg EW, Cauley JA, Stone K, Thompson TJ, Bauer DC, Cummings SR, Ensrud KE. Relationship of changes in physical activity and mortality among older women. *JAMA*. 2003;289(18):2379-86.

115. Lee DC, Sui X, Artero EG, Lee IM, Church TS, McAuley PA, *et al*. Long-term effects of changes in cardiorespiratory fitness and body mass index on all-cause and cardiovascular disease mortality in men: the aerobics center longitudinal study. *Circulation*. 2011;124(23):2483-90.

116. Wenger HA, Bell GJ. The interactions of intensity, frequency and duration of exercise training in altering cardiorespiratory fitness. *Sports Med*. 1986;3(5):346-56.

117. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, *et al*. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc*. 2000;32(9 Suppl):S498-504.

118. Dunstan DW, Thorp AA, Healy GN. Prolonged sitting: is it a distinct coronary heart disease risk factor? *Curr Opin Cardiol*. 2011;26(5):412-9.

119. Katzmarzyk PT, Church TS, Craig CL, Bouchard C. Sitting time and mortality from all causes, cardiovascular disease, and cancer. *Med Sci Sports Exerc*. 2009;41(5):998-1005.

120. Patel AV, Bernstein L, Deka A, Feigelson HS, Campbell PT, Gapstur SM, Colditz GA, Thun MJ. Leisure time spent sitting in relation to total mortality in a prospective cohort of US adults. *Am J Epidemiol*. 2010;172(4):419-29.

121. Stamatakis E, Hamer M, Dunstan DW. Screen-based entertainment time, all-cause mortality, and cardiovascular events: population-based study with ongoing mortality and hospital events follow-up. *J Am Coll Cardiol*. 2011;57(3):292-9.

122. Dunstan DW, Barr EL, Healy GN, Salmon J, Shaw JE, Balkau B, *et al.* Television viewing time and mortality: the Australian Diabetes, Obesity and Lifestyle Study (AusDiab). *Circulation*. 2010;121(3):384-91.

123. Wijndaele K, Brage S, Besson H, Khaw KT, Sharp SJ, Luben R, Wareham NJ, Ekelund U. Television viewing time independently predicts all-cause and cardiovascular mortality: the EPIC Norfolk study. *Int J Epidemiol*. 2011;40(1):150-9.

124. Warren TY, Barry V, Hooker SP, Sui X, Church TS, Blair SN. Sedentary behaviors increase risk of cardiovascular disease mortality in men. *Med Sci Sports Exerc*. 2010;42(5):879-85.

125. Thorp AA, Healy GN, Owen N, Salmon J, Ball K, Shaw JE, Zimmet PZ, Dunstan DW. Deleterious associations of sitting time and television viewing time with cardiometabolic risk biomarkers: Australian Diabetes, Obesity and Lifestyle (AusDiab) study 2004-2005. *Diabetes Care*. 2010;33(2):327-34.

126. Wijndaele K, Healy GN, Dunstan DW, Barnett AG, Salmon J, Shaw JE, Zimmet PZ, Owen N. Increased cardiometabolic risk is associated with increased TV viewing time. *Med Sci Sports Exerc*. 2010;42(8):1511-8.

127. Healy GN, Dunstan DW, Salmon J, Cerin E, Shaw JE, Zimmet PZ, Owen N. Breaks in sedentary time: beneficial associations with metabolic risk. *Diabetes Care*. 2008;31(4):661-6.

128. Healy GN, Matthews CE, Dunstan DW, Winkler EA, Owen N. Sedentary time and cardio-metabolic biomarkers in US adults: NHANES 2003-06. *Eur Heart J*. 2011;32(5):590-7.

129. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation*. 2007;115(4):459-67.

130. Berenson GS, Srinivasan SR, Bao W, Newman WP, 3rd, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. *N Engl J Med*. 1998;338(23):1650-6.

131. McGill HC, Jr., McMahan CA, Zieske AW, Tracy RE, Malcom GT, Herderick EE, Strong JP. Association of Coronary Heart Disease Risk Factors with microscopic qualities of coronary atherosclerosis in youth. *Circulation*. 2000;102(4):374-9.

132. Cohn JN. Introduction to surrogate markers. *Circulation*. 2004;109(25 Suppl 1):IV20-1.

133. Cohn JN, Quyyumi AA, Hollenberg NK, Jamerson KA. Surrogate markers for cardiovascular disease: functional markers. *Circulation*. 2004;109(25 Suppl 1):IV31-46.

134. Mancini GB, Dahlof B, Diez J. Surrogate markers for cardiovascular disease: structural markers. *Circulation*. 2004;109(25 Suppl 1):IV22-30.

135. Blacher J, Pannier B, Guerin AP, Marchais SJ, Safar ME, London GM. Carotid arterial stiffness as a predictor of cardiovascular and all-cause mortality in end-stage renal disease. *Hypertension*. 1998;32(3):570-4.

136. Barenbrock M, Kosch M, Joster E, Kisters K, Rahn KH, Hausberg M. Reduced arterial distensibility is a predictor of cardiovascular disease in patients after renal transplantation. *J Hypertens*. 2002;20(1):79-84.

137. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;55(13):1318-27.

138. Moens AL, Goovaerts I, Claeys MJ, Vrints CJ. Flow-mediated vasodilation: a diagnostic instrument, or an experimental tool? *Chest*. 2005;127(6):2254-63.

139. Wilkinson IB, Cockcroft JR, Webb DJ. Pulse wave analysis and arterial stiffness. *J Cardiovasc Pharmacol*. 1998;32 Suppl 3:S33-7.

140. Wexler L, Brundage B, Crouse J, Detrano R, Fuster V, Maddahi J, *et al.* Coronary artery calcification: pathophysiology, epidemiology, imaging methods, and clinical implications. A statement for health professionals from the American Heart Association. Writing Group. *Circulation*. 1996;94(5):1175-92.

141. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, *et al.* Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr*. 2008;21(2):93-111; quiz 89-90.

142. Davis PH, Dawson JD, Riley WA, Lauer RM. Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age: The Muscatine Study. *Circulation*. 2001;104(23):2815-9.

143. Freedman DS, Dietz WH, Tang R, Mensah GA, Bond MG, Urbina EM, Srinivasan S, Berenson GS. The relation of obesity throughout life to carotid intima-media thickness in adulthood: the Bogalusa Heart Study. *Int J Obes Relat Metab Disord*. 2004;28(1):159-66.

144. Freedman DS, Patel DA, Srinivasan SR, Chen W, Tang R, Bond MG, Berenson GS. The contribution of childhood obesity to adult carotid intima-media thickness: the Bogalusa Heart Study. *Int J Obes (Lond)*. 2008;32(5):749-56.

145. Ferreira I, Twisk JW, van Mechelen W, Kemper HC, Seidell JC, Stehouwer CD. Current and adolescent body fatness and fat distribution: relationships with carotid intima-media thickness and large artery stiffness at the age of 36 years. *J Hypertens*. 2004;22(1):145-55.

146. Ferreira I, Twisk JW, Van Mechelen W, Kemper HC, Stehouwer CD. Current and adolescent levels of cardiopulmonary fitness are related to large artery properties at age 36: the Amsterdam Growth and Health Longitudinal Study. *Eur J Clin Invest*. 2002;32(10):723-31.

147. Raitakari OT, Juonala M, Kahonen M, Taittonen L, Laitinen T, Maki-Torkko N, *et al.* Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *JAMA*. 2003;290(17):2277-83.

148. Juonala M, Jarvisalo MJ, Maki-Torkko N, Kahonen M, Viikari JS, Raitakari OT. Risk factors identified in childhood and decreased carotid artery elasticity in adulthood: the Cardiovascular Risk in Young Finns Study. *Circulation*. 2005;112(10):1486-93.

149. Huynh Q, Blizzard L, Sharman J, Magnussen C, Schmidt M, Dwyer T, Venn A. Relative contributions of adiposity in childhood and adulthood to vascular health of young adults. *Atherosclerosis*. 2013;228(1):259-64.

150. Quan HL, Blizzard CL, Sharman JE, Magnussen CG, Dwyer T, Raitakari O, Cheung M, Venn AJ. Resting Heart Rate and the Association of Physical Fitness With Carotid Artery Stiffness. *Am J Hypertens*. 2013 (doi: 10.1093/ajh/hpt161).

151. Oren A, Vos LE, Uiterwaal CS, Gorissen WH, Grobbee DE, Bots ML. Change in body mass index from adolescence to young adulthood and increased carotid intima-media thickness at 28 years of age: the Atherosclerosis Risk in Young Adults study. *Int J Obes Relat Metab Disord*. 2003;27(11):1383-90.

152. Duff GL, McMillan GC. Pathology of atherosclerosis. *Am J Med*. 1951;11(1):92-108.

153. McGill HC, Jr., Geer JC, Strong JP. Natural history of human atherosclerotic lesions. In: Sandler M, Bourne GH, editors. Atherosclerosis and its origin. New York: Academic Press; 1963. p. 39-65.

154. Holman RL, McGill HC, Jr., Strong JP, Geer JC. The natural history of atherosclerosis: the early aortic lesions as seen in New Orleans in the middle of the of the 20th century. *Am J Pathol*. 1958;34(2):209-35.

155. Strong JP, McGill HC, Jr. The natural history of coronary atherosclerosis. *Am J Pathol*. 1962;40:37-49.

156. Strong JP, McGill HC, Jr. The pediatric aspects of atherosclerosis. *J Atheroscler Res*. 1969;9(3):251-65.

157. Strong JP, McGill HC, Jr., Tejada C, Holman RL. The natural history of atherosclerosis; comparison of the early aortic lesions in New Orleans, Guatemala, and Costa Rica. *Am J Pathol*. 1958;34(4):731-44.

158. Newman WP, 3rd, Freedman DS, Voors AW, Gard PD, Srinivasan SR, Cresanta JL, *et al.* Relation of serum lipoprotein levels and systolic blood pressure to early atherosclerosis. The Bogalusa Heart Study. *N Engl J Med*. 1986;314(3):138-44.

159. Berenson GS, Wattigney WA, Tracy RE, Newman WP, 3rd, Srinivasan SR, Webber LS, Dalferes ER, Jr., Strong JP. Atherosclerosis of the aorta and coronary arteries and cardiovascular risk factors in persons aged 6 to 30 years and studied at necropsy (The Bogalusa Heart Study). *Am J Cardiol*. 1992;70(9):851-8.

160. McMahan CA, Gidding SS, Fayad ZA, Zieske AW, Malcom GT, Tracy RE, Strong JP, McGill HC, Jr. Risk scores predict atherosclerotic lesions in young people. *Arch Intern Med*. 2005;165(8):883-90.

161. Savva SC, Tornaritis M, Savva ME, Kourides Y, Panagi A, Silikiotou N, Georgiou C, Kafatos A. Waist circumference and waist-to-height ratio are better predictors of cardiovascular disease risk factors in children than body mass index. *Int J Obes Relat Metab Disord*. 2000;24(11):1453-8.

162. Schmidt MD, Dwyer T, Magnussen CG, Venn AJ. Predictive associations between alternative measures of childhood adiposity and adult cardio-metabolic health. *Int J Obes (Lond)*. 2011;35(1):38-45.

163. Juonala M, Raitakari M, J SAV, Raitakari OT. Obesity in youth is not an independent predictor of carotid IMT in adulthood. The Cardiovascular Risk in Young Finns Study. *Atherosclerosis*. 2006;185(2):388-93.

164. Wright CM, Parker L, Lamont D, Craft AW. Implications of childhood obesity for adult health: findings from thousand families cohort study. *BMJ*. 2001;323(7324):1280-4.

165. Mahoney LT, Burns TL, Stanford W, Thompson BH, Witt JD, Rost CA, Lauer RM. Coronary risk factors measured in childhood and young adult life are associated with coronary artery calcification in young adults: the Muscatine Study. *J Am Coll Cardiol*. 1996;27(2):277-84.

166. Ferreira I, van de Laar RJ, Prins MH, Twisk JW, Stehouwer CD. Carotid stiffness in young adults: a life-course analysis of its early determinants: the Amsterdam Growth and Health Longitudinal Study. *Hypertension*. 2012;59(1):54-61.

167. van de Laar RJ, Ferreira I, van Mechelen W, Prins MH, Twisk JW, Stehouwer CD. Lifetime vigorous but not light-to-moderate habitual physical activity impacts favorably on carotid stiffness in young adults: the amsterdam growth and health longitudinal study. *Hypertension*. 2010;55(1):33-9.

168. van de Laar RJ, Ferreira I, van Mechelen W, Prins MH, Twisk JW, Stehouwer CD. Habitual physical activity and peripheral arterial compliance in young adults: the Amsterdam growth and health longitudinal study. *Am J Hypertens*. 2011;24(2):200-8.

169. Li S, Chen W, Srinivasan SR, Bond MG, Tang R, Urbina EM, Berenson GS. Childhood cardiovascular risk factors and carotid vascular changes in adulthood: the Bogalusa Heart Study. *JAMA*. 2003;290(17):2271-6.

170. Frontini MG, Srinivasan SR, Xu J, Tang R, Bond MG, Berenson GS. Usefulness of childhood non-high density lipoprotein cholesterol levels versus other lipoprotein measures in predicting adult subclinical atherosclerosis: the Bogalusa Heart Study. *Pediatrics*. 2008;121(5):924-9.

171. Li S, Chen W, Srinivasan SR, Tang R, Bond MG, Berenson GS. Race (black-white) and gender divergences in the relationship of childhood cardiovascular risk factors to carotid artery intima-media thickness in adulthood: the Bogalusa Heart Study. *Atherosclerosis*. 2007;194(2):421-5.

172. Juonala M, Viikari JS, Ronnemaa T, Marniemi J, Jula A, Loo BM, Raitakari OT. Associations of dyslipidemias from childhood to adulthood with carotid intima-media

thickness, elasticity, and brachial flow-mediated dilatation in adulthood: the Cardiovascular Risk in Young Finns Study. *Arterioscler Thromb Vasc Biol*. 2008;28(5):1012-7.

173. Juonala M, Viikari JS, Kahonen M, Solakivi T, Helenius H, Jula A, *et al.* Childhood levels of serum apolipoproteins B and A-I predict carotid intima-media thickness and brachial endothelial function in adulthood: the cardiovascular risk in young Finns study. *J Am Coll Cardiol*. 2008;52(4):293-9.

174. Hartiala O, Magnussen CG, Kajander S, Knuuti J, Ukkonen H, Saraste A, *et al.* Adolescence risk factors are predictive of coronary artery calcification at middle age: the cardiovascular risk in young Finns study. *J Am Coll Cardiol*. 2012;60(15):1364-70.

175. Magnussen CG, Venn A, Thomson R, Juonala M, Srinivasan SR, Viikari JS, *et al.* The association of pediatric low- and high-density lipoprotein cholesterol dyslipidemia classifications and change in dyslipidemia status with carotid intima-media thickness in adulthood evidence from the cardiovascular risk in Young Finns study, the Bogalusa Heart study, and the CDAH (Childhood Determinants of Adult Health) study. *J Am Coll Cardiol*. 2009;53(10):860-9.

176. Li S, Chen W, Srinivasan SR, Berenson GS. Childhood blood pressure as a predictor of arterial stiffness in young adults: the bogalusa heart study. *Hypertension*. 2004;43(3):541-6.

177. Juonala M, Viikari JS, Ronnemaa T, Helenius H, Taittonen L, Raitakari OT. Elevated blood pressure in adolescent boys predicts endothelial dysfunction: the cardiovascular risk in young Finns study. *Hypertension*. 2006;48(3):424-30.

178. van de Laar RJ, Stehouwer CD, Boreham CA, Murray LM, Schalkwijk CG, Prins MH, Twisk JW, Ferreira I. Continuing smoking between adolescence and young adulthood is associated with higher arterial stiffness in young adults: the Northern Ireland Young Hearts Project. *J Hypertens*. 2011;29(11):2201-9.

179. Juonala M, Magnussen CG, Venn A, Gall S, Kahonen M, Laitinen T, *et al.* Parental smoking in childhood and brachial artery flow-mediated dilatation in young adults: the Cardiovascular Risk in Young Finns study and the Childhood Determinants of Adult Health study. *Arterioscler Thromb Vasc Biol*. 2012;32(4):1024-31.

180. Mikkila V, Rasanen L, Laaksonen MM, Juonala M, Viikari J, Pietinen P, Raitakari OT. Long-term dietary patterns and carotid artery intima media thickness: the Cardiovascular Risk in Young Finns Study. *Br J Nutr*. 2009;102(10):1507-12.

181. Kaikkonen JE, Jula A, Mikkila V, Juonala M, Viikari JS, Moilanen T, *et al.* Childhood serum fatty acid quality is associated with adult carotid artery intima media thickness in women but not in men. *J Nutr*. 2013;143(5):682-9.

182. Aatola H, Koivistoinen T, Hutri-Kahonen N, Juonala M, Mikkila V, Lehtimaki T, *et al.* Lifetime fruit and vegetable consumption and arterial pulse wave velocity in adulthood: the Cardiovascular Risk in Young Finns Study. *Circulation*. 2010;122(24):2521-8.

183. van de Laar RJ, Stehouwer CD, van Bussel BC, te Velde SJ, Prins MH, Twisk JW, Ferreira I. Lower lifetime dietary fiber intake is associated with carotid artery stiffness: the Amsterdam Growth and Health Longitudinal Study. *Am J Clin Nutr*. 2012;96(1):14-23.

184. van de Laar RJ, Stehouwer CD, van Bussel BC, Prins MH, Twisk JW, Ferreira I. Adherence to a Mediterranean dietary pattern in early life is associated with lower arterial stiffness in adulthood: the Amsterdam Growth and Health Longitudinal Study. *J Intern Med*. 2013;273(1):79-93.

Chapter 2

Methods

Chapter 2. Methods

Preface

This thesis aims to examine the relationship of fatness, fitness, physical activity and sedentary behaviour with vascular health and to investigate the possible mechanisms involved using an epidemiological approach. The data used for these analyses were from four large population-based samples, including those from the Burnie Take Heart project (Chapter 3), the Can Tho survey (Chapter 3), the Childhood Determinants of Adult Health study (Chapter 4, 5, 6, and 7), and the Cardiovascular Risk in Young Finns study (Chapter 6). This chapter briefly describes the participants and the methods of these samples that are relevant to this research. More details related to a specific sample can be found in the respective studies that are presented in the following Chapters 3–7. Data from all samples included in this thesis were approved by appropriate ethics committees.

The Burnie Take Heart (BTH) project

The BTH project was originally an initiative of the National Heart Foundation of Australia as an intervention to improve cardiovascular health in the community. The BTH project conducted two major surveys, pre- and post-intervention. The pre-intervention (baseline) survey was conducted between 1996 and 1997, followed by community-based promotions of public health with a focus on nutrition and physical activity. The post-intervention survey was conducted between 1998 and 1999. The study in Chapter 3 of this thesis used data from the post-intervention survey of the BTH project,[1] which is described in this section. This project was approved by the Ethics Committee of the University of Tasmania.

Study design

The BTH project included two cross-sectional surveys conducted during 1996-97 and repeated during 1998-99.

Sampling and participants

Participants aged 25-64 years were selected by age- and sex-stratified random sampling from among those on the Electoral Roll of registered voters in Tasmania (Australia) who had an

address within the Burnie municipalities, located in the north west of Tasmania as in Figure 2.1. The overall response rate was 69% (832/1205). The response rate of women (73%; 439/600) was greater than men (65%; 393/605). The age-specific participation was 66% (25-34 years), 67% (35-44 years), 71% (45-54 years) and 73% (55-64 years). Due to low response of younger persons in the pre-intervention survey, they were marginally oversampled in the post-intervention survey during 1998-99 to provide similar numbers of participants in each age group.

Figure 2.1. Location of Burnie in the north west Tasmania, Australia.

Measurements

Physical measurements of participants, including blood pressure and anthropometry, were obtained by trained field staff.

Blood pressure

Blood pressure was measured using a Dinamap Vital Signs Monitor 1846SX (Critikon Company, Tampa, FL, USA). This device was calibrated against a standard mercury sphygmomanometer before each week of clinic use. Correct cuff sizes were determined for the right upper arm before measuring blood pressure. Three readings of blood pressure were taken in an upright sitting position after the participants had rested for at least 10 minutes.

Anthropometry

This includes weight, height, and waist and hip circumference. Each participant's weight was measured to the nearest 0.1 kg, in bare feet without heavy clothing, using digital scales. Height was measured to the nearest 0.1 cm, in bare feet without headwear, using a stadiometer. Waist circumference at the narrowest point between the lower costal border and the iliac crest, and hip circumference at the greatest posterior protuberance of the buttocks, were measured to the nearest 0.1 cm. The mean was calculated from two waist and hip circumferences. If there was a difference greater than 2 cm (waist circumference) or 1.4 cm (hip circumference), a third measure was taken. A median of the three measures would then be calculated and used.

Other measurements

14 ml of blood taken from 9-hour fasting participants were sent to the same accredited teaching hospital laboratory to measure total cholesterol and plasma glucose. Level of education, type of employment, smoking (never smoker, ex-smoker, or current smoker), frequency of alcohol consumption, diet and physical activity were obtained from self-reported questionnaire. The questionnaire used in this survey was developed using questions from various standardised resources, including the National Heart Foundation Risk Factor Prevalence study (Survey No 3, 1989),[2] the short fat questionnaire,[3] the self-efficacy scales for exercise behaviours,[4] and the 1996 Tasmanian Food and Nutrition study.[5]

The Can Tho survey

Can Tho is the largest city of the Mekong Delta – literally called "the Nine Dragon River Delta" – and locates in the far southern region of Vietnam as illustrated in Figure 2.2. While being the main food production area for the country, health services for the Mekong Delta were reported to be below the country average.[6] The Can Tho survey was conducted in 2005 and aimed to study risk factors for non-communicable diseases among residents living in this area. Ethics approval was provided by the Can Tho University of Medicine and Pharmacy.

Study design

The Can Tho survey was designed as a cross-sectional survey following the World Health Organization STEPwise approach to surveillance of non-communicable disease (STEPS).[7]

Sampling and participants

The Can Tho survey was conducted among Can Tho adult residents aged 25-64 years. Participants were selected by multi-stage random sampling with age, sex and urban/rural stratification.[8-10] Briefly, the sampling process included 3 stages. Stage 1 was the selection of urban/rural-classified communes with probability proportional to size and with replacement. Stage 2 was the selection of health volunteers within each commune who were responsible for providing basic health services for residents living in their local areas. These health volunteers maintain and update the list of local residents regularly. Stage 3 was the selection of persons from lists of residents kept by health volunteers with stratification by sex and age group (25-34, 35-44, 45-54 and 55-64 years). 2683 persons were eligible. Of these, 73.7% (1978/2683) participated in the survey. Data collection was carried out from July to November 2005.

Figure 2.2. Location of Can Tho in the far south of Vietnam.

Measurements

Physical measurements of participants, including blood pressure and anthropometry, were obtained by trained field staff.

Blood pressure

Blood pressure was measured on the right upper arm using an Omron T9P digital automatic blood pressure monitor after the participants had rested for at least five minutes. This device was calibrated against a standard mercury sphygmomanometer before each day of clinic use. Two readings of blood pressure were taken for all participants. A third reading was taken for 24 men because there was a difference of greater than 25 mmHg for systolic blood pressure or 15 mmHg for diastolic blood pressure, following the STEPS protocols in 2005.[7] A mean of all three readings was used for analysis.

Anthropometry

Weight was measured in bare feet without heavy clothing using a Seca 767 digital scale. Height was measured in bare feet without headwear using a Seca 220 stadiometer. Waist circumference was measured at the narrowest point between the lower costal border and the iliac crest using a constant tension tape. Hip circumference was measured at the greatest posterior protuberance of the buttocks.

Other measurements

Total cholesterol and plasma glucose were measured in capillary blood of participants who had fasted for at least 12 hours using a Roche Diagnostics Accutrend Glucometer (Roche Group, Basel, Switzerland). Level of education, type of employment, smoking (never smoker, ex-smoker, or current smoker), frequency of alcohol consumption, fruit and vegetable consumption, and physical activity were recorded using the STEPS questionnaire.[7] Some locally relevant questions and response options were added to the questionnaire to suit the local needs (for example, types of work that were specific to the local area). These modifications were added in accordance to the STEPS protocols.[7] The questionnaire was translated to Vietnamese and back translated to English by independent translators to ensure the integrity of the original meaning of each question.

The Childhood Determinants of Adult Health (CDAH) study

The CDAH study (conducted during 2004-2006) is a 20-year follow-up of the 1985 Australian Schools Health and Fitness Survey (ASHFS), which collected an extensive range of lifestyle, physical and biological measures on a nationally representative sample of 8498 Australian schoolchildren aged 7-15 years. The CDAH study aims to determine the contribution of childhood risk factors to the development of cardio-metabolic diseases in adulthood. It is a member cohort of the International Childhood Cardiovascular Cohort (i3C) consortium, which contains several similar longitudinal studies in the world with the same principal aim as the CDAH's.

The 1985 ASHFS was approved by the State Directors General of Education. The CDAH follow-up study was approved by the Southern Tasmania Health and Medical Research Ethics Committee.

Study design

This study was designed as a cohort study.

Baseline data (the 1985 ASHFS)

Sampling and participants

The 1985 ASHFS was conducted on a nationally representative sample of 8498 Australian schoolchildren aged 7-15 years. The sampling procedure was reported elsewhere.[11] Briefly, these children were selected using two-stage random sampling. Stage 1 was the selection of schools with a probability proportional to enrolment numbers. Schools with total enrolment of less than 200 students (9.9% of primary schools and 3.1% of secondary schools) were excluded. Of the 121 schools selected, 90.1% (109/121) agreed to participate. The distribution of participating schools is shown in Figure 2.3. Stage 2 was the selection of children within each school with age and sex stratification. The study aimed for 500 boys and 500 girls from each year of age. Of the 12578 schoolchildren invited, 8498 (67.5%) children participated in the study. The detailed school and individual participant flow is described in Figure 2.4.

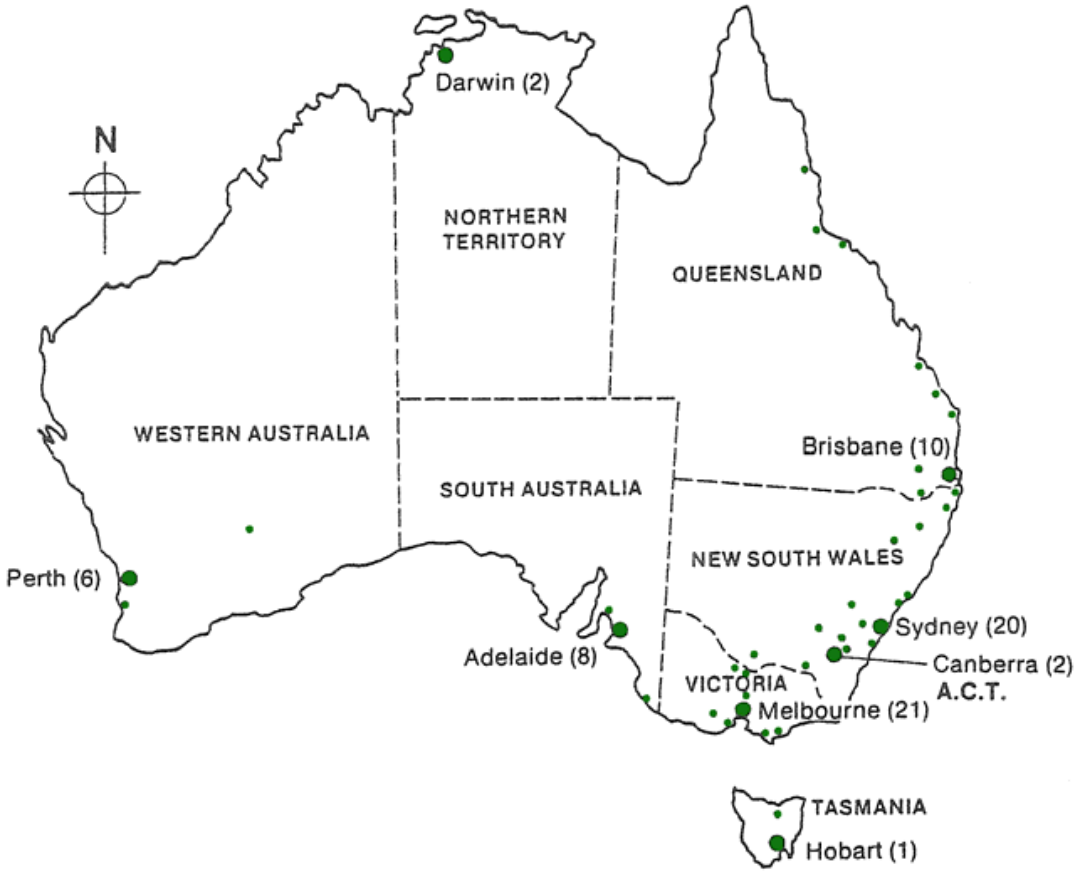


Figure 2.3. Distribution of schools participating in the 1985 ASHFS indicated by the green dots.

Measurements

In the 1985 ASHFS, measurements included a wide range of physical and biological parameters, including anthropometric measures (weight, height, waist circumference, hip circumference, and skinfolds), blood pressure, and fasting blood glucose and cholesterol. Height and weight were measured in bare feet without headwear and heavy clothing to the nearest 0.1 cm and 0.5 kg, respectively. Waist circumference was measured at the level of umbilicus. Hip circumference was measured at the level of the greatest posterior protuberance of the buttocks. Biceps, triceps, subscapular and suprailiac skinfolds were measured to the nearest 0.1 mm using Holtain Calipers (Holtain, Crymych, UK) only for those then aged 9, 12 and 15 years. Blood pressure (using a standard mercury sphygmomanometer) and blood test (using a Technicon Auto Analyzer II, Technicon Instrument corp, New York, USA) were measured only in those who were aged 9, 12 and 15 years. All measurements were done in clinics by trained field staff. Blood samples were taken by qualified nurses. Children aged nine years and older also completed a questionnaire on demographics, diet, physical activity and other lifestyle behaviours in small supervised groups. Data on parental highest education

was obtained by self-administered questionnaire. Socio-economic status based on residential postcodes was derived using the Australian Bureau of Statistics Index of Relative Socioeconomic Disadvantage that was constructed using information from the Australian population census.[12] The socio-economic status in childhood was determined using the 1981 census data.

Follow-up data (the CDAH study 2004-06)

Participants

During 2001–04, 80.5% (6840/8498) of the original participants were traced through the Australian Electoral Commission and the Australian National Death Index, and through school and family networks. Of these, 5170 (60.8% of the original participants) agreed to enrol in the CDAH study, and 2410 (28.4% of the original participants) attended one of the 34 clinics held across Australia during 2004–06. The detailed school and individual participant flow in the 1985 ASHFS and the CDAH study is described in Figure 2.4.

Study clinics

Clinics were held during 2004–06 in each state and territory of Australia, including New South Wales/Australian Capital Territory (nine clinics, 720 participants), Victoria (eight clinics, 705 participants), Queensland (eight clinics, 497 participants), Western Australia (three clinics, 205 participants), South Australia (three clinics, 190 participants), Tasmania (two clinics, 55 participants) and Northern Territory (one clinic, 38 participants). The clinic locations were chosen to maximise the proportion of enrolled participants living within a 10 km radius. These locations included community centres, schools, church halls or similar venues.

Two weeks before the clinic, participants were sent three questionnaires (general, diet and physical activity). They were asked to complete the questionnaires and bring them to the clinic. The data collection teams included ten data collectors, one field co-ordinator and a trained venipuncturist. Training for each test was provided by the same person for each state and territory. Clinics took approximately three hours to complete. Participants were required to fast for 12 hours before their clinic appointment. At the clinic, anthropometric measurements, blood pressure, vascular ultrasound examination and blood test were done before participants were provided breakfast. After breakfast, participants completed other

examinations including cardiorespiratory fitness and muscular strength, and were issued a pedometer. Those participants who enrolled in the CDAH study but refused or were unable to attend a clinic (n=2760) were asked to complete a full or short questionnaire, or visit local pathology centre for a blood collection. Because full data are not available for these participants, they were not included in the analyses used for this thesis.

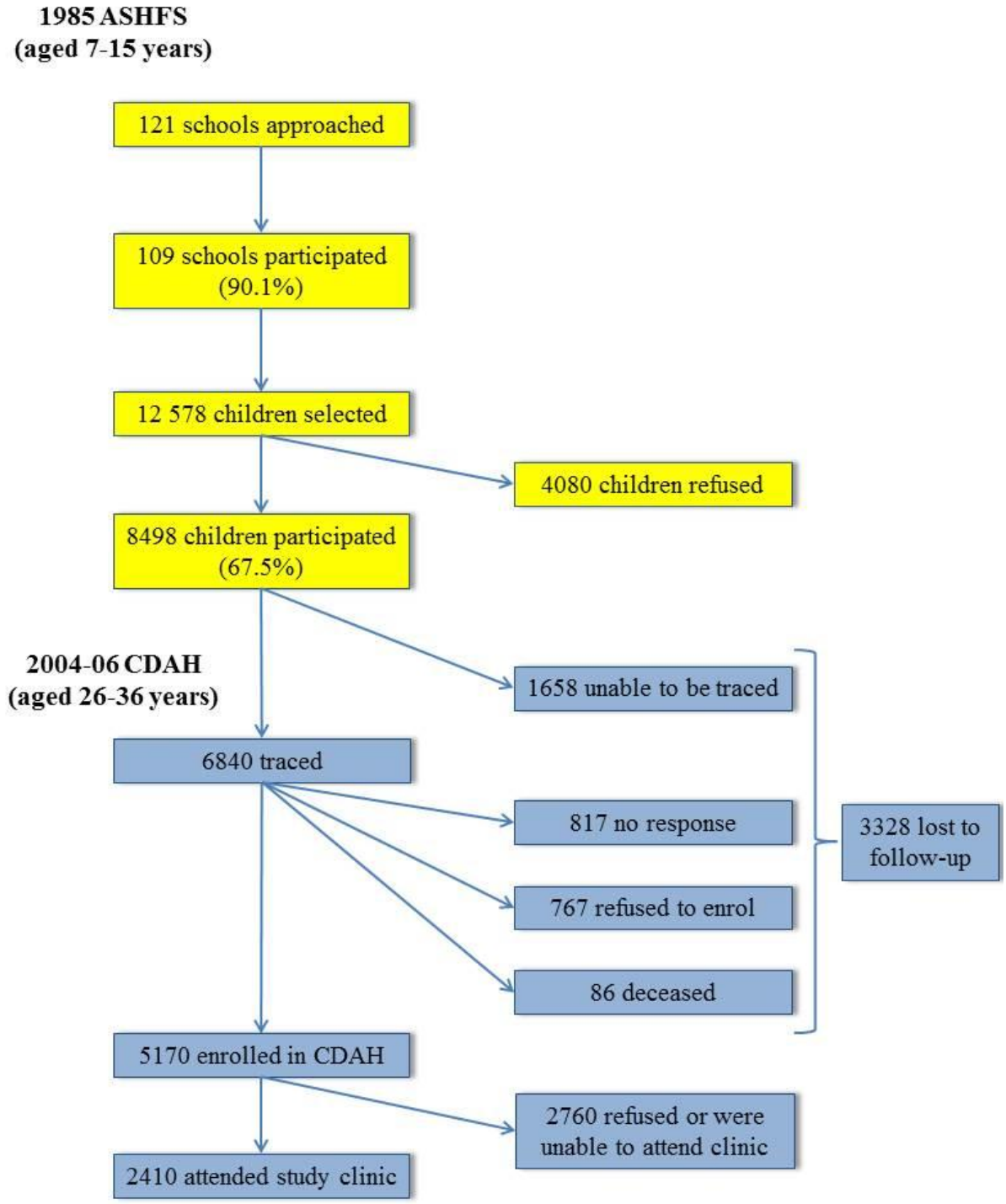


Figure 2.4. School and individual participant flow in the 1985 ASHFS and the CDAH study.

Measurements

Blood pressure

Blood pressure was measured supine during the ultrasound examination using an Omron M4 Digital Automatic Blood Pressure Monitor (Omron Corporation, Kyoto, Japan). A correct cuff for the right upper arm was chosen before measurements. A mean of two readings, which were measured at least one minute apart, was used for analysis.

Carotid intima-media thickness (IMT)

B-mode ultrasound studies of the left common carotid artery were performed using a portable Acuson Cypress (Siemens Medical Solutions USA Inc., Mountainview, CA) ultrasound machine with a 7.0 MHz linear-array transducer (as illustrated in Figure 2.5). Because the nature of clinical data collection for the CDAH study required an ultrasound machine to be moved around 34 clinics across Australia during 2004–06, the Acuson Cypress was identified as the only suitable portable system that incorporated ECG monitoring (necessary to ensure vascular measurements were collected at standardised phases in the cardiac cycle). Before its inclusion in the CDAH study, the measures of arterial structure and function derived from the portable Acuson Cypress were validated against those from a routinely-used clinic-based ultrasound machine like that used in the Cardiovascular Risk in Young Finns study (Acuson Sequoia 512, Siemens Medical Solutions USA Inc., Mountainview, CA).[13] All the ultrasound examinations were done by a single technician who travelled to each of the clinics.

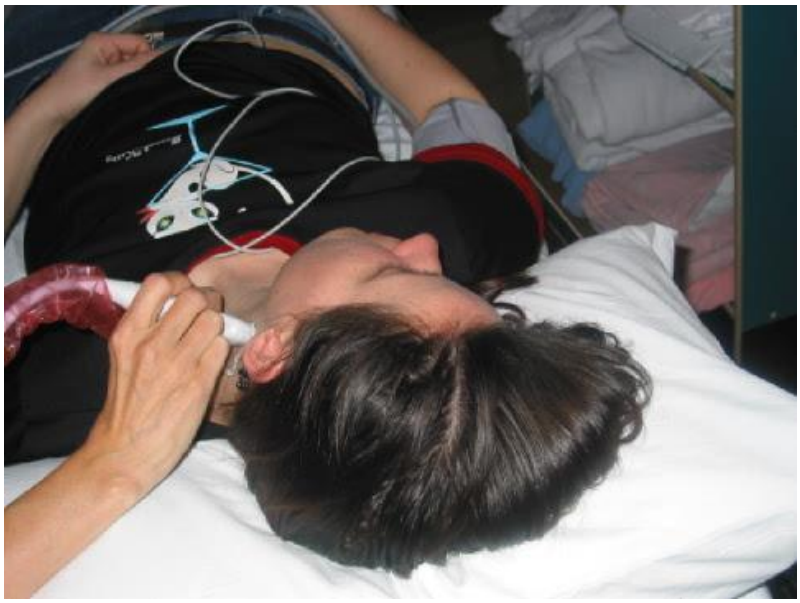


Figure 2.5. A carotid ultrasound examination in the CDAH study.

The B-mode ultrasound studies of carotid IMT followed a previously reported standardised protocol.[14] Briefly, the left common carotid artery and left carotid bifurcation were traced longitudinally so that the distal 10–30 mm of the artery was imaged with focus on the posterior (far) wall. A real-time image of three consecutive cardiac cycles was recorded. From the best-quality cardiac cycle, a total of 12 measurements at two positions were taken approximately 10 mm proximal from the bulb at the end-diastolic phase (coinciding with the R-wave on a continuously recorded ECG). All images were stored in digital format for off-line analysis using the Image Pro Plus version 5.02 (Media Cybernetics, Inc., Silver Spring, MA, USA). An ultrasound image of the carotid artery is shown in Figure 2.6. The mean and maximum of each of six measurements were calculated, and they were averaged to derive mean and maximum IMT. The measurements of IMT were made by three readers, blinded to participants' details. The mean maximum IMT measurements of the three readers were 0.588 mm ± 0.093 (n=769), 0.595 mm ± 0.103 (n=702), and 0.590 mm ± 0.074 (n=512). The measurements of the three readers were calibrated to have the same mean adjusted for factors that differed between the groups of subjects measured by each reader. This procedure is necessary to preserve the associations of IMT with the same independent variables used in the main analysis. For example, the association of maximum IMT with childhood weight z-scores adjusted for age and sex was r=0.080 (pre-calibration) and r=0.079 (post-calibration). Intra-reader reproducibility was assessed in a random subsample of 30 participants. The average absolute difference and standard deviation for replicate IMT measurements was 0.02 mm ± 0.04.[15]

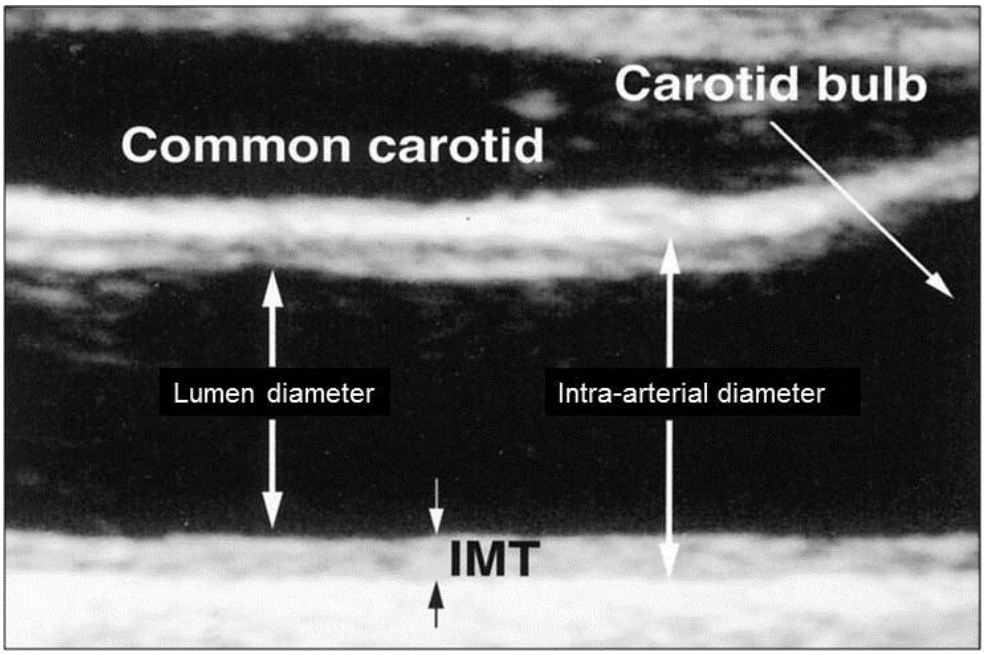


Figure 2.6. An ultrasound image of the carotid artery (IMT – intima-media thickness).

Arterial stiffness

The end-systolic and end-diastolic phases were determined based on the continuously recorded ECG (using end T-wave and R-peak). The end-systolic and end-diastolic carotid diameters, which were the maximum and minimum diameters during a cardiac cycle, were taken 10 mm proximal from the carotid bulb. These values, together with concomitant blood pressure measures, were used to calculate three indices of arterial stiffness as follows:

$$CD = ([D_{sbp} - D_{dbp}]/D_{dbp})/(SBP - DBP)$$

$$SI = \ln(SBP/DBP)/([D_{sbp} - D_{dbp}]/D_{dbp})$$

$$YEM = ([SBP - DBP) \times D_{dbp})/([D_{sbp} - D_{dbp}]/IMT)$$

where D_{sbp} is the end-systolic diameter, D_{dbp} is the end-diastolic diameter, SBP is brachial systolic blood pressure, and DBP is brachial diastolic blood pressure. Carotid distensibility (CD) measures passive expansion and contraction of the arterial wall with changes in pressure. Stiffness index (SI) is a measure of arterial stiffness designed to be relatively independent of blood pressure. Young's elastic modulus (YEM) is an estimate of arterial stiffness per mm of IMT.

Resting heart rate

Resting heart rate was measured while sitting using an Omron HEM907 Digital Automatic Blood Pressure Monitor (Omron Corporation, Kyoto, Japan) after resting for at least five minutes. A mean of three readings, taking approximately one minute for each reading, was used for analysis. Resting heart rate was also measured from the ECG during the ultrasound examination. Analyses using this value of resting heart rate provided the same results as using the resting heart rate recorded from the blood pressure monitor.

Anthropometry

Height and weight were measured in bare feet and light clothes, and without headwear, to the nearest 0.1 cm and 0.1 kg, respectively. Body mass index was calculated as weight (kg) divided by height in squared meter (m^2). Waist circumference was measured at the narrowest point between the lower costal border and iliac crest. Hip circumference was measured at the level of the greatest posterior protuberance of the buttocks. Skinfolds were measured to the nearest 0.5 mm at the bicep, tricep, iliac crest and supraspinale. Measures of skinfolds greater

than 40 mm were truncated due to caliper limitations and estimated values were imputed from body mass index and waist circumference using Tobit Regression.[16] The sum of four skinfolds was used for analysis.

Physical activity and sedentary behaviour

Data on physical activity in the CDAH study were self-reported using the long version of the International Physical Activity Questionnaire,[17] and was objectively measured using pedometers. The International Physical Activity Questionnaire has been shown to have acceptable reproducibility (one week test-retest intra-class correlation in the range of 0.74 to 0.89) and comparative validity (rank correlation with accelerometer counts range of 0.20 to 0.51),[17] and is presented in Appendix 9.

For self-reported physical activity, participants recorded total hours and minutes of the last seven days that were spent on four domains of physical activity including work-related, domestic, transport and leisure-time. The intensity (moderate or vigorous) was also recorded for work-related, domestic and leisure-time physical activity. Vigorous physical activities were defined as those that required hard physical effort and made the participants breathe much harder than normal. Moderate activities were defined as those that made the participants breathe somewhat harder than normal. Active transport was classified as moderate intensity. The minutes spent on the four domains were summed to obtain the total time spent on moderate-to-vigorous physical activity for the last seven days. These were weighted by their moderate and vigorous intensity – by assigning metabolic equivalent of task values of four and eight respectively – to obtain total energy expenditure.

Participants also reported how much time (hours and minutes) they spent on sitting on a weekday (Monday to Friday) and weekend day (Saturday and Sunday) during the last seven days using the International Physical Activity Questionnaire.[17] Time spent watching television, using a computer and playing video games were also recorded in the same manner. This item has also been shown to have good reproducibility (one week test-retest intra-class correlation of 0.82) and comparative validity (rank correlation with three day sedentary behavior log of 0.3).[18]

For objectively-measured physical activity, participants wore Yamax Digiwalker SW-200 pedometers to record daily steps over seven consecutive days. Of the 16,085 daily records collected, 328 records (2%) were excluded because the pedometers were worn for less than

eight hours, which was unlikely to represent a complete day. Another 11 records (0.07%) were also excluded because more than 60,000 steps per day were recorded, which were likely to be erroneous.[1] Average steps per day was calculated for participants who wore pedometers for at least four days, consistent with other studies;[19] 25 participants did not meet this criterion.

Cardiorespiratory fitness

Cardiorespiratory fitness was estimated as physical work capacity at a heart rate of 170 bpm (PWC_{170}). PWC_{170} was estimated using a bicycle ergometer (Monark Exercise AB, Vansbro, Sweden) pedaled at 60 rpm.[20] Participants pedaled continuously for 12 minutes at 60 rpm, which included three 4-minute periods where workload was increased at the end of every fourth minute. The workload increases were regulated so that heart rate achieved by the participants at the end of the first, the second, and the third period were greater than 115, 130 and 145 respectively. Steady state heart rate was recorded in the last 15 seconds of each period. Heart rate measurements were then plotted against mechanical power, and the data points were used to extrapolate to heart rate 170 bpm where the corresponding power estimate would represent the PWC_{170}. The greater values of PWC_{170} mean greater fitness. Because the absolute workload achieved is a function of muscle mass,[21] cardiorespiratory fitness was calculated as PWC_{170} adjusted for lean body mass to create an index uncorrelated with lean body mass. Formulas that were used to calculate lean body mass are presented in Appendix 5.A of Chapter 5, in which the association of cardiorespiratory fitness with vascular health is examined. Participants were asked not to exercise vigorously or eat a heavy meal two hours before testing, not to drink tea or coffee three hours before testing, and not to smoke one hour before testing. Participants with the following conditions were excluded from the test: body weight greater than 160 kg, being pregnant for more than three months, having current or past severe injuries or having hip or knee replacement, having resting blood pressure greater than 180 mmHg or having resting heart rate greater than 100 bpm. Of the 2410 participants attending clinic, 1960 (81.3%) completed this test.

Muscular strength

Five measures of strength were measured in different types of large muscles using hand-grip, shoulder-arm and leg-back dynamometers (Smedley's Dynamometer, TTM, Tokyo, Japan). Each measure was repeated twice with at least 1-minute rest apart. The maximum of the two attempts was used in analysis. Grip strength (left and right) was measured as participants held

the dynamometer with one hand, supported it on the opposite shoulder, and gripped with maximum force. Shoulder strength (pull and push) was measured as participants held the dynamometer in front of their chest so that their arms and elbows were parallel to the ground, and then pulled or pushed with maximum force. For leg strength, participants were asked to stand on the dynamometer with a straight back, flat against the wall, holding a hand bar with an overhand grip. Knees were flexed until an angle of 115º was obtained, at which position the bar was attached to the dynamometer by a chain. Participants then pulled the bar upward as far as possible. Other than leg strength that was measured to the nearest 1kg, the other four measures of muscular strength were measured to the nearest 0.5kg. Before testing in each Australian state or territory, the dynamometers were calibrated by either a private company accredited by the National Association of Testing Authorities, Australia, or by a hospital-based biomedical engineering department, through the entire range of measurement of the device.

Other measurements

Data on highest level of education, socio-economic status, smoking, alcohol consumption and female reproductive characteristics (including menstrual cycle regularity, age at menarche, parity and hormonal contraceptive use) were obtained using a self-administered questionnaire. Socio-economic status based on residential postcodes was derived using the Australian Bureau of Statistics Index of Relative Socioeconomic Disadvantage.[22] Smoking status was classified as never-smoker, ex-smoker, less than weekly, weekly or daily current-smoker. Alcohol consumption was calculated using a frequency grid.[23] All the blood tests were done in a single laboratory. High-density lipoprotein cholesterol (HDL-C) and triglycerides concentrations were measured in 12-hour overnight fasting blood samples using an Olympus AU5400 automated analyzer (Olympus Optical, Tokyo, Japan). Low-density lipoprotein cholesterol (LDL-C) concentration was calculated using the Friedewald formula.[24] Fasting plasma insulin was measured by a microparticle enzyme immunoassay kit (AxSYM, Abbot Laboratories, Abbot Park, IL, USA) and by electrochemiluminescence immunoassay (Elecsys Modular Analystics E170; Roche Diagnostics, Manheim, Switzerland) with interassay standardization.[16]

The Cardiovascular Risk in Young Finns (Young Finns) study

The Young Finns study is an on-going five-centre prospective cohort study (as shown in Figure 2.7) that collected baseline data in 1980 when the participants were aged 3–18 years. Thereafter, follow-up studies were done every three years up until 1992 to collect data on anthropometry, and physical and biological measurements. Ultrasound studies of the carotid artery were performed in the 21-year follow-up in 2001 and the 27-year follow-up in 2007 when the participants were aged 24–39 years and 30–45 years, respectively. The follow-up study in 2007 also measured average steps per day of the participants by using pedometers. These data in 2007 were used for analyses in Chapter 6 of this thesis, and are described in the following section. The study was conducted according to the guidelines of the Declaration of Helsinki, and was approved by local ethics committees. Similar to the CDAH study, the Young Finns study is also a member cohort of the i3C consortium.

Figure 2.7. The five centres of data collection in the Young Finns study.

Study design

This study was designed as a cohort study.

Sampling and participants

In 1980, 4320 Finnish children and adolescents were randomly selected from the Finnish Social Insurance Institution's national population register, stratified by sex and age groups (including 3, 6, 12, 15 and 18 year-old). The population register covers the entire population in Finland and is regularly updated. Of the 4320 invited, 3596 boys and girls (83.1%) agreed to participate in the study in 1980. Of the 3596 participants at baseline, 2204 (61.3%) agreed to continue participating in the 27-year follow-up in 2007. The detailed participant flow in the Young Finns study is described in Figure 2.8.

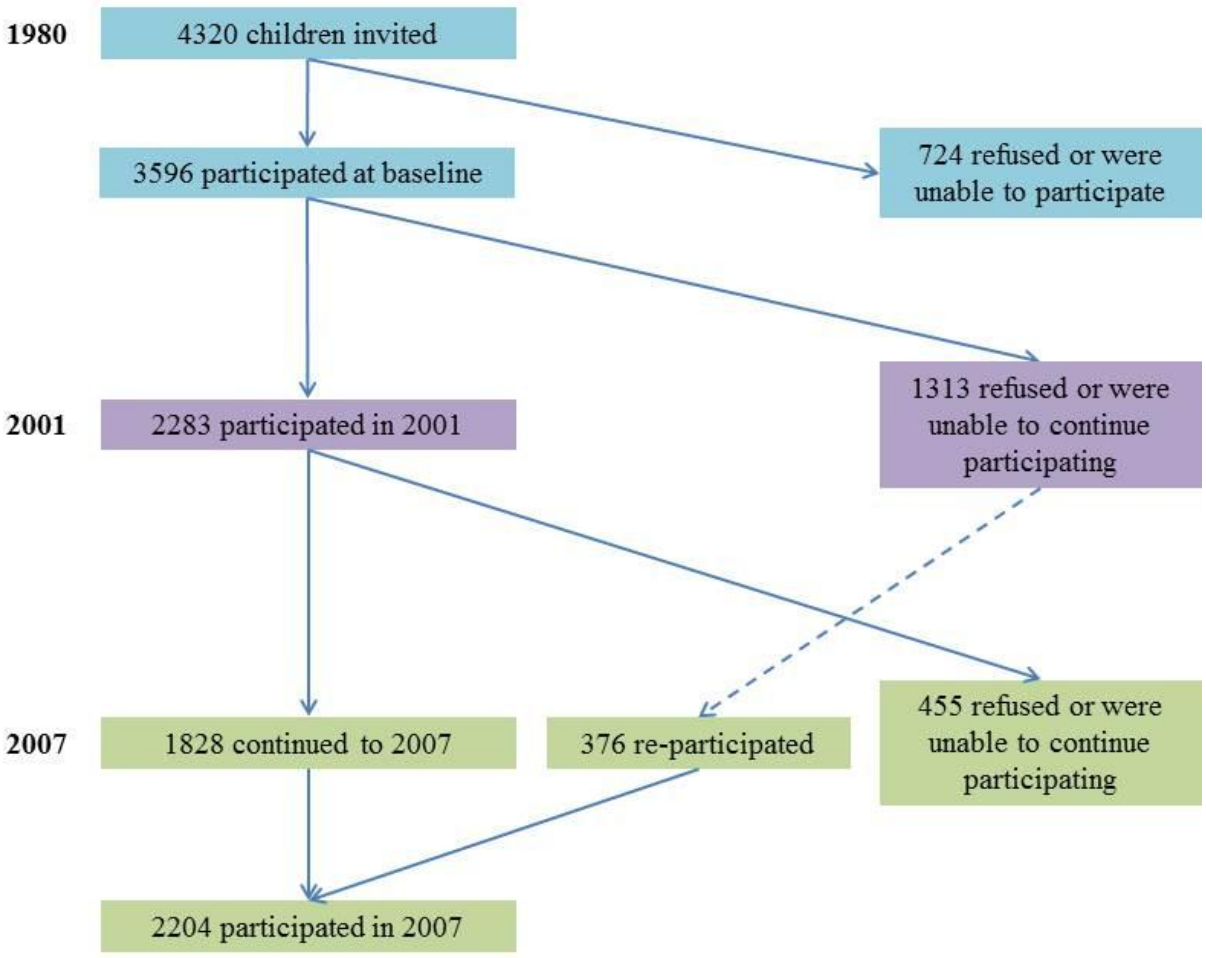


Figure 2.8. Participant flow in the Young Finns study.

Measurements

Blood pressure

In 2007, brachial blood pressure was measured on the right upper arm using a random-zero sphygmomanometer (Hawksley & Sons Ltd, Lancin, UK) after resting for at least five minutes. A correct cuff for the right upper arm was chosen before measurements. Systolic blood pressure was recorded using the first Korotkoff phase. Diastolic blood pressure at both the fourth and fifth Korotkoff phases was recorded. The value of diastolic pressure at the fifth Korotkoff phase was used for analysis. Readings were made to the nearest even number of mmHg. A mean of three readings was used for analysis.

Arterial stiffness

The ultrasound studies of the carotid artery (using Sequoia 512 ultrasound mainframes (Acuson, USA) with 13.0MHz linear-array transducers) followed the same standardised protocol that was used in the CDAH study.[14] All the ultrasound measurements were also made offline using stored digital images by one reader, blinded to participants' details. Again, similar to the CDAH study, the end-systolic and end-diastolic carotid diameters were used together with concomitant brachial blood pressure to calculate the three indices of arterial stiffness that were used in the CDAH study. To assess the reproducibility, re-examination of 57 randomly selected participants three months after the initial examination showed between-visits coefficients of variations of 6.4% for carotid intima-media thickness, and 14.3% for arterial stiffness.

Resting heart rate

Resting heart rate was measured by ECG during the ultrasound examination. All participants had rested for at least five minutes before the examination was conducted.

Anthropometry

Weight was measured in light clothes and bare feet to the nearest 0.1 kg using a digital scale. Height was measured in bare feet and without headwear to the nearest 0.5 cm using a wall-mounted stadiometer. Body mass index was calculated by weight (kg) divided by height in squared meter (m^2).

Physical activity

Similar to the CDAH study, physical activity in the Young Finns study was self-reported using a questionnaire and objectively-measured using pedometers. For self-reported physical activity, the amount of time per usual week that was spent on two domains of physical activity (leisure-time and transport) was recorded.[25] Participants reported leisure-time vigorous physical activity – which made the participants breathe much harder than normal or have shortness of breath – per usual week by choosing one of the following answer options: "none", "approximately 30 minutes", "1 hour", "2-3 hours", "4-6 hours" and "7 hours or more". The validity of this questionnaire was tested by an experimental study and showed comparable validity against accelerometers (correlation coefficients ranging from 0.26 to 0.40) and pedometers (correlation coefficients ranging from 0.30 to 0.39).[25] For objectively-measured physical activity, participants wore Omron Walking Style One (HJ-152R-E) pedometers for seven days.[26] Average number of steps per day was calculated for participants wearing pedometers at least eight hours per day for four days, consistent with other studies including CDAH.[19, 27]

Other measurements

Cardiorespiratory fitness was estimated in a random subsample of 538 participants (47.8% male) by a bicycle ergometer using hypothetical maximal workload sustainable for six minutes measured on the basis of age, sex, height, and weight.[28] Level of education, smoking and alcohol consumption were reported using a questionnaire. 12-hour overnight fasting concentrations of high density lipoprotein cholesterol and triglycerides were determined enzymatically in a clinical chemistry analyzer (AU400, Olympus Optical, Mishima, Japan). Low density lipoprotein cholesterol concentration was calculated using the Friedewald formula.[24] Insulin was measured by microparticle enzyme immunoassay kit (Abbott Laboratories, Diagnostic Division, Dainabot). Glucose concentrations were analyzed enzymatically (glucose dehydrogenase, Olympus Diagnostica GmbH).

Statistical analyses

All statistical analyses were performed using STATA 12 (Statacorp, College Station, Texas, USA). Statistical significance was set at a two-tailed p-value ≤ 0.05. The statistical methods used to address the research aims of this thesis are reported in details in the corresponding chapter. Chapter 3 included older adults many of whom had developed hypertension and were on anti-hypertensive medication. Therefore, they were excluded from analyses of the

relationship between BMI and blood pressure. Chapters 4–7 included only younger adults of whom very small proportions were on medication for hypertension or diabetes or had developed symptomatic cardiovascular disease. Excluding these participants made no material difference to the results.

Loss to follow-up of the ASHFS sample is selective, with those who participated in CDAH having poorer socio-economic status, lower school performance, greater BMI, and lower cardiorespiratory fitness ($p<0.05$) in childhood in 1985 than those who participated in CDAH. In consequence, the missing data for ASHFS subjects who did not participate in CDAH are not missing completely at random (MCAR), which requires the probability of dropout to be unrelated to the outcomes and covariates whether observed or not. In other words, MCAR requires the probability of dropout to be unrelated to every characteristic of the subject. If instead the probability of dropout is related to the covariates and to pre-dropout (observed) values of the outcomes, but not to the missing (unobserved) values of the response variables, the missing data would be missing at random (MAR). Whether missing data that are not MCAR are nevertheless MAR cannot be established from the observed data, because the data on the response variables for drop-outs are missing and therefore not available to test whether they are independent of the probability of dropout.

The distinction is important because if the missing data were MCAR, a complete case analysis of the data as has been undertaken in this thesis – using frequentist statistical procedures such as analysis of variance and linear regression – would be unbiased. If the missing data were MAR but not MCAR, ignoring the missing data would produce bias if participants with complete data differ from non-participants with incomplete data. Doing so would also reduce precision and study power. There are three general methods of dealing with missing data. They are (a) multiple imputation of the missing data with a correctly-specified imputation model, (b) modelling the relationship between the mean response and the probability of missingness using correctly-specified statistical models as part of the estimation process, and (c) the assignment of statistical weights to the participants. The third approach has been argued by Höfler *et al*[29] to be the most appropriate method for missing data due to dropout, when entire sets of data on responses and covariates are missing. In particular, the inverse probability weighting (IPW) of the non-missing data was employed. This involves modelling the probability of missingness as a function of covariates and pre-dropout responses. If the probabilities are estimated from a correctly-specified probability model, the bias (if any) would be removed if the missing data were MAR but not MCAR. This approach was not guaranteed to remove the bias due to missing data (if any) in the analyses undertaken

in the thesis because it could not be guaranteed that the missing data were MAR, though there was no reason to suspect otherwise. Nevertheless, analyses reported in the thesis were repeated using IPW as an attempt to gain insights into the extent of the bias (if any). In every instance, the change in the estimated associations was minor relative to the reported measure of association. This does not confirm the absence of bias because this procedure involved comparing a possibly biased measure of association with a possibly biased weighted measure of association in circumstances that the biases (if any) may be positively correlated. However, it provided some limited reassurance that the bias (if any) was unlikely to be substantial.

We outline below the calculation of the IPW weights and the IPW results for the analyses reported in Chapter 7. These analyses were chosen because – at the request of a reviewer of the manuscript reproduced in Chapter 7 – specific comment is made there about the results of the IPW analyses. In the interest of brevity, the calculation of IPW weights and the IPW results are not reported for analyses in Chapters 4–6. In each set of analyses, the results and conclusions were similar to those of Chapter 7.

Firstly, the weights were calculated from a logistic regression of a binary indicator for non-missingness on factors related to non-missingness for which data were available for all ASHFS subjects. These factors were socio-economic status, school academic performance, BMI and cardiorespiratory fitness measured by time to finish 1.6 km run. The results of the regression model are shown in the following Table 2.1. The weights used in the IPW analyses were the inverse of the predicted probabilities for each of the ASHFS subjects who participated in the CDAH follow-up. Among ASHFS subjects who are similar in the factors that predict non-missingess, the data for CDAH participants are used to represent the data for CDAH non-participants. The CDAH participants with high weights (low predicted probabilities of non-missingness) represent a relatively large number of CDAH non-participants similar to them in ASHFS factors that predict non-missingness, whereas those with low weights represent the missing data of relatively few of their similar CDAH non-participants. The following Table 2.2 shows the reported and IPW results for the major associations estimated in Chapter 7. It is readily seen that the estimates of association are in most cases almost unchanged, and changed by less than 5% in every case.

In the Young Finns study, there was no significant difference in anthropometry and demography at baseline in 1980 between the participants who attended clinic in 2007 and those who did not.

Table 2.1. Logistic regression model used to calculate the inverse probability weights in the CDAH study

Covariates	β	(SE)	[95% CI]
Male			
Socio-economic status	−0.14	(0.04)	[−0.23, −0.06]
School academic performance	−0.33	(0.04)	[−0.41, −0.24]
BMI	−0.12	(0.04)	[−0.19, −0.03]
Cardiorespiratory fitness	−0.08	(0.04)	[−0.17, −0.00]
Constant	−0.18	(0.16)	[−0.49, 0.13]
Female			
Socio-economic status	−0.15	(0.04)	[−0.23, −0.06]
School academic performance	−0.36	(0.04)	[−0.45, −0.28]
BMI	−0.10	(0.04)	[−0.18, −0.02]
Cardiorespiratory fitness	−0.10	(0.04)	[−0.19, −0.02]
Constant	0.05	(0.14)	[−0.22, 0.32]

Table 2.2. The associations of sitting time with health outcomes in CDAH study before and after inverse probability weighting

	Before inverse probability weighting		After inverse probability weighting	
	β	95% CI	β	95% CI
Men				
Carotid distensibility	−0.02	(−0.03, −0.01)	−0.02	(−0.04, −0.01)
Resting heart rate	0.37	(0.17, 0.56)	0.39	(0.20, 0.59)
Skinfolds	0.67	(0.13, 1.20)	0.70	(0.12, 1.29)
cMetS*	0.02	(0.01, 0.03)	0.02	(0.01, 0.03)
Women				
Carotid distensibility	−0.01	(−0.02, −0.00)	−0.01	(−0.02, −0.01)
Resting heart rate	0.10	(−0.08, 0.29)	0.10	(−0.12, 0.33)
Skinfolds	0.93	(0.38, 1.56)	0.90	(0.11, 1.65)
cMetS*	0.02	(0.00, 0.04)	0.02	(0.00, 0.04)

*continuous metabolic syndrome score

Postscript

The following chapters present studies that used data from the aforementioned samples to address the aims of this research. Specifically, Chapter 3 utilised data from the BTH project and the Can Tho survey to compare the associations of fatness with blood pressure between Caucasians and Asians; Chapter 4 utilised data from the 1985 ASHFS and the CDAH study to investigate the relative contribution of fatness in childhood and adulthood to adult vascular health; Chapter 5 utilised data from the CDAH study to examine the associations of physical fitness with vascular health and to investigate the possible mechanisms; Chapter 6 utilised data from the CDAH study and the Young Finns study to investigate the associations of different types of physical activity with vascular health; and Chapter 7 utilised data from the CDAH study to examine the associations of sitting time with vascular health.

References

1. Schmidt MD, Blizzard CL, Venn AJ, Cochrane JA, Dwyer T. Practical considerations when using pedometers to assess physical activity in population studies: lessons from the Burnie Take Heart Study. *Res Q Exerc Sport*. 2007;78(3):162-70.

2. Risk Factor Prevalence Study Management Committee. Risk Factor Prevalence Study: Survey No 3 1989. Canberra: National heart Foundation of Australia and Australian Institute of Health.1990.

3. Dobson AJ, Blijlevens R, Alexander HM, Croce N, Heller RF, Higginbotham N, *et al.* Short fat questionnaire: a self-administered measure of fat-intake behaviour. *Aust J Public Health*. 1993;17(2):144-9.

4. Sallis JF, Pinski RB, Grossman RM, Patterson TL, Nader PR. The development of self-efficacy scales for health-related diet and exercise behaviors. *Health Education Research*. 1988;3(3):283-92.

5. Menzies Centre for Population Health Research. Tasmanian Food and Nutrition Study Questionnaire. Hobart: Menzies Centre for Population Health Research.1996.

6. Education, Health, Culture and Living Standard 2007. Ha Noi: General Statistics Office; Available from: http://www.gso.gov.vn/default.aspx?tabid=395&idmid=3&ItemID=7673.

7. The STEPS manual. Geneva: World Health Organization; 2008 [updated 13 June 2008; cited 2010 Dec 17]; Available from: http://www.who.int/chp/steps/riskfactor/en/index.html.

8. Pham LH, Au TB, Blizzard L, Truong NB, Schmidt MD, Granger RH, Dwyer T. Prevalence of risk factors for non-communicable diseases in the Mekong Delta, Vietnam: results from a STEPS survey. *BMC Public Health*. 2009;9:291.

9. Au TB, Blizzard L, Schmidt M, Pham LH, Magnussen C, Dwyer T. Reliability and validity of the global physical activity questionnaire in Vietnam. *J Phys Act Health*. 2010;7(3):410-8.

10. Thuy AB, Blizzard L, Schmidt MD, Luc PH, Granger RH, Dwyer T. The association between smoking and hypertension in a population-based sample of Vietnamese men. *J Hypertens*. 2010;28(2):245-50.

11. Dwyer T, Gibbons LE. The Australian Schools Health and Fitness Survey. Physical fitness related to blood pressure but not lipoproteins. *Circulation*. 1994;89(4):1539-44.

12. McLennan W. 1996 Census of population and housing: socioeconomic index for areas. Canberra: Australian Bureau of Statistics; 1998.

13. Magnussen CG, Fryer J, Venn A, Laakkonen M, Raitakari OT. Evaluating the use of a portable ultrasound machine to quantify intima-media thickness and flow-mediated dilation: agreement between measurements from two ultrasound machines. *Ultrasound Med Biol*. 2006;32(9):1323-9.

14. Raitakari OT, Juonala M, Kahonen M, Taittonen L, Laitinen T, Maki-Torkko N, *et al.* Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *JAMA*. 2003;290(17):2277-83.

15. Juonala M, Magnussen CG, Venn A, Dwyer T, Burns TL, Davis PH, *et al.* Influence of age on associations between childhood risk factors and carotid intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study, the Childhood Determinants of Adult Health Study, the Bogalusa Heart Study, and the Muscatine Study for the International Childhood Cardiovascular Cohort (i3C) Consortium. *Circulation*. 2010;122(24):2514-20.

16. Dwyer T, Magnussen CG, Schmidt MD, Ukoumunne OC, Ponsonby AL, Raitakari OT, *et al.* Decline in physical fitness from childhood to adulthood associated with increased obesity and insulin resistance in adults. *Diabetes Care*. 2009;32(4):683-7.

17. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, *et al.* International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc*. 2003;35(8):1381-95.

18. Salmon J, Owen N, Crawford D, Bauman A, Sallis JF. Physical activity and sedentary behavior: a population-based study of barriers, enjoyment, and preference. *Health Psychol*. 2003;22(2):178-88.

19. Tudor-Locke CE, Myers AM. Methodological considerations for researchers and practitioners using pedometers to measure physical (ambulatory) activity. *Res Q Exerc Sport*. 2001;72(1):1-12.

20. Withers RT, Davies GJ, Crouch RG. A comparison of three W170 protocols. *Eur J Appl Physiol Occup Physiol*. 1977;37(2):123-8.

21. Buskirk E, Taylor HL. Maximal oxygen intake and its relation to body composition, with special reference to chronic physical activity and obesity. *J Appl Physiol*. 1957;11(1):72-8.

22. 2006 Census of population and housing: socioeconomic index for areas. Canberra: Australian Bureau of Statistics; 2008.

23. McLennan W, Podger A. National Nutrition Survey: User's Guide 1995. Canberra, Australia: Australian Bureau of Statistics; 1998.

24. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18(6):499-502.

25. Mansikkaniemi K, Juonala M, Taimela S, Hirvensalo M, Telama R, Huupponen R, *et al.* Cross-sectional associations between physical activity and selected coronary heart disease risk factors in young adults. The Cardiovascular Risk in Young Finns Study. *Ann Med*. 2012;44(7):733-44.

26. Hirvensalo M, Telama R, Schmidt MD, Tammelin TH, Xiaolin Y, Magnussen CG, Vkari JS, Raitakari OT. Daily steps among Finnish adults: variation by age, sex, and socioeconomic position. *Scand J Public Health*. 2011;39(7):669-77.

27. Cleland VJ, Schmidt MD, Salmon J, Dwyer T, Venn A. Correlates of pedometer-measured and self-reported physical activity among young Australian adults. *J Sci Med Sport*. 2011;14(6):496-503.

28. Arstila M, Impivaara O, Maki J. New ergometric reference values for clinical exercise tests. *Scand J Clin Lab Invest*. 1990;50(7):747-55.

29. Hofler M, Pfister H, Lieb R, Wittchen HU. The use of weights to account for non-response and drop-out. *Soc Psychiatry Psychiatr Epidemiol*. 2005;40(4):291-9.

Chapter 3

Blood pressure and body mass index: a comparison of the associations in Caucasian and Asian populations

Published in the journal

Hypertension Research 2012; 35(5):523-30.

Huynh L. Quan, Christopher L. Blizzard, Alison J. Venn, Au B. Thuy, Pham H. Luc, and James E. Sharman

Chapter 3. Blood pressure and body mass index: a comparison of the associations in Caucasian and Asian populations

Preface

In an attempt to better understand the associations of body size and fatness with vascular health, this chapter aims to compare the associations of body size and fatness with blood pressure in a population-based sample predominantly containing Caucasians (Burnie Take Heart project, Australia) to those in another population-based sample predominantly containing Asians (Can Tho survey, Vietnam). These two samples have similar sampling methodology and protocols, and included participants within the same age range. This provided a great opportunity to examine the racial differences between Caucasians and Asians in the associations of body size and fatness with blood pressure, which, to my knowledge, had never been reported. The following text in this chapter has been published in the journal *Hypertension Research*. Following on from this publication, a letter was submitted to the journal and the author response was also published in the journal *Hypertension Research* 2012; 35(9):961-2, which is presented in Appendix 3B.

Introduction

High blood pressure (BP) is strongly associated with an increased risk of cardiovascular disease (CVD), including heart disease and stroke, and is a major contributor to the total burden of death and disease worldwide.[1] BP is affected by genetic and lifestyle factors and is increased in those who are physically inactive, smokers, overweight or obese, have high dietary salt intakes or high alcohol consumption.[2] While much is known about the epidemiology of high BP in adults in developed countries, less is known about the prevalence and predictors of high BP in developing countries. In Vietnam, these issues have been investigated in a few published studies.[3-6] Mirroring reasonably well the results of studies in Western countries, predictors of elevated BP identified in these studies include increasing age, male sex, tobacco smoking, and alcohol consumption, indicators of overweight or body fatness, markers of low socioeconomic status including education and occupation, and marital status.

Obesity has been a serious public health problem in Caucasian populations for years, and is now an emerging problem in Asian populations[7] including the Vietnamese.[8] Positive associations between obesity and BP have been well established in both developed and developing countries.[9] Several studies have compared the relationship of body composition and BP in black and white racial groups[9] or between African and Asian populations.[10] However, to our knowledge, no study has reported such relationship in population-based samples of Caucasian and Asian populations, which was the principal aim of the study. This is an important step to better understand the potential cardiovascular consequences of increasing overweight and obesity in Asian populations.

Methods

Study population

The study used data from two population-based cross-sectional studies conducted using similar methodology: a survey by the Burnie Take Heart (BTH) project of residents of Burnie (Australia) in 1998–99 (n = 832 adults aged 25–64 years; 47% male; 69% response), and a survey of residents of Can Tho (CT) (Vietnam), conducted in 2005 (n = 1978 adults aged 25–64 years; 46% male; 74% response). The population of Burnie is predominantly Australian-born, Caucasian and English speaking. In 1996, when the BTH project commenced, only 0.03% of the population of Burnie was born overseas in a non-English speaking country.[11] Can Tho is the biggest city in the Mekong Delta, which is the far southern region of Vietnam and contains 20% of the country's population.[12] The study participants of this survey comprised 92% Vietnamese and 8% were of Chinese, Khmer or another ethnicity.

Sampling procedures and methods of data collection for the BTH and CT surveys have been presented elsewhere.[6, 13] Both surveys had approximately equal numbers of participants within four age categories (25–34 years, 35–44 years, 45–54 years and 55–64 years). In BTH, participants were selected by age- and sex-stratified random sampling from among those on the Electoral Roll of registered voters in Tasmania who had an address within the Burnie municipalities. In CT, participants were randomly selected from permanent residents in Cantho, by multistage sampling with age, sex and urban/rural stratification. Health volunteers, who are responsible for providing basic health services for an assigned local area, maintain and update the lists of the residents of the area regularly.

All participants provided written informed consent. In CT, those who could not sign provided verbal consent. The studies had approval from ethics committees of the University of Tasmania (BTH) and the Can Tho University of Medicine and Pharmacy (CT).

Measurements

Trained staff obtained physical measurements of participants, including BP and anthropometry. In both surveys, BP was measured at the mid-point of right upper arm, in an upright sitting position, with feet flat on the ground, back supported and no talking, after participants had rested for at least 5 minutes. Correct cuff sizes were determined before measurement based on right upper arm circumference. Three readings, at least 30 seconds apart (after the cuff was completely deflated), were taken in BTH, whereas a third reading was taken in CT only if there was a difference of more than 25 mmHg for systolic blood pressure (SBP) or 15 mmHg for diastolic blood pressure (DBP) between the first two readings (in accordance with the STEPSwise approach to surveillance of non-communicable diseases (STEPS) manual[14] in 2005). A mean of all measurements was used for analysis in both surveys. A Dinamap Vital Signs Monitor 1846SX (Critikon Company, Tampa, FL) was used in BTH. This device was calibrated against a mercury sphygmomanometer prior to each week of clinic use. An Omron T9P digital automatic blood pressure monitor was used in CT. This device was calibrated against a mercury sphygmomanometer prior to each day of clinic use.

Anthropometric measurements included weight, height, waist circumference and hip circumference. Each participant's weight was measured to the nearest 0.1kg, in bare feet without heavy clothing, using digital scales. Height was measured to the nearest 0.1cm, in bare feet without headwear, using a stadiometer. Waist circumference at the narrowest point between the lower costal border and the iliac crest, and hip circumference at the greatest posterior protuberance of the buttocks, were measured to the nearest 0.1cm using a non-stretching constant tension tape.

Total cholesterol and plasma glucose were measured via standard laboratory procedure in venous blood in participants who had fasted for at least nine hours (BTH) and in capillary blood in participants who had fasted for at least 12 hours using a Roche Diagnostics Accutrend Glucometer (CT).

Participants in both surveys completed questionnaires on demographic characteristics, socio-economic factors and cardiovascular behavioral risk factors (smoking, alcohol consumption,

diet and physical activity). In BTH, the questionnaire was based with minor modification on the questionnaire developed by the National Heart Foundation of Australia and Australian Institute of Health to determine the prevalence of cardiovascular risk factors in Australian adults.[15] The standardised STEPS survey methodology developed by the World Health Organization[14] was used in CT. Some locally relevant questions and response options were added to the STEPS questionnaire, in accordance with the STEPS protocols.[14] Whilst similar in most other respects, the questionnaires differed in the items used to assess physical activity. The BTH questions addressed time spent on vigorous and less vigorous exercise, and on vigorous tasks at work and around the house, during the past two weeks. The STEPS questionnaire addressed time on moderate and vigorous activities in three domains (work, transport and leisure) during a typical week.

Statistical analyses

Linear regression models including covariates for age and (where necessary) the square of age were used to produce the trend lines. The differences by sex in mean levels of BP reported in Table 2 were assessed from a regression model that included a single covariate for sex, and the differences by sex in the association with age in Figure 1 and Figure 2 were assessed from a regression model that also included product terms formed from the covariates for sex and age. Mean values of SBP, DBP, pulse pressure (PP = SBP − DBP) and mean arterial pressure (MAP = ⅓SBP + ⅔DBP) were calculated and reported in Table 2. For these analyses, as in the regression analyses, the BP measurements were transformed prior to analyses to remove skewness but all results are presented in the original units. Rank correlations of BP with indices of overweight and fatness presented in Supplementary Table 1 were calculated by applying Pearson's correlation coefficient to the ranks of the variables with age as a covariate. The trend lines presented in Figure 3 and Figure 4 were produced from linear regression models including as covariates linear predictors for age, body mass index (BMI) and the square of BMI (if required). The adjusted estimates reported in Supplementary Table 2 were produced by adding as covariates linear predictors for total years of smoking, weekly frequency of alcohol consumption, total metabolic equivalent (MET-minutes) of physical activity and the binary indicator of fruit and vegetable consumption (two or more servings of fruit and five or more servings of vegetable per day), and calculating the estimated effect of an additional one unit (1 kg/m^2) of BMI in the adjusted model. Further analyses of cholesterol were undertaken by including as covariates linear predictors for cholesterol and the product of cholesterol and age.

The analyses reported in Table 1, Figure 1 and Figure 2 were unweighted. All other analyses were weighted to the World Standard Population[16] to enable comparisons free of discrepancies due to the slight differences in the age distributions of the two samples. Specifically, this required us to attach a weight to each observation such that the age distribution of 25–34 year olds, 35–44 year olds, 45–54 year olds, and 55–64 year olds in each sample matched that of the World Standard Population.

Hypertension was defined as an average BP ≥ 140/90 mmHg, or use of antihypertensive medication. BMI was calculated as weight (kg) divided by height squared (m^2). All participants who were taking antihypertensive medication at the time of study clinics were excluded from the analyses.

Results

Characteristics of study participants are shown in Table 3.1. Participants were approximately equally distributed across age categories as a result of the sampling design. Mean ages were 44.6 (SD = 11.6) and 45.8 (SD = 10.5) years in BTH and CT respectively. Most subjects in BTH had completed secondary school level of education, but the majority in CT either had primary school as the highest level of education or had no formal education. A greater proportion of participants in BTH than in CT had values of BMI in the overweight or obese categories. Greater proportions of men than women were in these categories in BTH whilst the reverse was true in CT. Mean values of BMI, for men and women respectively, were 27.6 (SD = 3.9) and 27.4 (SD = 5.8) in BTH, and 21.0 (SD = 3.0) and 21.8 (SD = 3.3) kg/m^2 in CT. The mean values of weight, waist circumference and waist-hip ratio mirrored these differences. Cigarette smoking was very common among men in CT, but rare among women there. Relatively more male than female participants consumed alcohol regularly, with consumption highest among BTH participants.

Table 3.1. Characteristics of participants in Burnie Take Heart and Cantho surveys.

	Burnie Take Heart (n=832)		Cantho (n=1978)	
	Male	Female	Male	Female
Sample size	47.1%[392]	52.9%[440]	46.1%[911]	53.9% [1067]
Age, y				
25-34	23.2%[91]	25.7%[113]	17.2%[157]	18.8% [201]
35-44	25.8%[101]	24.4%[107]	26.9%[245]	27.4% [292]
45-54	24.7%[97]	25.7%[113]	29.7%[270]	28.2% [301]
>55	26.3%[103]	24.2%[106]	26.2%[239]	25.6% [273]
Education				
No formal education	0.5%[2]	0%[0]	38.0%[346]	55.7% [593]
Primary school	7.1%[28]	5.0%[22]	27.5%[250]	21.1% [225]
Secondary school	58.2%[228]	60.4%[265]	17.8%[162]	11.9% [127]
High school	8.7%[34]	12.3%[54]	10.9%[99]	7.2% [77]
Tertiary institution	25.5%[100]	22.3%[98]	5.8%[53]	4.1% [44]
Employment				
Student	0.5%[2]	0.5%[2]	0%[0]	0.1% [1]
Employed	75.3%[295]	52.0%[229]	92.1%[839]	69.7% [743]
Unemployed	6.4%[25]	1.6%[7]	1.9%[17]	1.7% [18]
Home duties	2.0%[8]	38.0%[167]	0.8%[7]	25.5% [272]
Retired	11.0%[43]	6.1%[27]	3.8%[35]	2.4% [26]
Disabled	4.8%[19]	1.8%[8]	1.4%[12]	0.6 [6]
BMI*, kg/m²	27.6(3.9)	27.4(5.9)	21.1(3.0)	21.8 (3.3)
Weight*, kg	84.3(13.2)	71.5(15.6)	55.4(9.2)	50.7 (8.4)
Waist*, cm	95.2(11.5)	84.2(14.2)	75.4(9.1)	73.5 (9.1)
Waist-hip ratio*	0.92(0.06)	0.80(0.05)	0.85(0.06)	0.82 (0.06)
Total cholesterol*, mmol/L	5.55(1.50)	5.42(1.08)	4.47(0.71)	4.78 (0.85)
Blood glucose*, mmol/L	4.55(0.61)	4.36(0.54)	3.54(0.85)	3.51 (0.92)
Smoker				
Never	49.1%[192]	54.2%[238]	16.4%[149]	98.2% [1047]
Former	27.9%[109]	23.0%[101]	14.3%[130]	0.3% [3]
Current	23.0%[90]	22.8%[100]	69.3%[631]	1.5% [16]

Drinker				
Never	13.3%[52]	29.5%[130]	13.9%[116]	90.0% [939]
< once a week	31.4%[123]	42.1%[185]	44.7%[373]	8.8% [92]
1-4 days a week	40.5%[159]	22.3%[98]	28.7%[239]	0.4% [4]
5+ days a week	14.8%[58]	6.1%[27]	12.7% [106]	0.8% [3]
Physical activity[†]				
Active hours/week	4(1.3, 8)	3(1, 6.5)	11.5(1, 36)	4.5(0, 28)
Total MET.hour/week[‡]	24(8, 57.6)	18(6, 40)	56(4, 168)	18.6(0, 112)
Active[§], %	62.76	56.15	52.75	42.21

The data displayed are in percentages and numbers, unless otherwise stated.

[*]Data shown are Mean (SD).

[†]Data shown are Median (Interquartile range).

[‡]Total Metabolic Equivalent Task unit (MET-hour) per week

[§]Active is defined as having at least equivalent 150 minutes of moderate activities per week.

Figure 3.1 depicts associations of SBP and DBP with age, by sex and population. Younger women in these samples of 25–64 year-olds had lower mean levels of both SBP and DBP than their male counterparts (as shown in Table 3.2), but this difference was diminished among older participants. Figure 3.2 displays trend lines depicting the association of MAP and PP with age. In both samples, younger men had higher mean values of MAP and PP than their female counterparts, but this difference was progressively diminished among older participants (BTH $p = 0.114$ (MAP), $p < 0.0001$ (PP); CT $p = 0.005$ (MAP), $p < 0.0001$ (PP)).

Mean values of four measures of BP are shown in Table 3.2, stratified by sex, age group and population. These sex and age groups were used in the stratified sampling design in each location. In each age group, mean SBP was higher among men in BTH than in CT whereas mean DBP was generally higher among men in CT than in BTH. This led to a higher mean level of PP among men in BTH than in CT. In general, men in BTH had marginally higher MAP than men in CT. Among women, a higher mean level of PP in BTH than in CT was also observed. While there were approximately equal mean levels of SBP among women in the two surveys, higher mean levels of DBP were observed in CT. Among women, mean levels of MAP were always higher for CT than for BTH participants in each of the four age groups.

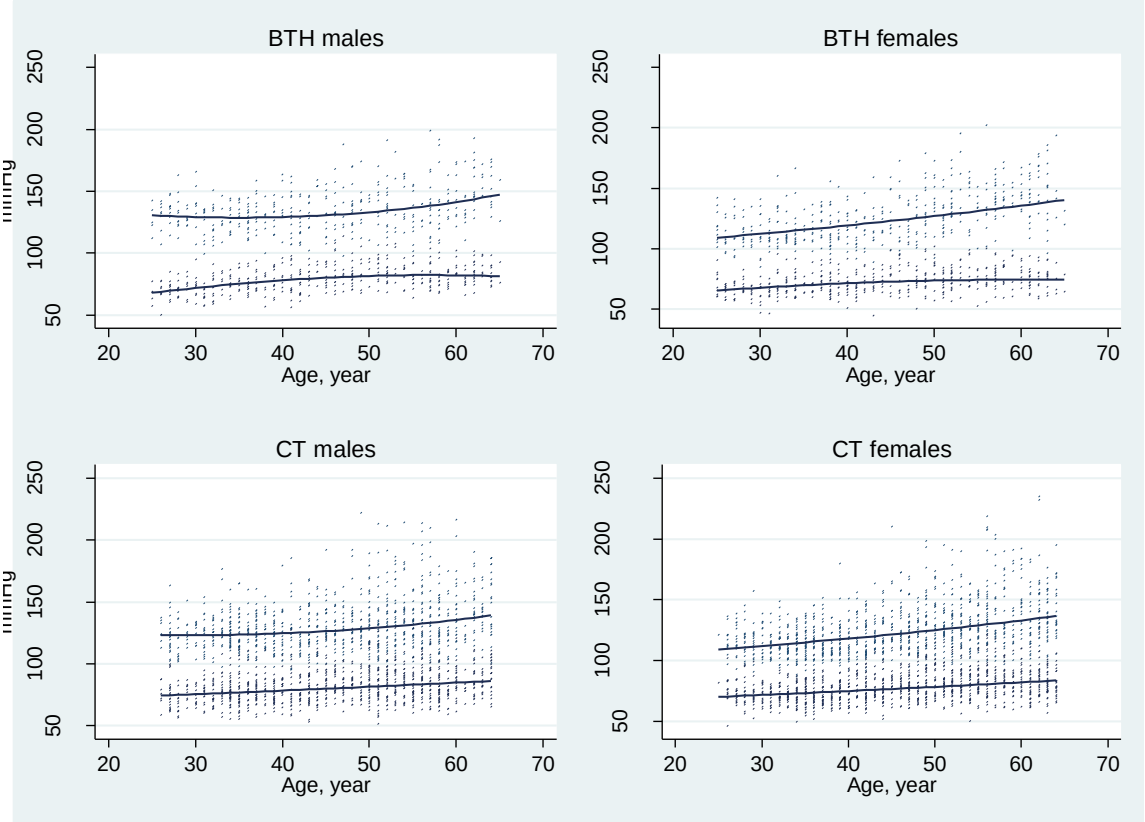


Figure 3.1 Associations of age with blood pressure, by population and sex. In each figure, the higher set of points and trend lines represent systolic blood pressure and the lower set represent diastolic blood pressure. BTH (Burnie Take Heart); CT (Can Tho).

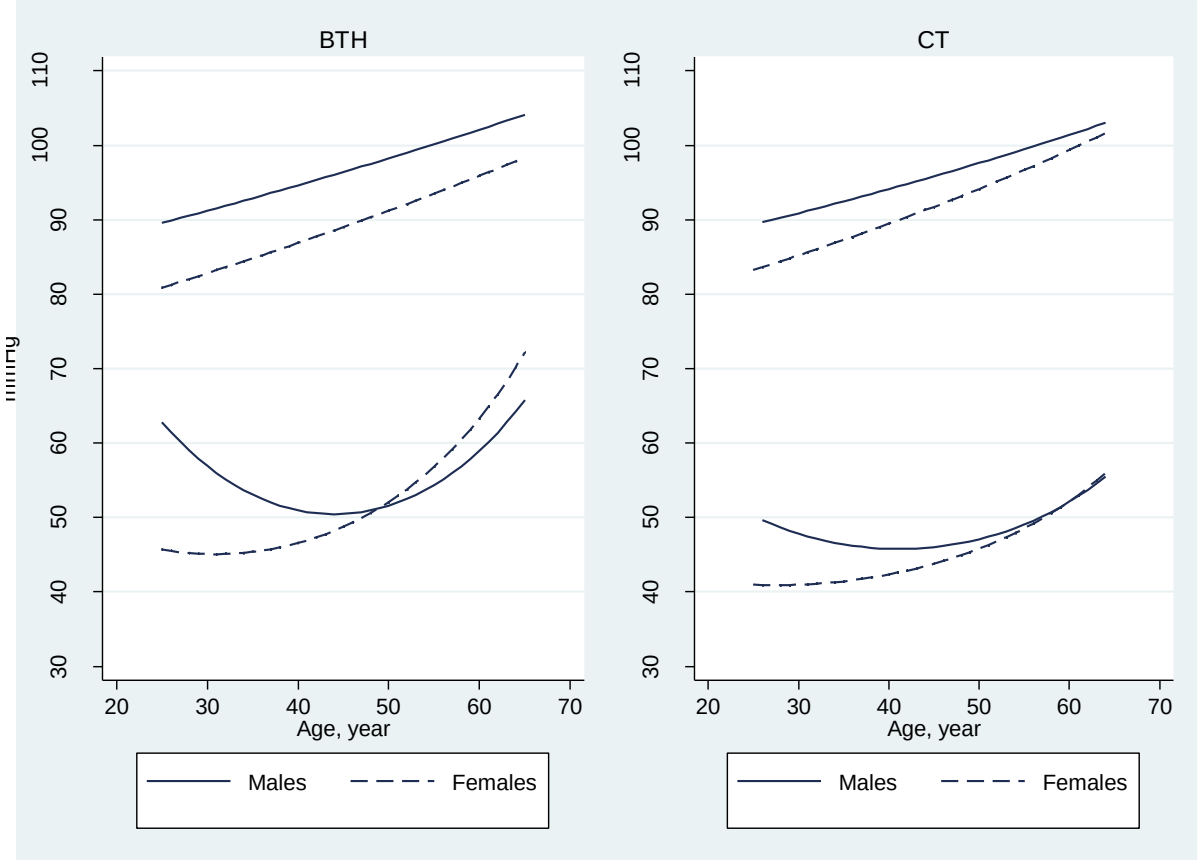


Figure 3.2. Trend lines depicting the association of mean arterial pressure (at top) and pulse pressure (at bottom) with age for men and women in the Burnie Take Heart (BTH) study and Cantho (CT) survey.

Table 3.2. Mean values of blood pressure for subjects classified by sex and age group, by population

	Age group, year			
	25-34	35-44	45-54	55-65
	Mean(SD)	Mean(SD)	Mean(SD)	Mean (SD)
BTH				
Male				
SBP	129.2(12.6)	130.9(14.5)	136.3(18.7)	142.1 (19.9)
DBP	71.7(8.2)	77.5(9.4)	83.3(10.0)	82.3 (8.9)
PP	56.8(10.4)	52.5(9.9)	52.1(11.4)	59.7 (14.7)
MAP	91.0(8.6)	95.5(10.3)	101.1(12.4)	102.2 (11.7)
Female				
SBP	112.8(12.8)	116.8(13.5)	130.6(20.1)	143.0 (19.4)
DBP	67.5(8.6)	70.9(8.8)	75.8(11.1)	76.5 (9.8)
PP	45.4(8.8)	45.6(8.4)	54.3(14.2)	66.5 (16.0)
MAP	82.6(9.4)	86.4(9.9)	94.1(13.1)	98.6 (11.5)
CT				
Male				
SBP	124.3(12.9)	124.0(15.2)	130.4(19.4)	135.6 (22.4)
DBP	75.5(9.8)	77.4(11.5)	83.9(13.1)	83.2 (12.4)
PP	48.1(8.9)	46.0(8.8)	47.4(11.4)	51.7 (14.0)
MAP	91.9(10.1)	92.9(12.0)	99.4(14.7)	100.8 (15.0)
Female				
SBP	113.9(12.0)	115.9(13.8)	127.1(19.0)	135.5 (23.0)
DBP	72.4(8.3)	73.7(9.9)	80.3(11.9)	81.9 (12.5)
PP	41.2(7.3)	42.0(7.6)	46.8(10.9)	53.5 (15.3)
MAP	86.4(9.1)	87.9(10.8)	95.9(13.7)	99.9 (15.2)

mmHg is the unit of blood pressure.

Abbreviations: BTH (Burnie Take Heart), CT (Cantho), SBP (Systolic blood pressure), DBP (Diastolic blood pressure), PP (Pulse pressure), MAP (Mean arterial pressure), SD (Standard deviation).

Age-adjusted rank correlations of BP with various indices of overweight and fatness, stratified by sex and population, are shown in Table 3.A.1 (Appendix 3.A). There were moderate associations between body fatness and BP measures among men and women with the exception of PP among CT women, for which the associations were weak. The strength of correlations with BP was similar across body fatness measures and, in subsequent analyses we present data for BMI only, given that this is a commonly used index in research and clinical practice.

Figure 3.3 illustrates the estimated relationships of SBP, DBP and MAP with BMI, by sex and population, after adjusting for age. In each population, the trends of the relationships were similar for men and women. MAP increased with BMI among BTH women, but declined at high and increasing levels of BMI among BTH men. For the CT sample, MAP increased with BMI because both SBP and DBP increased with BMI.

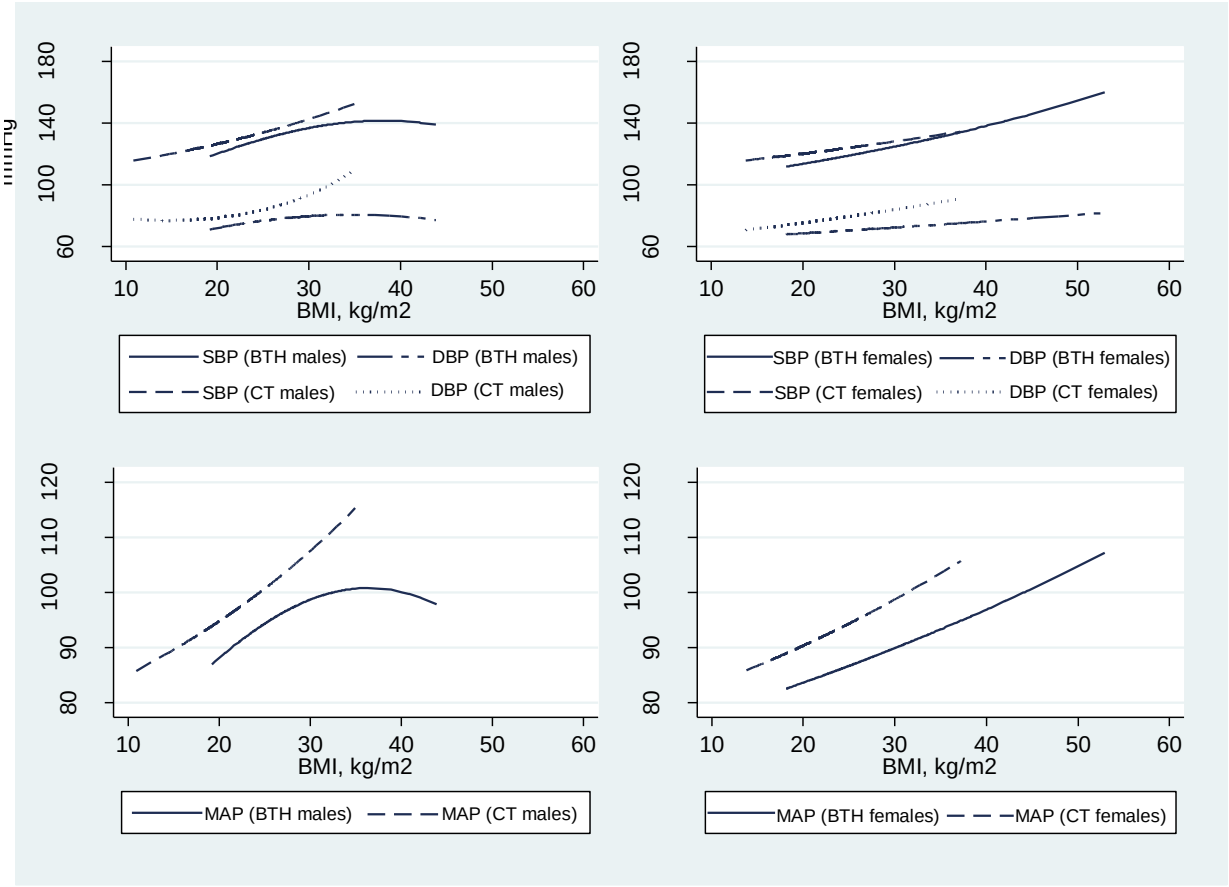


Figure 3.3. Age-adjusted associations of three indices of blood pressure with body mass index, by population and sex. BTH (Burnie Take Heart), CT (Cantho), SBP (systolic blood pressure), DBP (diastolic blood pressure), MAP (mean arterial pressure), BMI (body mass index)

The values of PP plotted against BMI in Figure 3.4 showed that PP increased with BMI among the BTH samples, but not among the CT samples. These differing results for PP were not due to different distributions of BMI in the two populations. Restricting the analyses to the 95.9% of BTH men and 71.3% of CT men whose BMI fell in the 19.2 (BTH minimum) to 34.9 (CT maximum) kg/m^2 range, and to the 92.7% of BTH women and 87.5% of CT women whose BMI fell in the 18.2 (BTH minimum) to 37.2 (CT maximum) kg/m^2 range, all relationships between PP and BMI were linear and positive for BTH participants (men $p < 0.001$, women $p < 0.001$) but negative for CT participants (men $p = 0.324$, women $p = 0.358$).

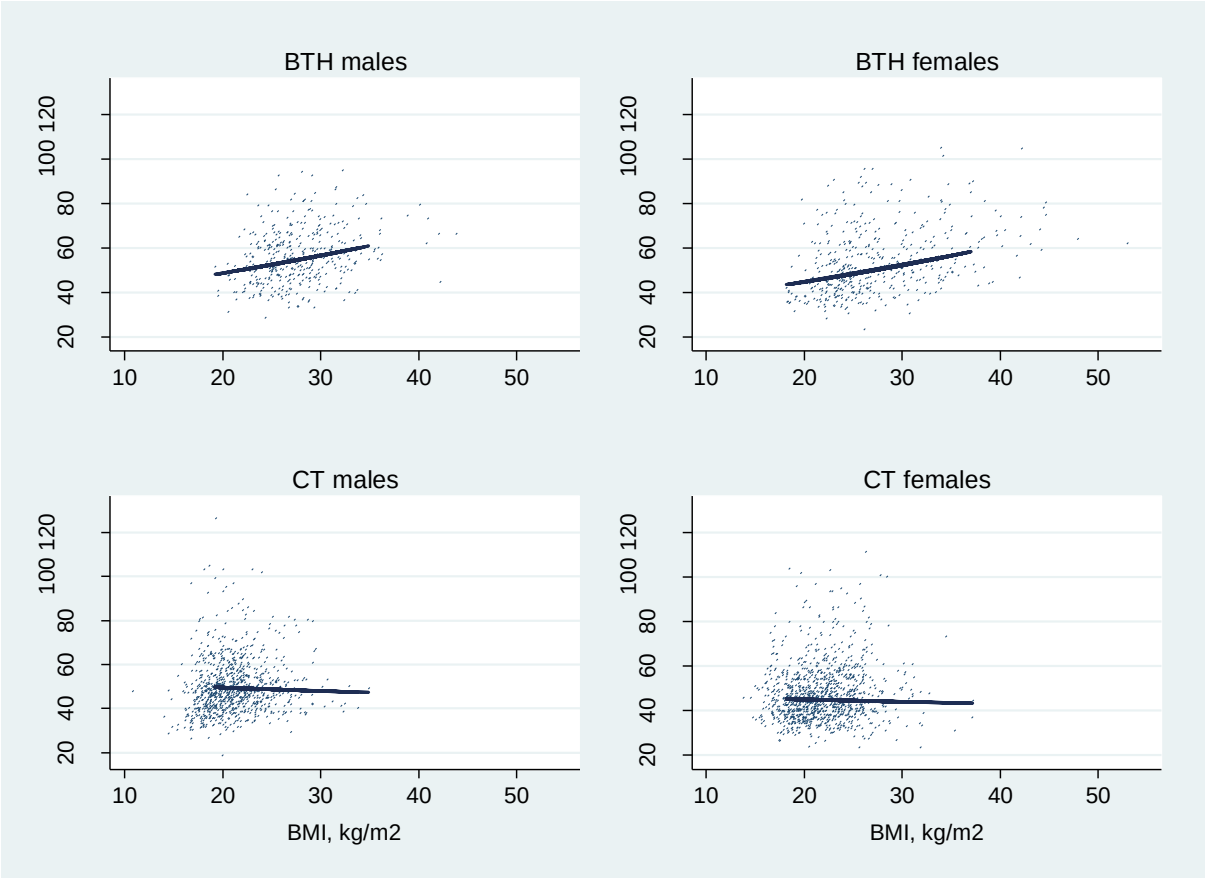


Figure 3.4. Age-adjusted associations of pulse pressure with body mass index, by population and sex. The trend lines are plotted over the range of overlapping BMI in the two populations: 19.2–34.9 kg/m^2 for men, and 18.2–37.2 kg/m^2 for women.

Abbreviation: BTH (Burnie Take Heart), CT (Cantho), BMI (body mass index).

We investigated whether these relationships were independent of other factors that may be associated with BP, such as years of smoking, weekly frequency of alcohol intake, dietary consumption of fruit and vegetables, and physical activity. However, adjusting for these factors had little impact (as shown in Table 3.A.2 of Appendix 3.A).

To determine whether differences in metabolic parameters could account for the different patterns of association between PP and BMI in the two populations, we adjusted the associations for fasting blood total cholesterol and glucose concentrations. Cholesterol was positively associated with PP among BTH women ($p = 0.018$) and negatively associated with PP among CT men ($p = 0.04$), but adjusting for it had only a marginal effect on the estimated association of PP with BMI in each population (data not shown). Glucose was not a significant predictor of BP among BTH participants, but was a significant positive predictor of MAP among CT participants (men $p < 0.001$, women $p = 0.072$). However, adjusting for glucose only marginally reduced the positive linear slope between MAP and BMI among CT participants (data not shown).

Finally, whilst the proportion with hypertension among BTH men (37.1%, 95% confidence interval (CI): 32.7%, 42.0%) and BTH women (28.2%, 95% CI: 24.2%, 32.9%) exceeded the respective proportion among CT men (30.8%, 95% CI: 28.0%, 33.8%) and CT women (21.3%, 95% CI: 18.9%, 24.0%), only 13.8% of the hypertensives in CT reported taking antihypertensive medication compared to 33.1% in BTH. These subjects were excluded from analyses but, in the remaining sample, the proportion with non-medicated SBP > 180 mmHg and/or non-medicated DBP > 110 mmHg among CT subjects (3.7%) was more than twice that among BTH subjects (1.8%). Particularly for SBP, this can be observed in Figure 1. To investigate whether this greater proportion of high values among the CT sample had influenced our results, we repeated the analyses further excluding non-medicated subjects with SBP > 180 mmHg and/or DBP > 110 mmHg. No marked differences were found (data not shown).

Discussion

This study examined the associations of BP with age and body composition in population-based samples of Caucasians and Asians. The main findings of the study were significant differences in the relationships between PP and body composition for Caucasians compared with Asians. The relationships between BP and age, and between other indices of BP and body composition, were generally similar between populations. Although further work is

required, these observations provide new information regarding race, body composition and BP that may help inform public health planning in the future.

Whilst there were major discrepancies in the associations between PP and BMI, it was interesting to find similarities in the two populations for the age–BP relationships. The fall (or leveling off) of DBP together with the rise of SBP and PP with increasing age (particularly after the 5th decade) among both BTH and CT participants in these cross-sectional associations is consistent with age-related abnormalities of the arterial wall resulting in large artery stiffness.[17, 18] This effect has been demonstrated to increase cardiovascular risk,[19] probably owing to concomitant raised central BP. We also observed a lower mean PP in young women than young men, and this sex difference gradually narrowed and reversed at the fifth and sixth decade in BTH and CT respectively. These findings are consistent with results from other studies[18, 20] and suggest that – regardless of differences in race, culture and demography – Caucasian and Asian people probably have similar physiology in relation to vascular aging.

Increasing BMI was associated with significant increases in PP among participants in BTH, but not among participants in CT. The difference was not due to different distributions of BMI in the two populations, because around 80% of the men and 90% of the women in the two populations had BMI in the same range, and we estimated the relationships among participants in the same range of BMI. The difference in PP between the two populations in response to increasing body composition suggests the possibility of different pathophysiology related to hypertension in Caucasians and Asians. In BTH, higher PP with increasing BMI may be indicative of increased large artery stiffness, similar to the association between higher PP and increasing age after about 50 years. Conversely, in CT, we observed increases of both SBP and DBP with associated increase in MAP but not in PP. This type of hypertension in CT is more typical of essential hypertension, in which both SBP and DBP are raised. Although speculative, this may be a result of increased circulatory volume or peripheral vascular resistance, possibly due to high sodium intake,[21] rather than being due to increased large artery stiffness per se. This conclusion is not necessarily consistent with some studies that have reported increased arterial stiffness in Asians compared with Caucasians.[22-25] These studies included only participants of South Asian origin, who are known to have higher rates of diabetes and premature coronary artery disease[26, 27] than the South-East Asian participants in this study. Other studies are required to elucidate causes of these racial differences in BP.

Some studies[28, 29] have also shown that at any value of SBP, cardiovascular risk is higher with lower DBP. Whether there is any difference in overall cardiovascular risk associated with increased BMI and the consequent BP differences between populations is unknown. Importantly, adjustment for other potential confounders such as tobacco smoking, alcohol consumption, fruit and vegetable consumption and physical activity showed negligible effects on the relationship of BP and BMI. Whatever the reasons for the observed differences between these Caucasian and Asian populations, it is reasonable to conclude that these modifiable lifestyle behaviors did not play a major role. Of course the BMI–BP differences between Caucasians and Asians might be explained by genetic factors or other unmeasured lifestyle or environmental influences.

A number of mechanisms by which obesity might contribute to vascular stiffness have been proposed. In obesity, macrophages accumulate in adipose tissue.[30] This is believed to lead to the chronic state of low-grade inflammation (vascular and systemic) and endothelial dysfunction in obese people.[31] Other artery-stiffening mechanisms of obesity may work through the functions of hormones such as insulin and leptin. An excess of circulatory insulin will promote sodium retention by increasing tubular reabsorption,[32] stimulate sympathetic activity,[33] proliferate vascular smooth muscle cells,[34] promote endothelial dysfunction and impair vasodilator activity.[35] Another possible mechanism of obesity-induced arterial stiffness is hyperleptinemia, which is also known to stimulate the sympathetic nervous system[36] and induce endothelial dysfunction.[37]

Hypercholesterolemia is also associated with increased large artery stiffness in Caucasians[38] and this is known to affect peripheral BP. In this study, fasting serum total cholesterol was a significant positive predictor of PP in BTH women, though adjusting for total cholesterol had negligible effects on the relationship of PP and BMI. Similarly, fasting blood glucose was positively associated with MAP among CT participants, but played a negligible role in the relationship of MAP and BMI. Therefore it seems reasonable to suggest that the difference in associations of BP and BMI between Caucasians and Asians observed in this study was not due to serum total cholesterol or glucose.

A limitation of this study was the cross-sectional design. Also there was a lack of information on sodium intake which is known to be associated with hypertension and arterial stiffness. Whilst sodium consumption has been greatly reduced in western countries due to high awareness of cardiovascular risks, Asian countries generally have higher mean sodium intakes.[21] This might help to explain the differences observed in this study between

Caucasians and Asians. Using different BP devices in the two surveys would be a limitation if there were systematic errors between the two devices in measuring SBP and/or DBP, but only if these errors influenced the estimated relationships between PP and BMI. With the effect of minimising this possibility, each BP device was calibrated against a standard mercury sphygmomanometer before each clinic examination for accuracy.

Conclusions

In conclusion, the principal finding in this study was that independent of conventional risk factors (e.g. age, smoking, alcohol, diet and physical inactivity), BMI was positively associated with PP (and possibly large artery stiffness) among Caucasians, but not among Asians. This may be an important observation because increased PP is an independent predictor of myocardial infarction, congestive heart failure and cardiovascular death, even in hypertensive patients undergoing successful antihypertensive drug therapy.[39] Our findings provide additional evidence for the importance of weight reduction to improve cardiovascular risk. The difference in associations of BMI and BP between Caucasians and Asians suggests different pathophysiology related to hypertension, and the possibility of different approaches to prevention and treatment of hypertension might be applied to the two populations. Future studies could perhaps focus on genetic and environmental factors to answer this important question.

Postscript

The results of this chapter suggest that obesity-induced hypertension in Caucasians may be related to increased large artery stiffness. This finding led to the examination of the associations of body size and fatness in childhood and adulthood with adult arterial structure and function measured by ultrasound among young Caucasian adults, which are presented in Chapter 4. Rather than focus on pulse pressure, which is not a reliable indicator of arterial stiffness among young adults, carotid artery stiffness measured by ultrasound was used in analyses instead.

References

1. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet. 1997 May 3;349(9061):1269-76.

2. Kornitzer M, Dramaix M, De Backer G. Epidemiology of risk factors for hypertension: implications for prevention and therapy. Drugs. 1999 May;57(5):695-712.

3. Van Minh H, Thanh LC, Thi BN, do Trinh T, Tho TD, Valensi P. Insulinaemia and slight overweight: the case of Vietnamese hypertensives. Int J Obes Relat Metab Disord. 1997 Oct;21(10):897-902.

4. Minh HV, Byass P, Chuc NT, Wall S. Gender differences in prevalence and socioeconomic determinants of hypertension: findings from the WHO STEPs survey in a rural community of Vietnam. J Hum Hypertens. 2006 Feb;20(2):109-15.

5. Hoang VM, Byass P, Dao LH, Nguyen TK, Wall S. Risk factors for chronic disease among rural Vietnamese adults and the association of these factors with sociodemographic variables: findings from the WHO STEPS survey in rural Vietnam, 2005. Prev Chronic Dis. 2007 Apr;4(2):A22.

6. Pham LH, Au TB, Blizzard L, Truong NB, Schmidt MD, Granger RH, Dwyer T. Prevalence of risk factors for non-communicable diseases in the Mekong Delta, Vietnam: results from a STEPS survey. BMC Public Health. 2009;9:291.

7. Ramachandran A, Snehalatha C. Rising burden of obesity in Asia. J Obes. 2010;2010.

8. Tuan NT, Tuong PD, Popkin BM. Body mass index (BMI) dynamics in Vietnam. Eur J Clin Nutr. 2008 Jan;62(1):78-86.

9. Doll S, Paccaud F, Bovet P, Burnier M, Wietlisbach V. Body mass index, abdominal adiposity and blood pressure: consistency of their association across developing and developed countries. Int J Obes Relat Metab Disord. 2002 Jan;26(1):48-57.

10. Tesfaye F, Nawi NG, Van Minh H, Byass P, Berhane Y, Bonita R, Wall S. Association between body mass index and blood pressure across three populations in Africa and Asia. J Hum Hypertens. 2007 Jan;21(1):28-37.

11. 1996 Census of Population and Housing: Burnie and Devenport Suburbs. Australian Bureau of Statistics; 2001 [updated 26 November 2007; cited 2011 March 7]; Available from: http://www.abs.gov.au/ausstats/abs@.nsf/ProductsbyReleaseDate/11DAAF72D3D02EB2CA25739F000E542F?OpenDocument.

12. Population and population density in 2009 by province. Hanoi: General Statistics Office of Vietnam; [updated 2009; cited 2011 January 5]; Available from: http://www.gso.gov.vn/default_en.aspx?tabid=467&idmid=3&ItemID=9882.

13. Schmidt MD, Blizzard CL, Venn AJ, Cochrane JA, Dwyer T. Practical considerations when using pedometers to assess physical activity in population studies: lessons from the Burnie Take Heart Study. Res Q Exerc Sport. 2007 Jun;78(3):162-70.

14. The STEPS manual. Geneva: World Health Organization; 2008 [updated 13 June 2008; cited 2010 Dec 17]; Available from: http://www.who.int/chp/steps/riskfactor/en/index.html.

15. Risk Factor Prevalence Study: Survey No 3 1989. Canberra: National Heart Foundation of Australia and Australian Institute of Health; 1990.

16. Breslow NE, Day NE. Rates and Rate Standardization. In: Breslow NE, Day NE, editors. Statistical Methods in Cancer Research, Vol II, The Design and Analysis of Cohort Studies (IARC Scientific Publications No 82). Lyon: International Agency for Research on Cancer; 1987. p. 48-79.

17. Milch RA. Matrix properties of the aging arterial wall. Monogr Surg Sci. 1965 Dec;2(4):261-342.

18. Franklin SS, Gustin Wt, Wong ND, Larson MG, Weber MA, Kannel WB, Levy D. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. Circulation. 1997 Jul 1;96(1):308-15.

19. Vlachopoulos C, Aznaouridis K, O'Rourke MF, Safar ME, Baou K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. Eur Heart J. 2010 Aug;31(15):1865-71.

20. Skurnick JH, Aladjem M, Aviv A. Sex differences in pulse pressure trends with age are cross-cultural. Hypertension. Jan;55(1):40-7.

21. Brown IJ, Tzoulaki I, Candeias V, Elliott P. Salt intakes around the world: implications for public health. Int J Epidemiol. 2009 Jun;38(3):791-813.

22. Pinto ES, Mensah R, Meeran K, Cameron JD, Murugaesu N, Bulpitt CJ, Rajkumar C. Peripheral arterial compliance differs between races: comparison among Asian, Afro-Caribbeans, and white Caucasians with type 2 diabetes. Diabetes Care. 2005 Feb;28(2):496.

23. Din JN, Ashman OA, Aftab SM, Jubb AW, Newby DE, Flapan AD. Increased arterial stiffness in healthy young South Asian men. J Hum Hypertens. 2006 Feb;20(2):163-5.

24. Gunarathne A, Patel JV, Gammon B, Hughes EA, Lip GY. Impact of mean arterial blood pressure on higher arterial stiffness indices in South Asians compared to white Europeans. J Hypertens. 2008 Jul;26(7):1420-6.

25. Rezai MR, Wallace AM, Sattar N, Finn JD, Wu FC, Cruickshank JK. Ethnic differences in aortic pulse wave velocity occur in the descending aorta and may be related to vitamin D. Hypertension. 2011 Aug;58(2):247-53.

26. Gupta M, Brister S. Is South Asian ethnicity an independent cardiovascular risk factor? Can J Cardiol. 2006 Mar 1;22(3):193-7.

27. Enas EA, Mohan V, Deepa M, Farooq S, Pazhoor S, Chennikkara H. The metabolic syndrome and dyslipidemia among Asian Indians: a population with high rates of diabetes and premature coronary artery disease. J Cardiometab Syndr. 2007 Fall;2(4):267-75.

28. Benetos A, Zureik M, Morcet J, Thomas F, Bean K, Safar M, Ducimetiere P, Guize L. A decrease in diastolic blood pressure combined with an increase in systolic blood pressure is associated with a higher cardiovascular mortality in men. J Am Coll Cardiol. 2000 Mar 1;35(3):673-80.

29. Blacher J, Staessen JA, Girerd X, Gasowski J, Thijs L, Liu L, Wang JG, Fagard RH, Safar ME. Pulse pressure not mean pressure determines cardiovascular risk in older hypertensive patients. Arch Intern Med. 2000 Apr 24;160(8):1085-9.

30. Cancello R, Tordjman J, Poitou C, Guilhem G, Bouillot JL, Hugol D, Coussieu C, Basdevant A, Bar Hen A, Bedossa P, Guerre-Millo M, Clement K. Increased infiltration of macrophages in omental adipose tissue is associated with marked hepatic lesions in morbid human obesity. Diabetes. 2006 Jun;55(6):1554-61.

31. Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? Arterioscler Thromb Vasc Biol. 1999 Apr;19(4):972-8.

32. Rocchini AP, Key J, Bondie D, Chico R, Moorehead C, Katch V, Martin M. The effect of weight loss on the sensitivity of blood pressure to sodium in obese adolescents. N Engl J Med. 1989 Aug 31;321(9):580-5.

33. Anderson EA, Hoffman RP, Balon TW, Sinkey CA, Mark AL. Hyperinsulinemia produces both sympathetic neural activation and vasodilation in normal humans. J Clin Invest. 1991 Jun;87(6):2246-52.

34. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care. 1991 Mar;14(3):173-94.

35. Kim JA, Montagnani M, Koh KK, Quon MJ. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. Circulation. 2006 Apr 18;113(15):1888-904.

36. Rahmouni K, Haynes WG, Mark AL. Cardiovascular and sympathetic effects of leptin. Curr Hypertens Rep. 2002 Apr;4(2):119-25.

37. Korda M, Kubant R, Patton S, Malinski T. Leptin-induced endothelial dysfunction in obesity. Am J Physiol Heart Circ Physiol. 2008 Oct;295(4):H1514-21.

38. Wilkinson I, Cockcroft JR. Cholesterol, lipids and arterial stiffness. Adv Cardiol. 2007;44:261-77.

39. Safar ME. Systolic blood pressure, pulse pressure and arterial stiffness as cardiovascular risk factors. Curr Opin Nephrol Hypertens. 2001 Mar;10(2):257-61.

Appendix 3.A. Additional tables

Additional Table 3.A.1. Age-adjusted rank correlations of blood pressure and indices of overweight and fatness, by sex and population

	Weight	Weight adjusted for height and age	Weight to height ratio	BMI	WC	Waist adjusted for height and age	WHR
Males							
SBP							
BTH	0.276	0.314	0.323	0.331	0.278	0.307	0.207
CT	0.221	0.242	0.250	0.256	0.253	0.257	0.233
DBP							
BTH	0.219	0.236	0.234	0.228	0.238	0.262	0.218
CT	0.208	0.203	0.244	0.248	0.276	0.272	0.262
PP							
BTH	0.190	0.243	0.238	0.268	0.184	0.212	0.125
CT	0.130	0.170	0.133	0.137	0.112	0.123	0.107
MAP							
BTH	0.279	0.306	0.310	0.308	0.291	0.316	0.239
CT	0.220	0.227	0.254	0.260	0.276	0.276	0.259
Females							
SBP							
BTH	0.404	0.424	0.359	0.354	0.364	0.394	0.224
CT	0.159	0.157	0.164	0.160	0.144	0.141	0.118
DBP							
BTH	0.199	0.217	0.175	0.175	0.170	0.218	0.144
CT	0.246	0.245	0.254	0.245	0.225	0.221	0.156
PP							
BTH	0.394	0.402	0.368	0.359	0.363	0.371	0.241
CT	0.014	0.012	0.013	0.015	0.012	0.011	0.040
MAP							
BTH	0.312	0.334	0.273	0.271	0.275	0.316	0.159
CT	0.216	0.215	0.223	0.216	0.197	0.193	0.146

Abbreviations: BTH (Burnie Take Heart), CT (Cantho), BMI (Body mass index), WC (Waist circumference), WHR (Waist to hip ratio), SBP (Systolic blood pressure), DBP (Diastolic blood pressure), PP (Pulse pressure), MAP (Mean arterial pressure).
For BTH, $r \geq 0.125$ represent $p < 0.05$, $r \geq 0.159$ represent $p < 0.01$ and $r \geq 1.90$ represent $p < 0.001$
For CT, $r \geq 0.107$ represent $p < 0.05$, $r \geq 0.117$ represent $p < 0.001$

Additional Table 3.A.2. Differences in four measures of blood pressure per unit difference in body mass index (kg/m²) adjusted for smoking, alcohol intake, diet and physical activity, classified by population and sex

	Adjusted for age	Adjusted for age and smoking	Adjusted for age and alcohol intake	Adjusted for age and diet	Adjusted for age and physical activity
Males					
SBP					
BTH	1.69(1.09, 2.28)	1.69(1.09, 2.30)	1.65(1.05, 2.25)	1.66(1.06, 2.25)	1.62(1.02, 2.22)
CT	1.58(1.14, 2.03)	1.65(1.18, 2.12)	1.57(1.13, 2.02)	1.59(1.15, 2.04)	1.64(1.19, 2.09)
DBP					
BTH	0.77(0.40, 1.14)	0.79(0.42, 1.15)	0.76(0.38, 1.13)	0.78(0.40, 1.15)	0.77(0.39, 1.14)
CT	1.43(1.05, 1.81)	1.47(1.08, 1.86)	1.39(1.01, 1.76)	1.43(1.05, 1.81)	1.42(1.04, 1.81)
PP					
BTH	0.73(0.45, 1.00)	0.73(0.45, 1.01)	0.72(0.44, 0.99)	0.71(0.44, 0.99)	0.70(0.42, 0.98)
CT	−0.17(−0.49, 0.16)	−0.15(−0.49, 0.18)	−0.16(−0.49, 0.16)	- 0.16(- 0.49, 0.16)	−0.09(−0.42, 0.23)
MAP					
BTH	1.07(0.67, 1.47)	1.09(0.69, 1.48)	1.05(0.65, 1.45)	1.06(0.66, 1.47)	1.05(0.64, 1.45)
CT	1.26(0.94, 1.59)	1.34(1.00, 1.68)	1.25(0.93, 1.57)	1.27(0.95, 1.60)	1.29(0.96, 1.61)
Females					
SBP					
BTH	1.11(0.86, 1.35)	1.11(0.87, 1.35)	1.11(0.86, 1.35)	1.10(0.86, 1.34)	1.08(0.84, 1.32)
CT	0.78(0.45, 1.12)	0.81(0.47, 1.14)	0.82(0.48, 1.15)	0.83(0.49, 1.16)	0.82(0.48, 1.15)

DBP					
BTH	0.37(0.21, 0.54)	0.38(0.21, 0.55)	0.38(0.21, 0.55)	0.37(0.21, 0.54)	0.37(0.21, 0.54)
CT	0.85(0.63, 1.07)	0.87(0.65, 1.09)	0.88(0.66, 1.10)	0.89(0.67, 1.11)	0.88(0.66, 1.10)
PP					
BTH	0.74(0.56, 0.91)	0.72(0.55, 0.89)	0.73(0.55, 0.91)	0.73(0.55, 0.91)	0.71(0.54, 0.89)
CT	−0.10(−0.28, 0.08)	−0.09(−0.27, 0.08)	−0.08(−0.27, 0.09)	−0.08(−0.27, 0.09)	−0.08(−0.26, 0.09)
MAP					
BTH	0.62(0.45, 0.80)	0.63(0.45, 0.81)	0.63(0.45, 0.81)	0.62(0.45, 0.80)	0.62(0.44, 0.79)
CT	0.83(0.58, 1.09)	0.85(0.60, 1.10)	0.86(0.61, 1.11)	0.87(0.62, 1.12)	0.86(0.60, 1.11)

Abbreviations: SBP (Systolic blood pressure), DBP (Diastolic blood pressure), PP (Pulse pressure), MAP (Mean arterial pressure), BTH (Burnie Take Heart), CT (Cantho).

Smoking and alcohol intake were associated with BP (not PP) among CT men. Weighted to the standard population, the correlations among CT men were $r = 0.098$ (SBP, $p = 0.004$), $r = 0.158$ (DBP, $p < 0.001$) and $r = 0.140$ (MAP, $p < 0.001$) for total years of smoking, and $r = 0.071$ (SBP, $p = 0.038$), $r = 0.135$ (DBP, $p < 0.001$) and $r = 0.112$ (MAP, $p = 0.001$) for weekly frequency of alcohol intake. Dietary consumption of fruit and vegetables was negatively associated with SBP ($r = – 0.085$, $p = 0.008$), DBP ($r = − 0.098$, $p = 0.002$) and MAP ($r = − 0.093$, $p = 0.003$) among CT women. Physical activity was inversely associated with SBP ($r = − 0.147$, $p = 0.005$) and PP ($r = − 0.167$, $p = 0.002$) among BTH women.

Appendix 3.B. Elevated blood pressure in different populations: the role of dietary salt consumption

Published in the journal *Hypertension Research* 2012; 35(9):961-2.

Huynh L. Quan, Christopher L. Blizzard, Alison J. Venn and James E. Sharman

Preface

This invited correspondence was published in the journal *Hypertension Research* as a communication to Fujisawa and colleagues who commented on the paper presented above in this chapter.

Content

In a fascinating account of a natural experiment on the possible impacts of lifestyle on blood pressure (BP), Fujisawa *et al*[1] report the relationship of BP with age and with body mass index (BMI) among people living in two regions of Papua, Indonesia. One study site was Soroba village in the central highlands where the indigenous inhabitants were reported by the authors to maintain a traditional way of life. The study sample from this village included 46 men and 54 women with mean systolic and diastolic BP of 118mmHg and 73mmHg respectively. The other study site was the small mercantile town of Bade in the southern coastal lowlands where, it was reported by the authors, the residents practice a more modern lifestyle with increasing dietary intake of salt and sugar. The study sample from this town included 38 men and 50 women with mean systolic and diastolic BP of 144mmHg and 80mmHg respectively. The prevalence of hypertension (systolic BP $\geq$ 140mmHg or diastolic BP $\geq$ 80mmHg or using anti-hypertensive medication) was 8% in the Soroba sample, and 56% in the Bade sample.

Probably contributing to these marked differences in BP, the subjects from Bade were about 10 years older on average and were more often overweight or obese (26 persons in the Bade sample but only 3 persons in the Soroba sample had BMI > 25 kg/m², and median BMI was around 2 kg/m² greater for the Bade sample despite the slightly lesser proportion of males). In unadjusted analyses, Fujisawa *et al*[1] found no association of blood pressure with age or BMI among the subjects from Soroba, but a positive association of BP with age and BMI in the

sample from Bade, and attribute their findings to the impact of social globalisation on human physiology.

Although details of the sampling design were not provided, it seems clear that the population of Soroba contains individuals who, in adult life, have remained lean with low BP. As Fujisawa *et al*[1] noted, the pathophysiological phenomenon of little or no BP rise with increasing age, and a low prevalence of hypertension, has been identified in other remote populations of the world. For those remote populations included in the INTERSALT study,[2] the favorable BP patterns among remote populations were attributed to their low salt intake[3, 4] rather than other lifestyle factors or unusual population genetics.[5, 6]

In our population-based study,[7] we studied samples of the Caucasian (Australian) and Asian (Vietnamese) populations selected by stratified multi-stage random sampling. The mean systolic BP in each sample was around 15 mm Hg higher than that in the similarly aged sample from Soroba, and the percentages with hypertension were 32.4% in the Caucasian sample and 25.7% in the Asian sample. The higher BP of the Vietnamese participants than of those from Soroba is apparent despite almost identical median BMI. Relative to the men and women in the Soroba sample, the Vietnamese women had higher mean systolic BP (126 mm Hg) and higher percentage with hypertension (21.3%) despite almost no exposure to personal tobacco smoking or alcohol, and similar body size. Higher salt intake is a possible culprit.

In formal analyses, we found similar positive associations of BP with age in the Caucasian and Asian samples irrespective of sex. In both populations, there was a fall (or leveling off) of diastolic BP together with a rise of systolic BP and pulse pressure (PP) with increasing age particularly after the fifth decade. This is consistent with age-related abnormalities of the arterial wall resulting in large artery stiffness.[8, 9] To examine the relationship between BP and BMI, we adjusted for age and restricted the analysis to the range of overlapping BMI in the two populations. We found that PP was positively associated with BMI among the Caucasians, but not among the Asians. This may be indicative of increased large artery stiffness among the Caucasians, similar to the positive association of PP with age after about 50 years of age. Conversely, an increase in mean arterial pressure (arising from increases in both systolic and diastolic BP) with increasing BMI was observed among the Asians, suggesting a more typical type of essential hypertension rather than arterial stiffness induced hypertension. This may be a result of increased circulatory volume or peripheral vascular resistance, possibly due to higher salt intake among the Asians.[10] These differences suggest different pathophysiology related to hypertension in Caucasians and Asians.

In summary, these data appear consistent with the hypothesis that high salt intake is a key factor in the development of elevated BP. Lowering dietary salt intake is strongly recommended to reduce cardiovascular risk associated with hypertension.

References

1. Fujisawa M, Ishimoto Y, Chen W, Ida Bagus Manuaba I, Del Saz EG, Okumiya K, *et al.* Correlation of systolic blood pressure with age and body mass index in native Papuan populations. *Hypertens Res*. 2012 Sep;35(9):959-60.

2. Stamler J. The INTERSALT Study: background, methods, findings, and implications. *Am J Clin Nutr*. 1997 Feb;65(2 Suppl):626S-42S.

3. Page LB, Damon A, Moellering RC, Jr. Antecedents of cardiovascular disease in six Solomon Islands societies. *Circulation*. 1974 Jun;49(6):1132-46.

4. Page LB, Vandevert DE, Nader K, Lubin NK, Page JR. Blood pressure of Qash'qai pastoral nomads in Iran in relation to culture, diet, and body form. *Am J Clin Nutr*. 1981 Apr;34(4):527-38.

5. Poulter N, Khaw KT, Hopwood BE, Mugambi M, Peart WS, Rose G, Sever PS. Blood pressure and its correlates in an African tribe in urban and rural environments. *J Epidemiol Community Health*. 1984 Sep;38(3):181-5.

6. He J, Tell GS, Tang YC, Mo PS, He GQ. Effect of migration on blood pressure: the Yi People Study. *Epidemiology*. 1991 Mar;2(2):88-97.

7. Quan HL, Blizzard CL, Venn AJ, Thuy AB, Luc PH, Sharman JE. Blood pressure and body mass index: a comparison of the associations in the Caucasian and Asian populations. *Hypertens Res*. 2012 May;35(5):523-30.

8. Milch RA. Matrix properties of the aging arterial wall. *Monogr Surg Sci*. 1965 Dec;2(4):261-342.

9. Franklin SS, Gustin Wt, Wong ND, Larson MG, Weber MA, Kannel WB, Levy D. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. *Circulation*. 1997 Jul 1;96(1):308-15.

10. Brown IJ, Tzoulaki I, Candeias V, Elliott P. Salt intakes around the world: implications for public health. *Int J Epidemiol*. 2009 Jun;38(3):791-813.

Chapter 4

Relative contributions of adiposity in childhood and adulthood to vascular health of young adults

Published in the journal

Atherosclerosis 2013; 228(1):259-64.

Huynh L. Quan, Christopher L. Blizzard, James E. Sharman, Costan G. Magnussen, Michael Schmidt, Terence Dwyer and Alison J. Venn

Chapter 4. Relative contributions of adiposity in childhood and adulthood to vascular heath of young adults

Preface

The findings presented in the previous chapter implicated that, for Caucasians, greater body size and fatness may be associated with hypertension through higher large artery stiffness. Using more direct and sophisticated measures of vascular health, this chapter aims to examine the associations of body size and fatness in both childhood and adulthood with arterial structure and function in adulthood, and to determine whether body size and fatness in adulthood have any effects on adult vascular health that are independent of adult body size and fatness. The following text of this chapter has been published in the journal *Atherosclerosis*.

Introduction

Vascular damage is suggested to have origins in childhood obesity,[1, 2] but it is unclear whether this is a direct effect of childhood adiposity as suggested by recent studies[3, 4] or an indirect effect arising from tracking of obesity from childhood to adulthood. A key research question is whether childhood adiposity influences adult vascular health independently of adult adiposity. Some measures of vascular health associated with cardiovascular risk include carotid intima-media thickness (IMT) and three measures of large artery stiffness (LAS) including carotid distensibility (CD), stiffness index (SI) and Young's elastic modulus (YEM).[5-7] Whilst IMT[8-13] – and recently CD, SI and YEM[14] – have been reported to be associated with childhood body mass index (BMI), it is unclear whether these associations are independent of adult adiposity or indeed whether childhood BMI in this context is an appropriate measure of childhood adiposity.[15, 16]

This study aimed to investigate the association of childhood body size or adiposity with adult vascular health. We hypothesised childhood body size or adiposity to have positive effects on adult IMT and LAS that are independent of adult body size or adiposity. Clarifying this matter will provide information critical for determining when and how clinical and public health interventions should be undertaken to reduce cardiovascular risk.

Methods

Study population

This study used data from the Childhood Determinants of Adult Health (CDAH) study, a prospective cohort study with baseline data collected in 1985 on a nationally representative sample of 8498 Australian schoolchildren aged 7-15 years.[17] During 2001-2004, 5170 (60.8%) of them enrolled in the follow-up study (CDAH). Of these, 2410 attended one of 34 study clinics across Australia during May 2004–May 2006 when aged 26-36 years. In this study, analyses were restricted to 2328 non-pregnant subjects (49.4% male) with physical measurements at both time-points (1985, 2004-2006) and vascular ultrasound parameters at follow-up.

Body size or adiposity

Weight, height, and waist and hip circumference were measured in childhood and adulthood.[16] BMI was calculated as weight(kg)/height(m)^2. Body surface area was measured as [weight(kg)×height(cm)/3600]$^{0.5}$. Waist-to-hip and waist-to-height ratios were calculated as waist(cm)/hip(cm) and waist(cm)/height(cm) respectively. While skinfolds at four locations in adulthood were measured for all clinic participants, skinfolds in childhood were measured only for those then aged 9, 12 and 15 years.[16] The sum of four skinfolds was used in subsequent analyses.

Carotid intima-media thickness

B-mode ultrasound studies of carotid IMT were performed using a portable Acuson Cypress (Siemens Medical Solutions USA Inc., Mountainview, CA) ultrasound machine with a 7.0MHz linear-array transducer by a single technician,[18] following previously reported standardised protocol.[10] (Please see Appendix 4.A for more details.)

Blood pressure (BP) and LAS

Brachial BP was measured supine during the ultrasound study using an Omron M4 Digital Automatic Blood Pressure Monitor (Omron Corporation, Kyoto, Japan) with a mean of two readings used in this study. Electrocardiogram-based end-systolic and end-diastolic diameters, which were maximum and minimum diameters during a cardiac cycle, were taken 10mm proximal from the carotid bulb. Three measures of LAS were calculated as follows:

$$CD = ([D_{sbp} - D_{dbp}]/D_{dbp})/(SBP - DBP)$$

$$SI = \ln(SBP/DBP)/([D_{sbp} - D_{dbp}]/D_{dbp})$$

$$YEM = ([SBP - DBP) \times D_{dbp})/([D_{sbp} - D_{dbp}]/IMT)$$

where D_{sbp} is the end-systolic diameter, D_{dbp} is the end-diastolic diameter, SBP is brachial systolic BP, and DBP is brachial diastolic BP. CD measures passive expansion and contraction of the arterial wall with changes in pressure. SI is a measure of LAS designed to be relatively independent of BP. YEM is an estimate of LAS per mm of IMT.

Covariates

Covariates included socioeconomic status, smoking, alcohol consumption, female reproductive characteristics and fasting blood biochemistry. (Please see Appendix 4.A for details.)

Statistical analyses

Other than for the summary statistics reported in Table 4.1, all physical measurements, BP, and cardio-metabolic parameters were converted to z-scores specific to each sex and year of age by subtracting from each measurement the mean for that sex and age category and dividing by its standard deviation (SD). Spearman correlation coefficients (r) are reported. For other analyses, the right-skewed outcome data (IMT, CD, SI and YEM) were appropriately transformed (by taking logarithms for example) prior to estimation of means or the estimation of associations using linear regression methods. The regression estimates reported are in original units of the outcomes for one-SD increase in the study factor.[19] The IMT measurements were calibrated to eliminate the minor differences (< 1.2%) in means between the readers. All covariates were linearly scaled because careful checking did not reveal non-linear relationships. Age- and sex-specific linear regression analyses were conducted for childhood measures of body size or adiposity. Childhood obesity was classified as normal weight, overweight and obese using the International Obesity Taskforce (IOTF) BMI cut-points.[20] Adulthood obesity was classified as normal weight (adult BMI < 25kg/m^2), overweight (25 ≤ BMI < 30kg/m^2) and obese (BMI ≥ 30kg/m^2). Analyses using childhood BMI z-scores based on the IOTF reference population[20] provided no marked differences (not shown). STATA 12.0 was used for analysis.

Results

Table 4.1 shows participants' characteristics at baseline and follow-up. Participants were aged 7-15 years at baseline, and were of mean age 31.5 (SD = 2.6) years at follow-up. The men generally had higher carotid IMT and stiffer arteries than women ($p<0.001$).

There were strong relationships among the three measures of LAS (CD, SI and YEM) with correlation coefficients in the range 0.84-0.96 (all $p < 0.001$) in absolute value. IMT was used in the calculation of YEM, and this measure of LAS was most strongly correlated with IMT (men $r = 0.372$, women $r = 0.317$; both $p < 0.001$).

Among the measures of body size or adiposity, height had the greatest correlation between childhood and adulthood values (men $r = 0.659$, women $r = 0.716$), followed by weight (men $r = 0.529$, women $r = 0.565$) and BMI (men $r = 0.530$, women $r = 0.530$). Of the 259 overweight or obese participants in childhood, 53.3% (138/259) remained obese and 12.4% (32/259) were normal weight as adults.

Table 4.2 shows that correlations of adult IMT and LAS with age- and sex-specific standardised measures of body size in childhood were marginally stronger for height than for weight (see Figure 4.B.1 of Appendix 4.B for age-stratified associations) and somewhat weaker for waist-based measures. The correlations of IMT and LAS with child height-adjusted-for-weight were only slightly different from those with child height not adjusted for weight (not shown). The correlations with adult measures were stronger than those with the corresponding childhood measures, and strongest with weight.

Table 4.1. Participants' characteristics at baseline and follow-up

	Baseline			Follow-up
	7-9 years	10-12 years	13-15 years	26-36 years
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Male	341 (46.5%)*	408 (49.8%)*	401 (51.8%)*	1150 (49.4%)*
Weight, kg	27.7 (4.7)	37.0 (6.9)	54.1 (10.6)	83.5 (13.8)
Height, cm	131.3 (7.5)	145.7 (7.9)	165.7 (9.7)	179.5 (6.7)
BMI, kg/m²	16.1 (1.5)	17.3 (2.0)	19.5 (2.4)	25.9 (3.8)
Waist, cm	57.1 (4.3)	62.7 (5.9)	70.8 (6.2)	88.0 (9.7)
Waist-hip ratio	0.86 (0.04)	0.85 (0.04)	0.83 (0.04)	0.84 (0.05)
Waist-height ratio	0.44 (0.03)	0.43 (0.03)	0.43 (0.03)	0.49 (0.06)
Sum of skinfolds†, mm	31.0 (9.5)	36.8 (15.8)	35.7 (12.3)	61.7 (25.9)
Intima-media thickness, mm				0.61 (0.10)
Carotid distensibility, %/10mmHg				1.94 (0.64)
Stiffness index				5.29 (1.82)
Young's elastic modulus, mmHg.mm				293.3 (111.4)
Female	393 (53.5%)*	412 (50.2%)*	373 (48.2%)*	1178 (50.6%)*
Weight, kg	27.1 (5.0)	37.6 (7.8)	51.2 (8.0)	65.7 (12.9)
Height, cm	129.7 (7.4)	146.4 (8.6)	160.8 (6.2)	165.6 (6.3)
BMI, kg/m²	16.1 (1.7)	17.5 (2.2)	19.7 (2.4)	23.8 (4.2)
Waist, cm	55.8 (5.0)	61.2 (6.4)	66.6 (6.5)	75.7 (9.6)

Waist-hip ratio	0.84 (0.05)	0.81 (0.05)	0.78 (0.05)	0.74 (0.05)
Waist-height ratio	0.43 (0.03)	0.42 (0.04)	0.42 (0.04)	0.46 (0.06)
Sum of skinfolds†, mm	41.1 (15.9)	47.1 (17.6)	59.0 (20.3)	73.4 (30.8)
Intima-media thickness, mm				0.58 (0.08)
Carotid distensibility, %/10mmHg				2.35 (0.79)
Stiffness index				4.83 (1.68)
Young's elastic modulus, mmHg.mm				230.3 (87.4)

*Data are number (percentage).

†Childhood skinfolds were available for 9, 12 and 15 year-olds only (males n=383, females n=403).

Table 4.2. Spearman correlations of age- and sex-specific standardised body size and adiposity in childhood and adulthood with adult carotid intima-media thickness and large artery stiffness

	IMT	CD	SI	YEM
Childhood				
Male				
Weight	0.066*	−0.067*	0.050	0.097**
Height	0.075*	−0.065*	0.049	0.099**
BMI	0.074*	−0.052	0.035	0.085**
Weight adj. for height	0.023	−0.007	−0.005	0.022
Waist	0.063*	−0.077*	0.048	0.109***
Waist adj. for height	0.027	−0.055	0.029	0.075*
Waist-hip ratio	0.024	−0.020	0.003	0.054
Waist-height ratio	0.022	−0.051	0.025	0.069*
Sum of skinfolds†	0.086	−0.080	0.027	0.107
Female				
Weight	0.083**	−0.029	−0.008	0.043
Height	0.098**	−0.055	0.020	0.081*
BMI	0.051	−0.009	−0.016	0.017
Weight adj. for height	−0.004	0.014	−0.028	−0.023
Waist	0.049	−0.020	−0.021	0.035
Waist adj. for height	0.010	0.007	−0.036	0.001
Waist-hip ratio	−0.026	0.008	−0.025	−0.005
Waist-height ratio	0.005	0.011	−0.038	−0.005
Sum of skinfolds†	0.043	0.039	−0.096	−0.018
Adulthood				
Male				
Weight	0.110***	−0.176***	0.095**	0.207***
Height	0.078*	−0.091**	0.090**	0.112***
BMI	0.097**	−0.148***	0.057	0.177***
Weight adj. for height	0.096**	−0.152***	0.062	0.180***
Waist	0.068*	−0.169***	0.074*	0.187***
Waist adj. for height	0.060	−0.158***	0.063*	0.174***
Waist-hip ratio	0.046	−0.130***	0.049	0.146***

Waist-height ratio	0.049	−0.131***	0.041	0.142***
Sum of skinfolds	–0.010	−0.122***	0.051	0.100**
Female				
Weight	0.090**	−0.118***	0.044	0.128***
Height	0.043	−0.054	0.035	0.062
BMI	0.082**	−0.118***	0.042	0.123***
Weight adj. for height	0.081**	−0.118***	0.046	0.123***
Waist	0.082**	−0.114***	0.034	0.118***
Waist adj. for height	0.079*	−0.106***	0.034	0.113***
Waist-hip ratio	0.066*	−0.114***	0.062	0.129***
Waist-height ratio	0.073*	−0.095**	0.027	0.100**
Sum of skinfolds	0.032	−0.094**	0.023	0.087**

Abbreviation: IMT (intima-media thickness), CD (carotid distensibility), SI (stiffness index), YEM (Young's elasticity modulus), and BMI (body mass index).

*p < 0.05; **p < 0.01; ***p < 0.001.

†Data were available for 9, 12 and 15 year-olds only.

We next investigated whether childhood body size or adiposity were associated with adult IMT and LAS independently of adult adiposity. Increases in childhood body size were associated with age-specific increases in adult IMT of 1.0–1.5μm (male) and 0.9–1.1μm (female) per cm increase in height, 0.9–2.9μm (male) and 0.6–1.5μm (female) per kg increase in weight, and 3.3–5.7 (male) and 0.8–1.5μm (female) per kg/m^2 increase in BMI. Table 4.3 presents the estimated response of adult IMT and LAS to one-SD increase in body size or adiposity. Where the childhood measure was significantly associated with LAS (any of CD, SI and YEM), adjusting for the adult measure substantially attenuated its estimated coefficients. Adjustment for adult height, BMI or body surface area also substantially attenuated the estimated effects of its childhood antecedents on LAS. Typically, the effect of adjustment was to reverse the sign of the childhood measure. In age-stratified analyses (not shown), this crossover in signs was most pronounced and consistent for those of pre-pubertal age in 1985 (men then aged 7–11 years, women then aged 7–9 years). For IMT, adjustment for adult weight reduced the coefficients of child weight by 46% (male) and 70% (female) and of child height by 44% (male) and 27% (female). Adjusted for adult BMI, one SD of child height was associated with increases in adult IMT of 7.0μm (1.0–13.3) among males and 6.0μm (1.0–11.0) among females. The association of child height with adult IMT was also independent of adult height (not shown). Adjusted for age and sex, one SD of child BMI and body surface area was associated with 4.7μm (0.8–8.6) and 7.5μm (0.4–11.1) increase in adult IMT respectively. Further adjustment for adult BMI or body surface area reduced the effects of child BMI or body surface area on adult IMT by 60% and 53% respectively.

Table 4.4 shows mean values of IMT and LAS for participants cross-classified as normal weight or overweight/obese in childhood and as non-obese or obese in adulthood. Participants who were obese as adults had the greatest LAS and this was most pronounced for those of them who were normal in childhood. In contrast, the relative weight gain between childhood and adulthood was not as consequential for IMT.

Table 4.3. Regression of adult carotid intima-media thickness and three measures of large artery stiffness on age- and sex-specific standardised measures of body size and adiposity in childhood when aged 7–15 years and as adults aged 26–36 years

	IMT	CD	SI	YEM
Study factor	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Male				
Child weight and adult weight				
Child weight only	0.89 (0.20, 1.50)	−4.22 (−8.06, −0.38)	7.65 (−3.01, 18.41)	11.07 (4.40, 17.75)
Adult weight only	1.04 (0.41, 1.67)	−10.85 (−14.71, −6.99)	16.16 (4.79, 27.53)	22.46 (15.26, 29.65)
Child adjusted for adult	0.48 (−0.25, 1.21)	2.54 (−2.12, 7.20)	−1.47 (−14.13, 11.18)	−1.16 (−8.66, 6.34)
Adult adjusted for child	0.75 (−0.01, 1.51)	−12.28 (−16.93, −7.63)	17.06 (3.28, 30.84)	23.21 (14.48, 31.94)
Child height and adult weight				
Child height only	0.80 (0.17, 1.43)	−3.63 (−7.61, 0.35)	7.32 (−3.79, 18.44)	9.76 (2.89, 16.64)
Adult weight only	1.04 (0.41, 1.67)	−10.85 (−14.71, −6.99)	16.16 (4.79, 27.53)	22.46 (15.26, 29.65)
Child adjusted for adult	0.45 (−0.23, 1.14)	1.04 (−3.32, 5.41)	1.00 (−10.97, 12.97)	1.02 (−6.11, 8.14)
Adult adjusted for child	0.84 (0.15, 1.53)	−11.19 (−15.43, −6.95)	15.45 (2.99, 27.92)	21.75 (13.88, 29.62)
Female				
Child weight and adult weight				
Child weight only	0.48 (−0.02, 0.97)	−0.29 (−5.18, 4.60)	−5.96 (−15.61, 3.69)	1.64 (−3.48, 6.76)
Adult weight only	0.68 (0.18, 1.18)	−8.23 (−13.05, −3.41)	2.14 (−7.87, 12.14)	10.24 (4.81, 15.68)

Child adjusted for adult	0.14 (−0.46, 0.74)	6.73 (0.68, 12.77)	−10.65 (−22.28, 0.98)	−6.00 (−11.96, −0.05)
Adult adjusted for child	0.60 (−0.01, 1.21)	−12.02 (−17.85, −6.19)	8.55 (−3.92, 21.02)	14.11 (7.29, 20.93)
Child height and adult weight				
Child height only	0.66 (0.17, 1.14)	−3.58 (−8.35, 1.19)	2.45 (−7.28, 12.18)	5.83 (0.68, 10.97)
Adult weight only	0.68 (0.18, 1.18)	−8.29 (−13.09, −3.48)	2.37 (−7.59, 12.34)	10.24 (4.81, 15.68)
Child adjusted for adult	0.48 (−0.04, 1.00)	−0.69 (−5.83, 4.45)	1.84 (−8.60, 12.29)	2.51 (−2.90, 7.91)
Adult adjusted for child	0.49 (−0.05, 1.02)	−8.03 (−13.20, −2.86)	1.68 (−9.02, 12.38)	9.21 (3.41, 15.00)

Abbreviation: IMT (intima-media thickness), CD (carotid distensibility), SI (stiffness index) and YEM (Young's elastic modulus).

Outcome variables were IMT, CD, SI and YEM. The covariates were mean-corrected standard deviation scores of child weight, adult weight and child height, and with adult age as an additional covariate.

β (95% CI) denotes regression coefficient (95% confidence interval) multiplied by 100 for better display.

Table 4.4. Intima-media thickness and three measures of large artery stiffness in participants cross-classified by childhood and adulthood obesity

		IMT (mm)	CD (%/10mmHg)	SI	YEM (mmHg.mm)
	n	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Male					
Normal child – Not obese adult	906	0.607 (0.098)	1.98 (0.63)	5.23 (1.76)	286.4 (105.5)
Overweight/Obese child – Not obese adult	55	0.637 (0.103)	1.89 (0.61)	5.42 (1.98)	315.2 (109.8)
Normal child – Obese adult	117	0.622 (0.106)	1.77 (0.62)	5.61 (2.02)	325.7 (145.2)
Overweight/Obese child – Obese adult	72	0.614 (0.110)	1.80 (0.65)	5.43 (2.04)	318.2 (123.7)
Female					
Normal child – Not obese adult	944	0.576 (0.080)	2.36 (0.77)	4.84 (1.64)	229.4 (83.9)
Overweight/Obese child – Not obese adult	66	0.567 (0.067)	2.55 (0.66)	4.60 (1.20)	209.8 (61.4)
Normal child – Obese adult	101	0.582 (0.084)	2.11 (0.89)	5.27 (2.27)	258.6 (124.5)
Overweight/Obese child – Obese adult	66	0.582 (0.094)	2.38 (0.87)	4.45 (1.60)	235.5 (98.8)

Abbreviations: IMT (intima-media thickness), CD (carotid distensibility), SI (stiffness index) and YEM (Young's elastic modulus).

Childhood obesity was classified as normal or overweight/obese by using the International Obesity Taskforce BMI cut-points. Adulthood obesity was classified as not obese (adult BMI<30kg/m^2) or obese (adult BMI≥30kg/m^2).

All models were adjusted for adult age.

Finally, we investigated whether these relationships were independent of potential confounders or altered by potential effect modifiers. Adjusting for childhood exposure to parental smoking, alcohol consumption in childhood, adult smoking, parity and oral contraceptive use did not appreciably alter the coefficient of the adult body size or adiposity measures (not shown). Adjustment for childhood BP (a potential mediator measured for 9, 12 and 15 year-olds only) and age of menarche (found to be negatively associated with adult IMT in girls) reduced the estimated effects of child height on adult IMT by around 30% and 15% respectively (not shown). Adjustment for BP, lipids, insulin and glucose substantially reduced the estimated effects of adulthood adiposity (ranging from 50–70%) on adult IMT (not shown).

Discussion

This study examined the relationships of body size or adiposity in childhood (7–15 years) and 20 years later in adulthood (26–36 years) with adult IMT and LAS on a large population-based sample of Australians. LAS was found to depend primarily on current adiposity and was greatest for those who were normal weight in childhood but obese as adults, whereas IMT was positively associated with body size or adiposity in both childhood and adulthood.

For LAS, adjusting for the adult measure of adiposity almost eliminated the estimated effect of its childhood antecedents. This suggests that increases in body size or adiposity after childhood influence LAS in early adulthood, and that the importance of larger size in childhood is primarily that larger children are very likely to become larger adults with greater LAS on average. Of those who were overweight or obese in childhood in our study, only 12.4% were normal weight adults. The coefficient of the childhood measure was greatly attenuated, and in some cases the diminution of effect was so comprehensive that all that remained was a weak association of reverse sign, when adjusted for its adult value. This change in sign is interpreted in life-course epidemiology as evidence that changes in the explanatory factor during the intervening period have affected the outcome of interest.[21, 22] In other words, it was the magnitude of adiposity gain from childhood to adulthood that was associated with LAS. This is consistent with our results because LAS appeared to be greatest in obese adults, and this was most pronounced for those of them who were normal weight in childhood. In our study this reverse in sign was most pronounced for those of pre-pubertal age at baseline, suggesting that subsequent growth spurts and fat deposition during puberty may influence LAS. Alternatively, or in unison, the action of sex hormones may modify (by

magnifying) the effect of growth in body size or adiposity. This could explain why correlations of childhood adiposity with CD, SI and YEM found in this study were weaker than those reported in an analysis of the Young Finns cohort.[14] The participants in that study had a wider range of ages (3–18 years) and included older subjects. However, it might also be explained by other differences in methodology, including lack of adjustment for baseline age of participants in that study.

In contrast, greater body size or adiposity in both childhood and adulthood were associated with thickened IMT. This was also found in a pooled analysis of our data with data from three other cohorts.[23] This is consistent with recent evidence showing increased IMT in overweight and obese children.[3, 4] The stronger association of adult IMT with child height than with other childhood measures of body size argues against the use of height-for-weight indices such as child BMI to predict adult IMT. Our results also suggest that in the relationship between childhood body size and IMT, height is the most relevant measure of body size for participants of pre-pubertal age and weight becomes relatively more important thereafter commencing in the pubertal years. This may be due to higher BP and earlier sexual maturation in taller children.[24] Our study revealed a reduced effect of childhood height on adult IMT after adjustment for childhood BP, and for age of menarche in girls. Our study also revealed BP, lipids, insulin, and glucose to be possible intermediary factors in the relationship of adiposity with IMT. This finding suggests that childhood obesity, which predisposes to obesity in adulthood, contributes to increases in these cardio-metabolic risk factors for obese adults, and thereby influences adult IMT 20 years later. Among the same persons in young adulthood, weight and weight-for-height indices captured the relationship better than height.

This study was a follow-up of a large nationally-representative sample of Australian schoolchildren on whom standardised measurements were made of an extensive range of study factors. Loss to follow-up has occurred, with non-participants at follow-up having higher mean BMI in childhood than the participants,[16] but this was an analytical investigation of a large sample from a well-characterised study population for which the distributional range of confounders and effect modifiers was not restricted by sampling or diminished by attrition. Threats to external validity are less of an issue in these circumstances.[25] An additional strength of this study was its relatively contemporary cohort with childhood anthropometric measurements made in 1985. Most other studies have followed historical cohorts of children lacking the upper extremes of body size or adiposity observed more recently. Although the prevalence of childhood overweight and obesity in this study was not

as extreme as that reported for present-day Australian children,[26] participants in our study were fully exposed to the risk factors that have subsequently led to dramatic increases in overweight and obesity in contemporary young adults.

The limitations of this study need to be recognised. Whilst a recent meta-analysis has questioned the prognostic value of IMT,[27] several studies have reported carotid artery stiffness to be an independent predictor of cardiovascular events and all-cause mortality in kidney disease patients,[28] and the measures of carotid artery stiffness used in this study were recognised by expert consensus.[28] Anthropometric measurements at additional time-points would have better discerned the critical periods of exposure. Using an ultrasound machine with a higher transducer frequency[29] and automatic border detection software may have provided better accuracy in IMT measurements. However, the coefficient of variation (calculated as SD/mean) in our IMT measurements was 0.1639 (male) and 0.1379 (female), which were very similar to those of the Cardiovascular Risk Factors of Young Finns study[10] that used a 13MHz transducer (male 0.1606, female 0.1376). Our IMT measurements were also sensitive enough to detect siginificant associations of adult IMT with childhood body size or adiposity 20 years earlier. Transducer compression due to limited ultrasound penetrance in obese participants may have occurred. However, our data suggests that transducer compression (if any) was not sufficient to mask associations because adjustment for it did not change our results. Another potential limitation of this study was the use of brachial pulse pressure in calculation of carotid LAS when it is preferable to use the carotid pressure itself. With one exception,[8] studies of childhood adiposity and adult vascular health[9-14] have not followed-up beyond early adult years. Atherosclerosis develops very slowly throughout life and, possibly, an independent relationship of childhood adiposity with adult IMT will be better discerned at a later stage.

Conclusions

In summary, whilst LAS depended primarily on current adiposity and was worst for those who gained their excess weight after childhood, carotid IMT was positively influenced by body size in both childhood and adulthood. This suggests that accumulation of IMT occurs slowly from childhood to adulthood, whereas LAS is more dynamic and dependent on current adiposity and magnitude of adiposity gain between childhood and adulthood. Our findings demonstrate direct (IMT) and indirect (LAS) consequences of childhood body size or

adiposity on adult vascular health, and efforts to achieve a healthy weight to reduce cardiovascular risk should be started early in life and maintained through adulthood.

Postscript

The findings from this chapter showed detrimental effects of greater body size and fatness in both childhood and adulthood on adult vascular health. The association of another important physical health metric (physical fitness) with vascular health is examined in Chapter 5.

References

1. Berenson GS, Srinivasan SR, Bao W, Newman WP, 3rd, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. *N Engl J Med*. 1998 Jun 4;338(23):1650-6.

2. Celermajer DS, Ayer JG. Childhood risk factors for adult cardiovascular disease and primary prevention in childhood. *Heart*. 2006 Nov;92(11):1701-6.

3. Iannuzzi A, Licenziati MR, Acampora C, Salvatore V, Auriemma L, Romano ML, Panico S, Rubba P, Trevisan M. Increased carotid intima-media thickness and stiffness in obese children. *Diabetes Care*. 2004 Oct;27(10):2506-8.

4. Woo KS, Chook P, Yu CW, Sung RY, Qiao M, Leung SS, Lam CW, Metreweli C, Celermajer DS. Overweight in children is associated with arterial endothelial dysfunction and intima-media thickening. *Int J Obes Relat Metab Disord*. 2004 Jul;28(7):852-7.

5. Hirai T, Sasayama S, Kawasaki T, Yagi S. Stiffness of systemic arteries in patients with myocardial infarction. A noninvasive method to predict severity of coronary atherosclerosis. *Circulation*. 1989 Jul;80(1):78-86.

6. Salomaa V, Riley W, Kark JD, Nardo C, Folsom AR. Non-insulin-dependent diabetes mellitus and fasting glucose and insulin concentrations are associated with arterial stiffness indexes. The ARIC Study. Atherosclerosis Risk in Communities Study. *Circulation*. 1995 Mar 1;91(5):1432-43.

7. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation*. 2007 Jan 30;115(4):459-67.

8. Wright CM, Parker L, Lamont D, Craft AW. Implications of childhood obesity for adult health: findings from thousand families cohort study. *BMJ*. 2001 Dec 1;323(7324):1280-4.

9. Oren A, Vos LE, Uiterwaal CS, Gorissen WH, Grobbee DE, Bots ML. Change in body mass index from adolescence to young adulthood and increased carotid intima-media thickness at 28 years of age: the Atherosclerosis Risk in Young Adults study. *Int J Obes Relat Metab Disord*. 2003 Nov;27(11):1383-90.

10. Raitakari OT, Juonala M, Kahonen M, Taittonen L, Laitinen T, Maki-Torkko N, Jarvisalo MJ, Uhari M, Jokinen E, Ronnemaa T, Akerblom HK, Viikari JS. Cardiovascular

risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *JAMA*. 2003 Nov 5;290(17):2277-83.

11. Freedman DS, Dietz WH, Tang R, Mensah GA, Bond MG, Urbina EM, Srinivasan S, Berenson GS. The relation of obesity throughout life to carotid intima-media thickness in adulthood: the Bogalusa Heart Study. *Int J Obes Relat Metab Disord*. 2004 Jan;28(1):159-66.

12. Juonala M, Raitakari M, J SAV, Raitakari OT. Obesity in youth is not an independent predictor of carotid IMT in adulthood. The Cardiovascular Risk in Young Finns Study. *Atherosclerosis*. 2006 Apr;185(2):388-93.

13. Freedman DS, Patel DA, Srinivasan SR, Chen W, Tang R, Bond MG, Berenson GS. The contribution of childhood obesity to adult carotid intima-media thickness: the Bogalusa Heart Study. *Int J Obes (Lond)*. 2008 May;32(5):749-56.

14. Juonala M, Jarvisalo MJ, Maki-Torkko N, Kahonen M, Viikari JS, Raitakari OT. Risk factors identified in childhood and decreased carotid artery elasticity in adulthood: the Cardiovascular Risk in Young Finns Study. *Circulation*. 2005 Sep 6;112(10):1486-93.

15. Savva SC, Tornaritis M, Savva ME, Kourides Y, Panagi A, Silikiotou N, Georgiou C, Kafatos A. Waist circumference and waist-to-height ratio are better predictors of cardiovascular disease risk factors in children than body mass index. *Int J Obes Relat Metab Disord*. 2000 Nov;24(11):1453-8.

16. Schmidt MD, Dwyer T, Magnussen CG, Venn AJ. Predictive associations between alternative measures of childhood adiposity and adult cardio-metabolic health. *Int J Obes (Lond)*. 2011 Jan;35(1):38-45.

17. Dwyer T, Gibbons LE. The Australian Schools Health and Fitness Survey. Physical fitness related to blood pressure but not lipoproteins. *Circulation*. 1994 Apr;89(4):1539-44.

18. Magnussen CG, Fryer J, Venn A, Laakkonen M, Raitakari OT. Evaluating the use of a portable ultrasound machine to quantify intima-media thickness and flow-mediated dilation: agreement between measurements from two ultrasound machines. *Ultrasound Med Biol*. 2006 Sep;32(9):1323-9.

19. Hosmer D, Blizzard L. Estimating effects for non-linearly scaled covariates in regression models Part I - Linear link function models. *Australasian Epidemiologist*. 2004;11(1):40-7.

20. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ*. 2000 May 6;320(7244):1240-3.

21. Cole TJ. Modeling postnatal exposures and their interactions with birth size. *J Nutr*. 2004 Jan;134(1):201-4.

22. De Stavola BL, Nitsch D, dos Santos Silva I, McCormack V, Hardy R, Mann V, Cole TJ, Morton S, Leon DA. Statistical issues in life course epidemiology. *Am J Epidemiol*. 2006 Jan 1;163(1):84-96.

23. Juonala M, Magnussen CG, Berenson GS, Venn A, Burns TL, Sabin MA, Srinivasan SR, Daniels SR, Davis PH, Chen W, Sun C, Cheung M, Viikari JS, Dwyer T, Raitakari OT. Childhood adiposity, adult adiposity, and cardiovascular risk factors. *N Engl J Med*. 2011 Nov 17;365(20):1876-85.

24. Daniels SR, Obarzanek E, Barton BA, Kimm SY, Similo SL, Morrison JA. Sexual maturation and racial differences in blood pressure in girls: the National Heart, Lung, and Blood Institute Growth and Health Study. *J Pediatr*. 1996 Aug;129(2):208-13.

25. Miettinen O. Theoretical epidemiology. Principles of occurrence research in medicine. New York: Wiley; 1985.

26. Magarey AM, Daniels LA, Boulton TJ. Prevalence of overweight and obesity in Australian children and adolescents: reassessment of 1985 and 1995 data against new standard international definitions. *Med J Aust.* 2001 Jun 4;174(11):561-4.

27. Den Ruijter HM, Peters SA, Anderson TJ, Britton AR, Dekker JM, Eijkemans MJ, Engstrom G, Evans GW, de Graaf J, Grobbee DE, Hedblad B, Hofman A, Holewijn S, Ikeda A, Kavousi M, Kitagawa K, Kitamura A, Koffijberg H, Lonn EM, Lorenz MW, Mathiesen EB, Nijpels G, Okazaki S, O'Leary DH, Polak JF, Price JF, Robertson C, Rembold CM, Rosvall M, Rundek T, Salonen JT, Sitzer M, Stehouwer CD, Witteman JC, Moons KG, Bots ML. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. *JAMA*. 2012 Aug 22;308(8):796-803.

28. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J*. 2006 Nov;27(21):2588-605.

29. Sarkola T, Slorach C, Hui W, Bradley TJ, Redington AN, Jaeggi E. Transcutaneous very-high resolution ultrasound for the quantification of carotid arterial intima-media thickness in children - feasibility and comparison with conventional high resolution vascular ultrasound imaging. *Atherosclerosis*. 2012 Sep;224(1):102-7.

Appendix 4.A. Additional Methods

Carotid intima-media thickness (IMT)

The left common carotid artery and left carotid bifurcation were traced longitudinally so that the distal 10-30mm of the artery was imaged with focus on the posterior (far) wall. A real-time image of three consecutive cardiac cycles was recorded. From the best-quality cardiac cycle, a total of 12 measurements at two positions were taken approximately 10mm proximal from the bulb at the end-diastolic phase. The mean and maximum of each of six measurements were calculated, and they were averaged to derive mean and maximum IMT. The measurements of IMT were made by three readers. The mean maximum IMT measurements of the three readers were 0.588 mm ± 0.093 (n=769), 0.595 mm ± 0.103 (n=702), and 0.590 mm ± 0.074 (n=512). The measurements of the three readers were calibrated to have the same mean adjusted for factors that differed between the groups of subjects measured by each reader. This procedure is necessary to preserve the associations of IMT with the same independent variables used in the main analysis. For example, the association of maximum IMT with childhood weight z-scores adjusted for age and sex was r=0.080 (pre-calibration) and r=0.079 (post-calibration). Intra-reader reproducibility was assessed in a random subsample of 30 participants. The average absolute difference and standard deviation for replicate IMT measurements was 0.02±0.04mm.[1]

Covariates

Socioeconomic status based on residential postcodes in childhood was derived using the Australian Bureau of Statistics Index of Relative Socioeconomic Disadvantage.[2] Information on smoking, alcohol consumption, and female reproductive characteristics (including menstrual cycle regularity, age at menarche, parity and hormonal contraceptive use) was obtained by self-administered questionnaire. Childhood age and age of menarche (for girls) were used to approximate likely pre-, peri- and post-pubertal status of participants in 1985. Alcohol consumption at follow-up was calculated from a food frequency questionnaire using a frequency grid.[3] Glucose, high-density lipoprotein cholesterol and triglyceride concentrations were measured in 12-hour overnight fasting blood samples using an Olympus AU5400 automated analyzer (Olympus Optical, Tokyo, Japan). Low-density lipoprotein cholesterol concentration was calculated using the Friedewald formula.[4] Fasting plasma insulin was measured by a microparticle enzyme immunoassay kit (AxSYM, Abbot Laboratories, Abbot Park, IL, USA) and by electrochemiluminescence immunoassay (Elecsys

Modular Analystics E170; Roche Diagnostics, Manheim, Switzerland) with interassay standardization.[5]

References

1. Juonala M, Magnussen CG, Venn A, Dwyer T, Burns TL, Davis PH, *et al.* Influence of age on associations between childhood risk factors and carotid intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study, the Childhood Determinants of Adult Health Study, the Bogalusa Heart Study, and the Muscatine Study for the International Childhood Cardiovascular Cohort (i3C) Consortium. *Circulation*. 2010;122(24):2514-20.

2. McLennan W. 1996 Census of population and housing: socioeconomic index for areas. Canberra: Australian Bureau of Statistics; 1998.

3. McLennan W, Podger A. National Nutrition Survey: User's Guide 1995. Canberra, Australia: Australian Bureau of Statistics; 1998.

4. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18(6):499-502.

5. Dwyer T, Magnussen CG, Schmidt MD, Ukoumunne OC, Ponsonby AL, Raitakari OT, *et al.* Decline in physical fitness from childhood to adulthood associated with increased obesity and insulin resistance in adults. *Diabetes Care*. 2009;32(4):683-7.

Appendix 4.B. Additional figure

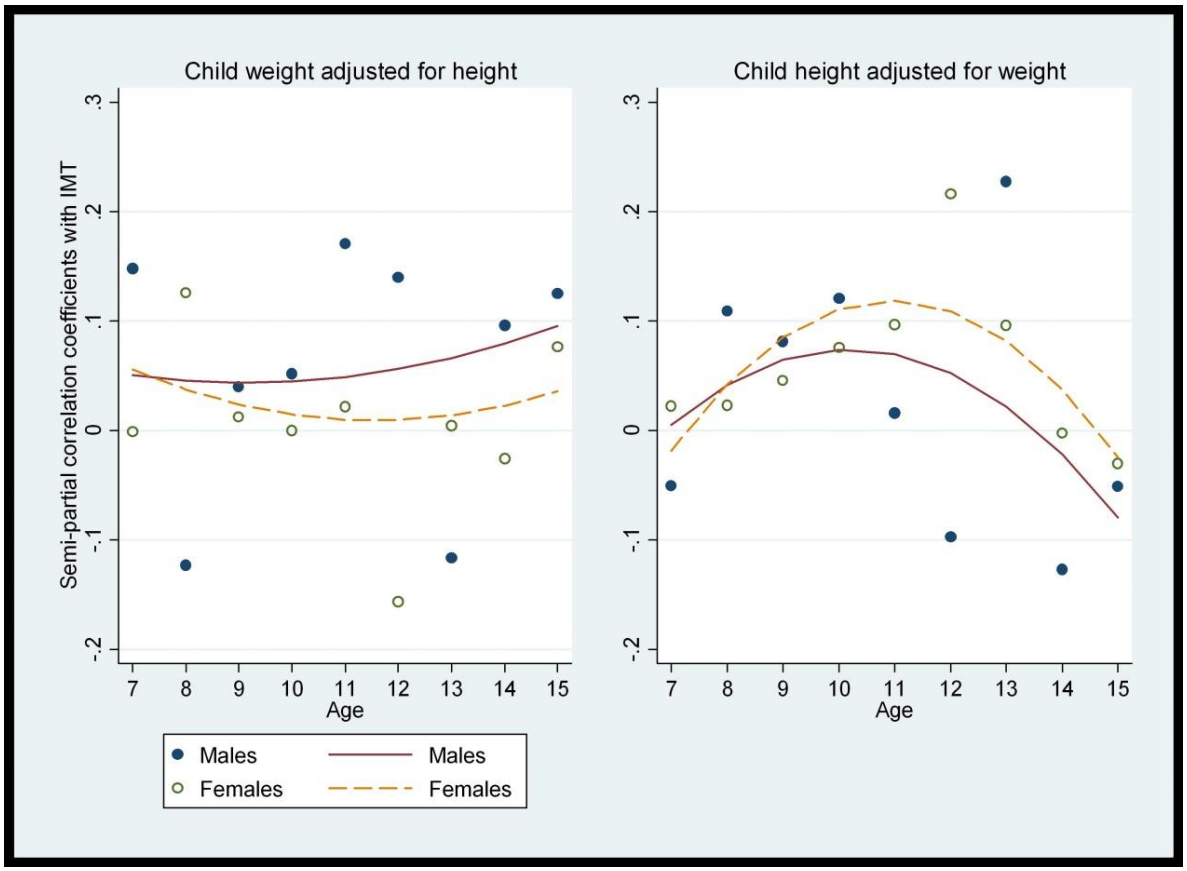


Figure 4.B.1. Semi-partial correlations of adult intima-media thickness with child weight and child height.

The figure shows semi-partial correlations of IMT with weight-adjusted-for-height and with height-adjusted-for-weight. In the context of association with IMT, childhood size appeared to be better represented by height than by weight in the middle years of the age range studied (7-15 years) with weight becoming more important in the later years. There were similar age-specific patterns of association with CD, SI and YEM (not shown).

Chapter 5

Resting heart rate and the association of physical fitness with carotid artery stiffness

Advance published online in the journal

American Journal of Hypertension 2013 (doi: 10.1093/ajh/hpt161)

Huynh L. Quan, Christopher L. Blizzard, James E. Sharman, Costan G. Magnussen, Terence Dwyer, Olli Raitakari, Michael Cheung, and Alison J. Venn

Chapter 5. Resting heart rate and the association of physical fitness with carotid artery stiffness

Preface

The previous chapter shows that greater body size and fatness in both childhood and adulthood have detrimental effects on adult vascular health. This chapter aims to study the associations of physical fitness – another important health metric – with vascular health among young adults, and to investigate the possible mechanisms involved. The following text in this chapter has been published in the journal *American Journal of Hypertension*.

Introduction

Stiffening of the large arteries (carotid and aorta) independently predicts future cardiovascular events and all-cause mortality.[1-3] Fully understanding the determinants of arterial stiffness may lead to methods for reducing cardiovascular risk. Currently, there are no pharmacological agents targeted at reducing arterial stiffness. Improvements in lifestyles including regular exercise to increase cardiorespiratory fitness (CRF) have been shown to be associated with reduced arterial stiffness through a variety of mechanisms that remain unproven.[4] Strength training, however, has been reported to increase arterial stiffness.[5, 6]

Elevated resting heart rate (RHR) is an independent cardiovascular risk factor[7] that is positively associated with arterial stiffness.[8, 9] High RHR, possibly due to sympathetic hyperactivity, may directly increase arterial stiffness through greater cyclic mechanical shear-stress on the arterial wall.[10] Regular exercise to improve CRF reduces RHR,[11] and this could be a pathway by which arterial stiffness is reduced. In contrast, the relationship between arterial stiffness and strength training, which increases muscular strength and may also reduce RHR, remains controversial. Contrary to evidence from intervention studies showing an acute[12, 13] or chronic[5, 6] increase in arterial stiffness induced by strength training, some studies have shown no change[14, 15] or a decrease in arterial stiffness.[16] Despite the uncertain implication for arterial stiffness, strength training is recommended to improve general health.[17, 18]

The aim of this study was to investigate the associations of CRF and muscular strength with arterial stiffness in young adults, and to determine whether RHR had an intermediary role in any associations.

Methods

Study population

The Childhood Determinants of Adult Health (CDAH) study collected baseline data in 1985 on a nationally-representative sample of 8498 Australian schoolchildren aged 7–15 years.[19] In this study, the analyses were restricted to 2328 non-pregnant subjects (49.4% male) who attended clinics in the first follow-up during 2004–2006.[20] The CDAH study was approved by the local Ethics Committee.

Cardiorespiratory fitness and muscular strength

CRF was estimated as physical work capacity at a heart rate of 170bpm (PWC_{170}). PWC_{170} was measured using a bicycle ergometer (Monark Exercise AB, Vansbro, Sweden) pedaled at 60rpm.[21] Because the absolute workload achieved is a function of muscle mass,[22] CRF was calculated as PWC_{170} adjusted for lean body mass to create an index uncorrelated with lean body mass (see Appendix 5.A for more details).

Five measures of strength (left and right grip, shoulder push and pull, and leg strength) were measured using appropriate dynamometers (Smedley's Dynamometer, TTM, Tokyo, Japan). Detailed procedure is reported in Appendix 5.A. Principal components analysis was used to estimate the first principal component of the five measures of strength for men and women separately.[23] The first principal component was then adjusted for body weight to create an index uncorrelated with weight. This was the indicator of muscular strength used in this study.

Blood pressure and arterial stiffness

B-mode ultrasound studies of arterial stiffness were performed using a portable Acuson Cypress (Siemens Medical Solutions USA Inc., Mountainview, CA) platform with a 7.0MHz linear-array transducer by a single technician,[24] following standardized protocols.[25] Intima-media thickness (IMT), and end-systolic and end-diastolic diameters (with intra-class correlations of repeated measurements r=0.99) were measured from the posterior wall of the left common carotid artery.[20] Brachial systolic blood pressure (SBP) and diastolic blood

pressure (DBP) were measured supine during the ultrasound study.[20] Carotid distensibility (CD), the inverse of stiffness, was measured as:

$$CD = ([D_{sbp} - D_{dbp}]/D_{dbp})/(SBP - DBP)$$

where D_{sbp} is the end-systolic diameter, D_{dbp} is the end-diastolic diameter. CD is defined as the ability of the arterial wall to expand and contract passively with the changes in pressure.

Covariates

RHR was measured using an Omron HEM907 Digital Automatic Blood Pressure Monitor (Omron Corporation, Kyoto, Japan) after five-minute rest. A mean of three readings was used. RHR was also measured by electrocardiogram during the ultrasound procedure; analyses using this value of RHR provided the same results. Body mass index (BMI) was calculated as weight(kg)/height(m^2). Mean arterial pressure (MAP) was calculated (MAP = ⅓SBP+⅔DBP). Socio-economic status, smoking, alcohol consumption, and data on resistance-type activities (including work-related vigorous activities and strength training) were obtained by questionnaire.[20] Total minutes/week leisure-time physical activity was obtained using the International Physical Activity Questionnaire.[26] High-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), insulin, triglycerides and glucose were measured using 12-hour overnight fasting blood samples.[20]

Statistical analyses

Muscular strength and CRF were standardized z-scores for men and women separately. Values reported in Table 5.2 were calculated by applying Pearson's correlation coefficients to the ranks of the variables. For other analyses, right-skewed outcomes were transformed prior to analysis. The regression estimates reported are in original units of the outcomes for one standard deviation (SD) increase in the study factor.[27, 28] Direct and indirect associations (via RHR) of CRF and muscular strength with arterial stiffness were estimated by structural equation model analysis. Three levels of participation in resistance-type activities were defined as reporting no activities at all, either reporting strength training or occupational exposure to vigorous activities, or reporting both. For analyses, these ordered levels were graded by consecutive integer scores. Of the 2328 participants, 28 participants (1.2%) were on antihypertensive medication, two participants (0.08%) had had a heart attack, and three participants (0.13%) had had a stroke. Excluding these participants from analyses did not change our findings (not shown). The fit of all final models were assessed as being adequate.

Results

Table 5.1 displays participants' characteristics. Males had higher values of PWC_{170} and measures of strength, and greater body sizes (weight, height, BMI, waist circumference, and lean body mass) but smaller skinfolds than females. Males also had lower mean values of CD reflecting stiffer carotid arteries. Other than having lower RHR than women, the men generally had higher values of cardiovascular risk factors.

Table 5.2 shows correlations of CRF and muscular strength with CD that were almost unchanged after mutual adjustment. CRF was positively correlated with CD, but this correlation was almost eliminated after adjusting for RHR (men r=0.01, women r=0.04). Leisure-time physical activity was correlated (all p<0.001) with both CRF (men r=0.30, women r=0.33) and RHR (men r=−0.20, women r=−0.19). Men and women with strength training had lower CD on average than those without (p=0.05). The correlation between muscular strength and CD was much weaker among women who undertook strength training than women who did not (p=0.021). Muscular strength was not correlated with CD before adjusting for RHR among men, and among women with strength training (r=−0.01), but was negatively correlated with CD after adjusting for RHR (men r=−0.06, women with strength training r=−0.06). The correlation of muscular strength with participation in resistance-type activities (see Methods) was stronger for men (r=0.19 p<0.001) than for women (r=0.06 p=0.053). Among participants undertaking strength training, total time spent on training was more strongly correlated with muscular strength among men (r=0.16 p=0.02) than among women (r=0.08 p=0.237).

RHR was positively associated with arterial stiffness (Additional Figure 5.B.1 in Appendix 5.B) and was negatively associated with the difference between D_{sbp} and D_{dbp} (men r=−0.29, women r=−0.25, both p<0.001) but was not associated with carotid IMT (men r=−0.04 p=0.217, women r<0.01 p=0.877). Adjustment for blood pressure did not change the association of RHR with either CD or the difference between D_{sbp} and D_{dbp} (not shown).

We next examined which other factors might be associated with CRF and muscular strength to better understand the possible causal pathways in the associations of CRF and muscular strength with arterial stiffness. Additional Table 5.B.1 (Appendix 5.B) presents age-adjusted associations of CRF and muscular strength with RHR and with MAP, BMI, insulin, HDL-C, LDL-C and triglycerides, which are known to be associated with arterial stiffness. Among these factors, RHR was most strongly correlated with CRF (men r=−0.36, women r=−0.30)

and muscular strength (men r=−0.14, women r=−0.15). The associations of CRF and muscular strength with RHR were slightly reduced after mutual adjustment (not shown).

Table 5.1. Participants' characteristics

	Men	Women	
	Mean(SD)	Mean(SD)	p-values
Age (years)	31.6(2.6)	31.3(2.6)	0.044
PWC_{170} (watts)	193.7(45.1)	127.9(30.5)	<0.001
Right grip (kg)	48.8(7.7)	29.5(5.2)	<0.001
Left grip (kg)	46.9(7.7)	27.9(5.1)	<0.001
Shoulder push (kg)	49.1(13.0)	25.6(7.6)	<0.001
Shoulder pull (kg)	40.0(13.0)	20.9(7.1)	<0.001
Leg strength (kg)	167.9(38.9)	89.6(28.2)	<0.001
Weight (kg)	83.5(13.9)	65.8(12.9)	<0.001
Height (cm)	179.5(6.8)	165.6(6.3)	<0.001
Body mass index (kg/m^2)	25.9(3.9)	23.9(4.2)	<0.001
Waist circumference (cm)	88.0(9.8)	75.7(9.6)	<0.001
Sum of four skinfolds (mm)	61.7(25.9)	73.4(30.8)	<0.001
Lean body mass (kg)	63.6(7.7)	43.9(6.1)	<0.001
Resting heart rate (beats/minute)	68.3(9.9)	73.2(9.7)	<0.001
Systolic pressure (mmHg)	124.7(10.7)	110.5(10.1)	<0.001
Diastolic pressure (mmHg)	74.5(8.9)	69.8(8.6)	<0.001
Mean arterial pressure (mmHg)	91.3(8.7)	83.4(8.5)	<0.001
Insulin (mU/L)	6.3(4.0)	6.0(3.4)	0.001
HDL-cholesterol (mmol/L)	1.26(0.25)	1.51(0.33)	<0.001
LDL-cholesterol (mmol/L)	3.04(0.83)	2.74(0.74)	<0.001
Triglycerides (mmol/L)	1.03(0.65)	0.81(0.42)	<0.001
Carotid distensibility (%/10mmHg)	1.94(0.64)	2.35(0.80)	<0.001
Stiffness index	5.29(1.82)	4.83(1.68)	<0.001
Young's elastic modulus (mmHg.mm)	293.3(111.5)	230.3(87.4)	<0.001

Abbreviations: SD (standard deviation); PWC_{170} (physical work capacity at a heart rate of 170bpm); HDL (high-density lipoprotein); LDL (low-density lipoprotein).

Table 5.2. Rank correlations of cardiorespiratory fitness and muscular strength with carotid distensibility.

	Men	Women
Cardiorespiratory fitness†	0.121***	0.103**
Muscular strength‡	−0.002	−0.108**
Partial correlations§		
Cardiorespiratory fitness	0.128***	0.119***
Muscular strength	−0.020	−0.112**

**p<0.01; ***p<0.001.

†Sex-specific z-scores of cardiorespiratory fitness, which was PWC_{170} adjusted for lean body mass.

‡The first principal component of five measures of strength that was then adjusted for body weight and expressed as a sex-specific z-score.

§Correlations of cardiorespiratory fitness with carotid distensibility adjusting for muscular strength, and of muscular strength with carotid distensibility adjusting for cardiorespiratory fitness.

Table 5.3 shows the estimated change in CD with a one-SD increase of CRF and muscular strength after adjustment for relevant factors. For muscular strength, the regression coefficients were changed slightly-to-moderately by controlling for BMI or insulin, HDL-C, LDL-C and triglycerides, but the largest changes occurred on adjustment for RHR revealing a substantially stronger association. The direct and indirect effects (via RHR) of one-SD increase in muscular strength on CD were −0.03%/10mmHg (−0.07, −0.00) and 0.03%/10mmHg (0.02, 0.05) for men, and were −0.10%/10mmHg (−0.16, −0.05) and 0.03%/10mmHg (0.01, 0.04) for women. For CRF, adjustment for RHR reduced the association with CD by 93.7% (men) and 67.6% (women). The direct and indirect effects (via RHR) of one-SD increase in CRF on CD were 0.01%/10mmHg (−0.03, 0.05) and 0.07%/10mmHg (0.05, 0.09) for men, and were 0.01%/10mmHg (−0.05, 0.06) and 0.05%/10mmHg (0.03, 0.07) for women. Additional adjustment for MAP, BMI or blood biomarkers after adjustment for RHR slightly changed the coefficients produced by adjustment for RHR. There was no interaction of RHR with blood pressure and other factors (not shown). Further adjustment for socio-economic status, smoking and alcohol consumption did not alter these findings (not shown).

Table 5.3. Regression of carotid distensibility on cardiorespiratory fitness and muscular strength with adjustment for resting heart rate and other relevant factors.

	Men		Women	
	β (95% CI)*	R^2	β (95% CI)*	R^2
Cardiorespiratory fitness				
Unadjusted	7.7 (3.4, 12.0)	0.03	6.5 (1.1, 12.0)	0.02
Adjusted for				
Age	7.9 (3.6, 12.2)	0.03	7.4 (2.0, 12.8)	0.03
Age, MAP	6.4 (2.1, 10.8)	0.04	6.3 (1.0, 11.7)	0.05
Age, BMI	6.7 (2.3, 11.0)	0.04	5.8 (0.4, 11.3)	0.04
Age, Biomarkers†	6.4 (1.9, 10.8)	0.04	5.4 (−0.1, 11.0)	0.04
Age, RHR	0.5 (−3.8, 4.8)	0.12	2.4 (−3.1, 7.9)	0.10
Age, RHR, MAP	0.3 (−4.0, 4.6)	0.12	2.2 (−3.3, 7.7)	0.10
Age, RHR, BMI	−0.4 (−4.8, 3.9)	0.12	0.8 (−4.8, 6.4)	0.10
Age, RHR, Biomarkers†	−0.5 (−4.9, 3.9)	0.12	0.4 (−5.3, 6.1)	0.09
Muscular strength				
Unadjusted	−0.8 (−5.2, 3.5)	0.03	−8.2 (−13.4, −3.1)	0.04
Adjusted for				
Age	−0.4 (−4.8, 3.9)	0.03	−8.4 (−13.5, −3.2)	0.05
Age, MAP	−0.6 (−4.9, 3.7)	0.05	−8.9 (−14.0, −3.9)	0.06
Age, BMI	−1.2 (−5.9, 3.1)	0.04	−9.0 (−14.1, −3.9)	0.05
Age, Biomarkers†	−1.5 (−5.9, 2.9)	0.04	−9.0 (−14.1, −3.9)	0.06
Age, RHR	−3.6 (−7.7, 0.5)	0.13	−11.1 (−16.1, −6.2)	0.12
Age, RHR, MAP	−3.5 (−7.6, 0.6)	0.13	−11.2 (−16.1, −6.2)	0.13
Age, RHR, BMI	−4.1 (−8.2, −0.0)	0.14	−11.6 (−16.5, −6.6)	0.12
Age, RHR, Biomarkers†	−4.5 (−8.6, −0.3)	0.14	−11.4 (−16.4, −6.4)	0.12

Abbreviation: MAP (mean arterial pressure), BMI (body mass index), RHR (resting heart rate).

*Regression coefficient (95% confidence interval) multiplied by 100 for better display.

†Including adjustment for insulin, HDL-C, LDL-C, and triglycerides.

Whilst these cross-sectional data are silent about attribution of causation, Figure 5.1 shows hypothesised pathways through which CRF and muscular strength could affect arterial stiffness. An increase in CRF might reduce arterial stiffness mainly through reducing RHR. There are two possible pathways through which an increase in muscular strength may affect arterial stiffness. First, muscular strength may influence arterial stiffness directly, and possibly more so for women. Second, muscular strength may exert its influence indirectly by reducing RHR. If these pathways exist as postulated, our results suggest they are roughly counter-balanced for men.

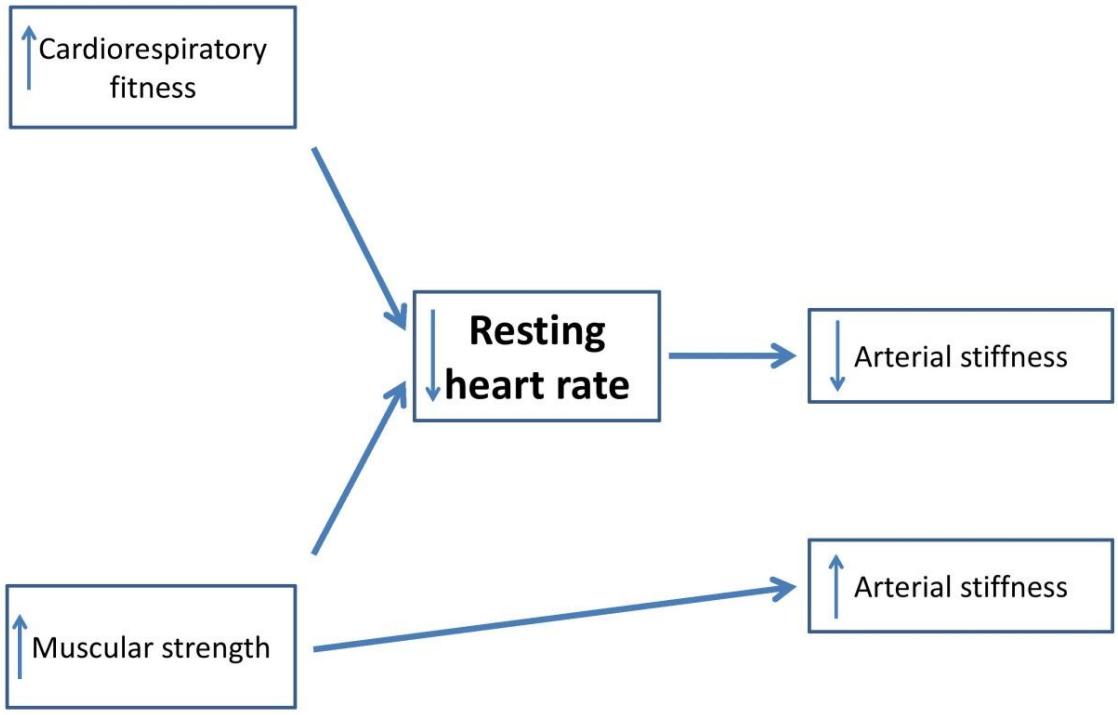


Figure 5.1. The pathways illustrate postulated direct and indirect effects of cardiorespiratory fitness and muscular strength on arterial stiffness.

Discussion

We found that arterial stiffness was negatively associated with CRF, but positively associated with muscular strength. Greater CRF and muscular strength were independently associated with lower RHR, and thereby, lower arterial stiffness. While the negative association of CRF with arterial stiffness appeared to be mediated by RHR, adjustment for RHR revealed a stronger positive association of muscular strength with arterial stiffness because the offsetting beneficial effects via lower RHR were removed. Adjustment for BMI, MAP or blood biomarkers did not change these findings. These results suggest that lower RHR is a key intermediary factor in the beneficial effect of CRF on arterial stiffness, and that the deleterious effect of greater muscular strength on arterial stiffness is partially offset by its indirect effect via lower RHR. If correct, these pathways enhance understanding of the mechanisms involved and clarify the controversial findings on strength training and cardiovascular health.

Women in this age range had lower carotid stiffness than men. This is consistent with previous findings.[25, 29] Whilst the relationship of CRF with arterial stiffness was similar for men and women, there were differences for muscular strength. Arterial stiffness was more strongly associated with muscular strength for women than for men and, for men, an association was revealed only after adjusting for RHR. The different ways in which men and women acquire muscular strength may play a part in this. Muscular strength was greater for men, and was associated with time spent on strength training and occupational exposure to vigorous activities. This suggests men are more likely to acquire muscular strength from participation in resistance-type activities. This is the mechanism proposed by which acquisition of muscular strength leads to increased arterial stiffness.[5] Results from sub-group analyses for women with strength training support this inference. The relationship between muscular strength and arterial stiffness was weaker for women with strength training than those without, and more like that of the men. Again, like the men, adjusting for RHR strengthened the relationship markedly.

The intermediary role of RHR may help explain previous inconsistent findings about strength training and arterial stiffness. Our findings are inconsistent with those from Fahs *et al*[30] that showed an inverse association of muscular strength with arterial stiffness among 79 men. While we adjusted our measures of strength for body weight to create an index uncorrelated with weight as recommended,[31] Fahs *et al*[30] divided muscular strength by body weight. Cole *et al*[31] indicated that this may produce a spurious association. Using our data, we noted that

the effect of dividing muscular strength by body weight was to reverse the sign of the correlations with CD, changing them from negative to positive. A spurious association arising in this way will be reduced by adjusting for weight and, consistent with this, adjusting for body weight or BMI eliminated the negative association in our data (not shown).

For CRF, its inverse association with arterial stiffness was mostly eliminated by controlling for RHR. This suggests RHR mediates the relationship between CRF and arterial stiffness. It might be argued that RHR may be a marker of CRF, so adjusting for RHR would eliminate any association of CRF with any outcomes. However, this was not true in our study. Findings from intervention studies suggest RHR to be an outcome of endurance training to improve CRF.[11] In our data, RHR could not be considered as a marker of CRF because the correlation between them was only weak-to-moderate. Furthermore, the results of adjusting for CRF and RHR are very different. For example, the association of muscular strength with arterial stiffness was substantially increased after adjusting for RHR (Table 5.3) but was slightly changed after adjusting for CRF (Table 5.2). Also suggesting they are associated with outcomes via different pathways, adjustment for RHR eliminated the association of CRF with arterial stiffness, but only weakly-to-moderately reduced the associations of CRF with other cardiovascular risk factors such as blood pressure, metabolic syndrome or fatness (not shown).

Our findings show physical fitness is associated with arterial stiffness even among young and generally-healthy adults with low levels of arterial stiffness, which is consistent with associations between physical activity and arterial stiffness among children and young adults reported in other studies.[32, 33] Because the association of CRF with arterial stiffness was independent of muscular strength and the association of muscular strength was independent of CRF, the effects on arterial stiffness for those who undertake both endurance and strength training may be the net effect from the two types of training. Although the direct detrimental effect of high muscular strength due to training on arterial stiffness may be partially offset by its indirect beneficial effect via RHR, individuals who do strength training might also benefit from endurance training to further minimise the adverse effects on arterial stiffness from strength training, as previously suggested.[34]

Though not completely understood, high RHR may increase mechanical load on the arterial wall and expose it to greater pressure and shear stress by shortening the diastolic period. This might lead to greater arterial wall stiffness possibly by promoting vascular smooth muscle cell growth and collagen deposition.[10, 35] Changes in heart rate can change the computed value of

CD. However, distinction needs to be drawn between the acute versus chronic exposure to changes in heart rate and the corresponding response in CD. In the acute setting,[36] the increase in blood pressure that accompanies the rise in heart rate will result in a *functional* increase in arterial stiffness. That is, there is temporary recruitment of collagenous fibres in the arterial wall to 'stiffen' the vessel against increased distending pressure.[37] On the other hand, chronic exposure to high RHR and blood pressure results in arterial wall remodelling and a *structural* increase in stiffness. Our study measured heart rate at rest and, the estimated relationship with arterial stiffness is likely to represent a chronic effect. The associations of RHR with either CD or carotid diameters remained unchanged after adjusting for blood pressure, which suggests that the relationship between RHR and CD was not due to an acute change in pressure. We therefore believe that the relationship between RHR and arterial stiffness observed in our study was due to structural changes in the arterial wall and not from artefact related to computation of CD.

It is well-known that blood pressure can influence arterial stiffness and independently predicts mortality.[38] Thus, any studies of arterial stiffness predicting mortality should account for blood pressure.[3] RHR independently predicts mortality[7] and is positively associated with arterial stiffness,[8, 9] but is generally not considered in studies of arterial stiffness. These data together suggest that future studies of arterial stiffness predicting mortality need to take account of RHR.

This study used a large nationally-representative sample of young Australians on whom standardized measurements were made of an extensive range of study factors. The few other studies of muscular strength and arterial stiffness have either used small samples or compared normal, sedentary controls with high-intensity trained athletes. A limitation of our study was the use of brachial, instead of carotid, pulse pressure to calculate CD. This is likely to have resulted in underestimation of the association between RHR and CD because the fittest people (with higher CD and lower RHR) would also be more likely to have the greatest systolic and pulse pressure amplification (higher brachial compared with central systolic and pulse pressure). The higher estimated values for SBP may therefore underestimate the calculated CD. The cross-sectional design limits the causal inference that can be drawn about the relationship of RHR with arterial stiffness. However, given evidence that endurance training to improve CRF reduces arterial stiffness,[4] we discount the possibility of reverse causation in our data (where greater arterial stiffness leading to higher RHR) because adjusting the association between CRF (an antecedent of arterial stiffness) and RHR by arterial stiffness had only the most minor impact in our data (not shown). This is consistent with recent

findings that CD and aortic distensibility decreased with increasing RHR.[9, 39] Because our study included data on young adults only, we cannot generalise our findings to older population.

Conclusions

In conclusion, our findings attribute a key intermediary role for RHR in the relationship between physical fitness and arterial stiffness. Higher CRF may reduce arterial stiffness by reducing RHR and while higher muscular strength is associated with greater arterial stiffness, the association is partially offset by reduced RHR. An indirect association of muscular strength with arterial stiffness via RHR would help reconcile the inconsistent evidence on the response of arterial stiffness to strength training, and provide some support for the inclusion of strength training in recommendations and guidelines for exercise to improve general health.

Postscript

This chapter examines the associations of physical fitness with arterial stiffness, and attributes a key intermediary role of RHR in those relationships. The next chapter studies the associations of different types of physical activity with arterial stiffness, and determines whether RHR also plays a key role.

References

1. Blacher J, Pannier B, Guerin AP, Marchais SJ, Safar ME, London GM. Carotid arterial stiffness as a predictor of cardiovascular and all-cause mortality in end-stage renal disease. *Hypertension*. 1998;32(3):570-4.

2. Barenbrock M, Kosch M, Joster E, Kisters K, Rahn KH, Hausberg M. Reduced arterial distensibility is a predictor of cardiovascular disease in patients after renal transplantation. *J Hypertens*. 2002;20(1):79-84.

3. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;55(13):1318-27.

4. Cameron JD, Dart AM. Exercise training increases total systemic arterial compliance in humans. *Am J Physiol*. 1994;266(2 Pt 2):H693-701.

5. Miyachi M, Kawano H, Sugawara J, Takahashi K, Hayashi K, Yamazaki K, Tabata I, Tanaka H. Unfavorable effects of resistance training on central arterial compliance: a randomized intervention study. *Circulation*. 2004;110(18):2858-63.

6. Cortez-Cooper MY, DeVan AE, Anton MM, Farrar RP, Beckwith KA, Todd JS, Tanaka H. Effects of high intensity resistance training on arterial stiffness and wave reflection in women. *Am J Hypertens*. 2005;18(7):930-4.

7. Palatini P, Benetos A, Grassi G, Julius S, Kjeldsen SE, Mancia G, *et al.* Identification and management of the hypertensive patient with elevated heart rate: statement of a European Society of Hypertension Consensus Meeting. *J Hypertens*. 2006;24(4):603-10.

8. Sa Cunha R, Pannier B, Benetos A, Siche JP, London GM, Mallion JM, Safar ME. Association between high heart rate and high arterial rigidity in normotensive and hypertensive subjects. *J Hypertens*. 1997;15(12 Pt 1):1423-30.

9. Tomiyama H, Hashimoto H, Tanaka H, Matsumoto C, Odaira M, Yamada J, *et al.* Synergistic relationship between changes in the pulse wave velocity and changes in the heart rate in middle-aged Japanese adults: a prospective study. *J Hypertens*. 2010;28(4):687-94.

10. Chatzizisis YS, Coskun AU, Jonas M, Edelman ER, Feldman CL, Stone PH. Role of endothelial shear stress in the natural history of coronary atherosclerosis and vascular remodeling: molecular, cellular, and vascular behavior. *J Am Coll Cardiol*. 2007;49(25):2379-93.

11. Huang G, Shi X, Davis-Brezette JA, Osness WH. Resting heart rate changes after endurance training in older adults: a meta-analysis. *Med Sci Sports Exerc*. 2005;37(8):1381-6.

12. DeVan AE, Anton MM, Cook JN, Neidre DB, Cortez-Cooper MY, Tanaka H. Acute effects of resistance exercise on arterial compliance. *J Appl Physiol*. 2005;98(6):2287-91.

13. Heffernan KS, Collier SR, Kelly EE, Jae SY, Fernhall B. Arterial stiffness and baroreflex sensitivity following bouts of aerobic and resistance exercise. *Int J Sports Med*. 2007;28(3):197-203.

14. Rakobowchuk M, McGowan CL, de Groot PC, Bruinsma D, Hartman JW, Phillips SM, MacDonald MJ. Effect of whole body resistance training on arterial compliance in young men. *Exp Physiol*. 2005;90(4):645-51.

15. Cortez-Cooper MY, Anton MM, Devan AE, Neidre DB, Cook JN, Tanaka H. The effects of strength training on central arterial compliance in middle-aged and older adults. *Eur J Cardiovasc Prev Rehabil*. 2008;15(2):149-55.

16. Okamoto T, Masuhara M, Ikuta K. Home-based resistance training improves arterial stiffness in healthy premenopausal women. *Eur J Appl Physiol*. 2009;107(1):113-7.

17. American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing and Prescription*. 8th ed. Baltimore: Lippincott Williams & Wilkins; 2010.

18. Fletcher GF, Balady GJ, Amsterdam EA, Chaitman B, Eckel R, Fleg J, *et al.* Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. *Circulation*. 2001;104(14):1694-740.

19. Dwyer T, Gibbons LE. The Australian Schools Health and Fitness Survey. Physical fitness related to blood pressure but not lipoproteins. *Circulation*. 1994;89(4):1539-44.

20. Huynh Q, Blizzard L, Sharman J, Magnussen C, Schmidt M, Dwyer T, Venn A. Relative contributions of adiposity in childhood and adulthood to vascular health of young adults. *Atherosclerosis*. 2013;228(1):259-64.

21. Withers RT, Davies GJ, Crouch RG. A comparison of three W170 protocols. *Eur J Appl Physiol Occup Physiol*. 1977;37(2):123-8.

22. Buskirk E, Taylor HL. Maximal oxygen intake and its relation to body composition, with special reference to chronic physical activity and obesity. *J Appl Physiol*. 1957;11(1):72-8.

23. Hotelling H. Analysis of a complex of statistical variables into principal components. *J Educ Psychol*. 1933;24(6):417-41.

24. Magnussen CG, Fryer J, Venn A, Laakkonen M, Raitakari OT. Evaluating the use of a portable ultrasound machine to quantify intima-media thickness and flow-mediated dilation: agreement between measurements from two ultrasound machines. *Ultrasound Med Biol*. 2006;32(9):1323-9.

25. Juonala M, Jarvisalo MJ, Maki-Torkko N, Kahonen M, Viikari JS, Raitakari OT. Risk factors identified in childhood and decreased carotid artery elasticity in adulthood: the Cardiovascular Risk in Young Finns Study. *Circulation*. 2005;112(10):1486-93.

26. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, *et al.* International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc*. 2003;35(8):1381-95.

27. Hosmer D, Blizzard L. Estimating effects for non-linearly scaled covariates in regression models Part I - Linear link function models. *Australasian Epidemiologist*. 11(1):40-7.

28. Hosmer D, Blizzard L. Estimating effects for non-linearly scaled covariates in regression models Part II - Non-linear link function models. *Australasian Epidemiologist*. 11(2):53-8.

29. Ferreira I, Twisk JW, van Mechelen W, Kemper HC, Seidell JC, Stehouwer CD. Current and adolescent body fatness and fat distribution: relationships with carotid intima-media thickness and large artery stiffness at the age of 36 years. *J Hypertens*. 2004;22(1):145-55.

30. Fahs CA, Heffernan KS, Ranadive S, Jae SY, Fernhall B. Muscular strength is inversely associated with aortic stiffness in young men. *Med Sci Sports Exerc*. 2010;42(9):1619-24.

31. Cole TJ, Fewtrell MS, Prentice A. The fallacy of using percentage body fat as a measure of adiposity. *Am J Clin Nutr*. 2008;87(6):1959; author reply -60.

32. van de Laar RJ, Ferreira I, van Mechelen W, Prins MH, Twisk JW, Stehouwer CD. Habitual physical activity and peripheral arterial compliance in young adults: the Amsterdam growth and health longitudinal study. *Am J Hypertens*. 2011;24(2):200-8.

33. Nettlefold L, McKay HA, Naylor PJ, Bredin SS, Warburton DE. The relationship between objectively measured physical activity, sedentary time, and vascular health in children. *Am J Hypertens*. 2012;25(8):914-9.

34. Kawano H, Tanaka H, Miyachi M. Resistance training and arterial compliance: keeping the benefits while minimizing the stiffening. *J Hypertens*. 2006;24(9):1753-9.

35. Giannoglou GD, Chatzizisis YS, Zamboulis C, Parcharidis GE, Mikhailidis DP, Louridas GE. Elevated heart rate and atherosclerosis: an overview of the pathogenetic mechanisms. *Int J Cardiol*. 2008;126(3):302-12.

36. Tan I, Butlin M, Liu YY, Ng K, Avolio AP. Heart Rate Dependence of Aortic Pulse Wave Velocity at Different Arterial Pressures in Rats. *Hypertension*. 2012;60(2):528-33.

37. Nichols WW, O'Rourke MF. McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles. 5th ed. London: Hodder Arnold; 2005.

38. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360(9349):1903-13.

39. Whelton SP, Blankstein R, Al-Mallah MH, Lima JA, Bluemke DA, Hundley WG, *et al.* Association of Resting Heart Rate With Carotid and Aortic Arterial Stiffness: Multi-Ethnic Study of Atherosclerosis. *Hypertension*. 2013;62(3):477-84.

Appendix 5.A. Additional Methods

Carotid artery stiffness

The other two measures of carotid artery stiffness that were measured in our study were stiffness index (SI) and Young's elastic modulus (YEM).

$$SI = \ln(SBP/DBP)/([D_{sbp}-D_{dbp}]/D_{dbp})$$

$$YEM = ([SBP-DBP)\times D_{dbp})/([D_{sbp}-D_{dbp}]/IMT)$$

SI is a measure of carotid artery stiffness designed to be relatively independent of blood pressure. YEM is an estimate of carotid artery stiffness per mm of carotid intima-media thickness (IMT). Using these two measures of carotid artery stiffness for analyses provided similar results as those of using carotid distensibility.

Lean body mass

Lean body mass was calculated from body density and percent body fat equations that used measures of skinfold thickness. Skinfolds were measured to the nearest 0.5mm at the biceps, triceps, iliac crest and subscapularis. Skinfold measures >40mm were truncated due to caliper limitations and estimated values were imputed from body mass index (BMI) and waist circumference using Tobit regression.[1] Body density was estimated from the log of the sum of four skinfolds using age-specific regression equations.[2, 3] Calculations of body fat were made from density using the Siri formula,[4] and lean body mass was estimated by subtracting fat mass from total body mass.

Estimation of body density using age-specific regression equations[2, 3]:

Males: Body density = $1.1765 - (0.0744 \times (\log_{10}(\text{sum of four skinfolds})))$

Females: Body density = $1.1567 - (0.0717 \times (\log_{10}(\text{sum of four skinfolds})))$

Calculation of the percentage of body fat using the Siri formula[4]*:*

Body fat percentage = (495/body density) – 450

Calculation of lean body mass

Lean body mass = body weight × ((100 – body fat percentage)/100)

Muscular strength

Five measures of strength were measured in different types of large muscles using hand-grip, shoulder-arm and leg-back dynamometers (Smedley's Dynamometer, TTM, Tokyo, Japan). Each measure was repeated twice with at least 1-minute rest apart. The maximum of the two attempts was used in analysis. Grip strength (left and right) was measured as participants held the dynamometer with one hand, supported it on the opposite shoulder, and gripped with maximum force. Shoulder strength (pull and push) was measured as participants held the dynamometer in front of their chest so that their arms and elbows were parallel to the ground, and then pulled or pushed with maximum force. For leg strength, participants were asked to stand on the dynamometer with a straight back, flat against the wall, holding a hand bar with an overhand grip. Knees were flexed until an angle of 115º was obtained, at which position the bar was attached to the dynamometer by a chain. Participants then pulled the bar upward as far as possible. Other than leg strength that was measured to the nearest 1kg, the other four measures of muscular strength were measured to the nearest 0.5kg. Before testing in each Australian state or territory, the dynamometers were calibrated by either a private company accredited by the National Association of Testing Authorities, Australia, or by a hospital-based biomedical engineering department, through the entire range of measurement of the device.

References

1. Dwyer T, Magnussen CG, Schmidt MD, Ukoumunne OC, Ponsonby AL, Raitakari OT, Zimmet PZ, Blair SN, Thomson R, Cleland VJ, Venn A. Decline in physical fitness from childhood to adulthood associated with increased obesity and insulin resistance in adults. *Diabetes Care*. 2009 Apr;32(4):683-7.

2. Durnin JV, Rahaman MM. The assessment of the amount of fat in the human body from measurements of skinfold thickness. *Br J Nutr*. 1967 Aug;21(3):681-9.

3. Durnin JV, Womersley J. Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16 to 72 years. *Br J Nutr*. 1974 Jul;32(1):77-97.

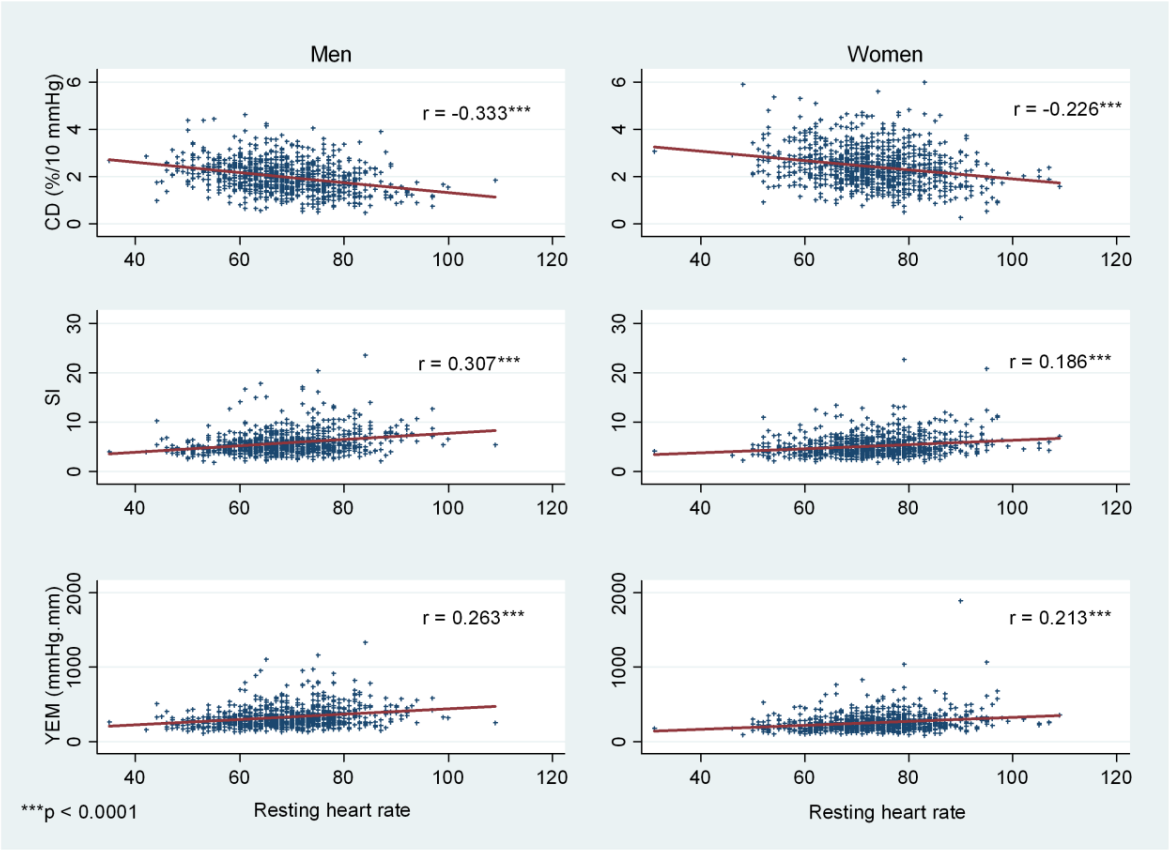
4. Siri W. Gross composition of the body. In: Lawrence J, Hamilton J, editors. Advances in Biological and Medical Physics. New York: Academic Press; 1956.

Appendix 5.B. Additional table and figure

Additional Table 5.B.1. Regression of resting heart rate and relevant cardiovascular risk factors on sex-specific z-scores of cardiorespiratory fitness and muscular strength.

	Muscular strength	Cardiorespiratory fitness
	β (95% CI)	β (95% CI)
Men		
Resting heart rate	−1.38 (−1.99, −0.78)	−3.56 (−4.10, −3.01)
Mean arterial pressure	0.16 (−0.37, 0.70)	−1.53 (−2.03, −1.02)
Body mass index	−0.17 (−0.40, 0.05)	−0.63 (−0.84, −0.42)
Insulin	−0.56 (−0.78, −0.34)	−0.97 (−1.16, −0.77)
HDL-cholesterol	0.02 (0.01, 0.03)	0.03 (0.01, 0.04)
LDL-cholesterol	0.02 (−0.03, 0.08)	−0.12 (−0.17, −0.07)
Triglycerides	−0.05 (−0.09, −0.01)	−0.10 (−0.13, −0.07)
Women		
Resting heart rate	−1.25 (−1.94, −0.76)	−2.94 (−3.51, −2.38)
Mean arterial pressure	−0.34 (−0.86, 0.17)	−0.82 (−1.32, −0.31)
Body mass index	−0.14 (−0.38, 0.09)	−0.67 (−0.89, −0.45)
Insulin	−0.13 (−0.34, 0.07)	−0.77 (−0.95, −0.59)
HDL-cholesterol	0.01 (−0.01, 0.03)	0.06 (0.04, 0.08)
LDL-cholesterol	−0.05 (−0.10, −0.01)	−0.10 (−0.14, −0.05)
Triglycerides	−0.03 (−0.06, −0.01)	−0.04 (−0.07, −0.02)

All models were adjusted for age.



Additional Figure 5.B.1. The associations of resting heart rate with three measures of carotid artery stiffness.

Abbreviations: CD (carotid distensibility), SI (stiffness index), and YEM (Young's elastic modulus).

Chapter 6

Vigorous physical activity and carotid distensibility in young and mid-aged adults

Currently under consideration with the journal

Medicine and Science in Sports and Exercise

(Manuscript submitted in 11/11/2013)

Huynh L. Quan, Christopher L. Blizzard, Olli Raitakari, James E. Sharman, Costan G. Magnussen, Terence Dwyer, Markus Juonala, Mika Kähönen, and Alison J. Venn

Chapter 6. Vigorous physical activity and carotid distensibility in young and mid-aged adults

Preface

The previous chapter shows the relationships of cardiorespiratory fitness and muscular strength – two important components of physical fitness – with arterial stiffness, and for the first time suggest the possible mechanisms involved in these relationships. This chapter aims to investigate the relationships of different types of physical activity (PA) – a means to improve fitness – with arterial stiffness, and the possible mechanisms involved in these relationships.

Introduction

Large arteries such as the carotid and aorta stiffen with age even in healthy individuals.[1] Decreased distensibility (or increased stiffness) of large arteries can independently predict cardiovascular events and all-cause mortality,[2-4] and is one of the most important contributors to the increased cardiovascular risk with ageing.[5] Given that there are currently no pharmacological agents that are targeted at reducing arterial stiffness, any lifestyle factors that can delay this process hold promise for reducing age-associated cardiovascular disease.

Intervention studies have reported light-to-moderate PA to increase arterial distensibility among older adults.[6, 7] However, it is unclear whether these results can be extrapolated to younger adults and there is limited information on the type of PA that exerts the most beneficial effect on arterial distensibility. Current guidelines[8] reflect the thinking that reduction in cardiovascular risks can be achieved by participating in either vigorous PA or light-to-moderate PA (with longer time required). Walking, assessed by questionnaire or by motion sensors such as pedometers or accelerometers, has been shown to have a range of cardio-metabolic benefits[9-11] but its association with arterial distensibility is less clear. Recent evidence suggests that vigorous PA may provide cardioprotective benefits that are beyond those achieved through light-to-moderate PA[12, 13] but associations of objectively measured steps/day with arterial distensibility have not been previously investigated. Clarifying this matter is important for informing advice on PA to promote cardiovascular health.

In this study, using data on 4503 young to mid-aged adults from two large population-based cohorts in Australia and Finland, we examined the relationship of different types of PA, including pedometer measured steps/day, with carotid artery distensibility and, for comparison, other cardiovascular risk factors. We sought to determine whether the association varied by type of PA and aimed to investigate the possible mechanisms.

Methods

This study included data from two large population-based prospective cohort studies in Australia and Finland. Each study was approved by local ethics committees. All participants provided written informed consent.

Australia: the Childhood Determinants of Adult Health study (CDAH)

Study population

The CDAH study collected baseline data in 1985 on a nationally-representative sample of 8498 Australian schoolchildren aged 7–15 years.[14] In this study, we included 2328 non-pregnant participants aged 26–36 years (49.4% male) who attended one of 34 study clinics across Australia at follow-up during May 2004–May 2006.[15] Of these participants, 1787 (76.8%) had their arterial distensibility measured.

Physical activity

Daily steps were recorded using Yamax Digiwalker SW-200 pedometers for seven days.[9] Average steps/day was calculated for participants wearing pedometers at least eight hours/day for at least four days,[16] consistent with other studies.[17] PA in previous week was self-reported using the International Physical Activity Questionnaire.[18] Minutes/week spent on work-related, domestic and recreational PA at moderate and vigorous intensity was recorded together with time spent in active transport (classified as moderate intensity). These were summed to obtain total minutes of moderate-to-vigorous PA, and moderate and vigorous activities were weighted – by assigning metabolic equivalent of task (MET) values of four and eight respectively – to obtain total energy expenditure.

Arterial distensibility and blood pressure

End-systolic and end-diastolic diameters, and intima-media thickness (IMT) of the left common carotid artery were measured using a portable Acuson Cypress (Siemens Medical Solutions USA Inc., Mountainview, CA) platform with a 7.0MHz linear-array transducer by a single technician, following a standardized protocol.[15, 19] Before its inclusion in the CDAH study, the ultrasound measures derived from this portable Acuson Cypress were validated against those from a routinely-used clinic-based ultrasound machine like that used in the Cardiovascular Risk in Young Finns study (Acuson Sequoia 512, Siemens Medical Solutions USA Inc., Mountainview, CA).[20] Brachial systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured during the ultrasound with a mean of two readings used in this study.[15] Carotid distensibility (CD), the inverse of stiffness, was calculated as follows[15, 21]:

$$CD = ([D_{sbp} - D_{dbp}]/D_{dbp})/(SBP - DBP)$$

where D_{sbp} and D_{dbp} are the end-systolic and end-diastolic diameters.

Other cardiovascular risk factors

Body mass index (BMI) was calculated as weight(kg)/height(m^2). Mean arterial pressure (MAP) was calculated as MAP = ⅓ SBP + ⅔ DBP. Resting heart rate (RHR) was measured while sitting after at least five-minute rest using an Omron HEM907 Blood Pressure Monitor (Omron Corporation, Kyoto, Japan). Concentrations of high-density lipoprotein cholesterol (HDL-C), triglycerides, insulin, and glucose were measured in 12-hour overnight fasting blood samples.[15] Low-density lipoprotein cholesterol (LDL-C) concentration was calculated using the Friedewald formula.[22] Because the absolute workload achieved is partly a function of muscle mass,[23] physical working capacity measured by a bicycle ergometer[24] at a heart rate of 170 beats per min was adjusted for lean body mass to create an index of cardiorespiratory fitness that is uncorrelated with lean body mass. This was previously described elsewhere.[21] The first principal component[25] of five measures of strength (left and right grip, shoulder push and pull, and leg strength) was measured by appropriate dynamometers (Smedley's Dynamometer, TTM, Tokyo, Japan) and adjusted for body weight to create an index of muscular strength that is uncorrelated with weight.[21] Data on socio-economic status, smoking and alcohol consumption were obtained by questionnaire.[15]

Finland: the Cardiovascular Risk in Young Finns study

Study population

The Young Finns study collected baseline data in 1980 on 3596 Finnish children and adolescents aged 3–18 years.[26] In this study, we included 2175 non-pregnant participants aged 30–45 years (45.8% male) who attended a clinic in Finland during the follow-up in 2007. Of these participants, 2169 (99.7%) had their arterial distensibility measured.

Physical activity

In 2007, participants of Young Finns study wore Omron Walking Style One (HJ-152R-E) pedometers to record daily steps for seven days.[27] Average steps/day was calculated for participants wearing pedometers at least eight hours/day for four days, consistent with other studies including CDAH.[9, 17] Leisure-time and transport PA were obtained by questionnaire, and a value of MET.hour/week was calculated based on these two subdomains of PA for Young Finns participants.[28] Vigorous leisure-time PA per usual week was reported by choosing one of the six response categories: "none", "approximately 30 minutes", "1 hour", "2–3 hours", "4–6 hours" and "7 hours or more".

Arterial distensibility and blood pressure

Using similar a standardized protocol as in CDAH,[15, 19] end-systolic and end-diastolic diameters, and IMT were measured from the left common carotid artery by Sequoia 512 ultrasound mainframes (Acuson) with 13.0MHz linear-array transducers, together with concomitant brachial blood pressure. CD was calculated using the same formula as in CDAH.[15, 19]

Other cardiovascular risk factors

Using similar standardized protocols and formulas as in CDAH, BMI and MAP were calculated, RHR was measured while sitting after at least five-minute rest, 12-hour overnight fasting concentrations of HDL-C, triglycerides, insulin, and blood glucose were measured,[19] LDL-C concentration was calculated using the Friedewald formula,[22] and data on socio-economic status, smoking and alcohol consumption were obtained by a questionnaire.[29] Cardiorespiratory fitness was objectively estimated in a random subsample of 538 participants

(47.8% male) by a bicycle ergometer using hypothetical maximal workload sustainable for six minutes measured on the basis of age, sex, height, and weight.[30]

Statistical analyses

Spearman correlations and relative risks (by log binomial regression) are reported in Table 6.2 and Table 6.3 respectively. For other analyses, right-skewed outcome data (CD and other risk factors) were transformed prior to estimation of their means or linear regression. The regression estimates reported are in the original units of the outcomes for one unit increase in the study factor.[31] Participants of each sex in each sample were classified as spending no time, <2hours/week, 2–3hours/week or >3hours/week in vigorous leisure-time PA. For estimation of trend, these ordered levels were graded by consecutive integer scores. For estimation of relative risk, low arterial distensibility was defined by having CD<10th percentile specific for each sample, each sex and each year of age. Based on the concept of "vascular age" for IMT,[32] we used linear regression to estimate sample- and sex-specific rate of decreasing CD per year of age after adjusting for BMI, PA, socio-economic status, smoking, and alcohol consumption. We then calculated the mean difference in "vascular age" of participants who spent at least one hour/week in vigorous PA, as in guidelines,[8] compared with that of those who did not by dividing the difference in CD by the rate of decreasing CD per year of age. The percentage by which RHR explained the relationship of PA with CD was calculated by subtracting the direct effect (adjusting for RHR and age) from the total effect (adjusting for age only), and then dividing by the total effect. The percentage was set at 100% if adjusting for RHR reversed the sign of the association.

Results

Characteristics of participants in the two samples are shown in Table 6.1. On average, the Young Finns participants were 6 years older than the CDAH participants. Other than having lower RHR, the men in each sample had lower CD and greater BMI, MAP, insulin, glucose, LDL-C and triglycerides, and lower HDL-C, than the women (all p<0.001). The risk factor profile of the Young Finns reflected their slightly older age.

Cardiorespiratory fitness was positively correlated with steps/day (CDAH men r=0.15, women r=0.21; Young Finns men r=0.33, women r=0.25; all p<0.001), and was more strongly correlated with self-reported vigorous leisure-time PA (CDAH men r=0.36 women r=0.35, Young Finns men r=0.41 women r=0.40, all p<0.001).

Table 6.1. Characteristics of participants in the two samples

	Men		Women	
	Mean	(SD)	Mean	(SD)
CDAH (n=2328) [a]	49.4%	(1150)	50.6%	(1178)
Age (year)	31.6	(2.6)	31.3	(2.6)
Body mass index (kg/m^2)	25.9	(3.9)	23.9	(4.2)
Average steps/day	8819	(3426)	8575	(2932)
Total active hours/week	11.3	(8.7)	10.8	(7.9)
Total physical activity (MET.hour/week)	52.6	(44.1)	42.2	(33.3)
Vigorous physical activity				
Any vigorous physical activity[a]	71.4%	(703)	49.2%	(536)
Average hours/week[b]	3.37	(3.41)	2.23	(2.32)
Any vigorous work-related activity[a]	39.9%	(393)	16.2%	(176)
Average hours/week[b]	3.40	(3.39)	2.32	(2.91)
Any vigorous domestic activity[a]	40.0%	(394)	22.2%	(242)
Average hours/week[b]	1.93	(1.83)	1.67	(1.58)
Any vigorous leisure-time activity[a]	48.7%	(479)	40.0%	(436)
Average hours/week[b]	2.13	(2.13)	1.83	(1.66)
Carotid distensibility (%/10mmHg)	1.94	(0.64)	2.35	(0.79)
Stiffness index	5.29	(1.82)	4.83	(1.68)
Young's elastic modulus (mmHg.mm)	293.3	(111.5)	230.3	(87.4)
Heart rate at rest (bpm)	68.3	(9.9)	73.2	(9.7)
Systolic pressure (mmHg)	124.6	(10.7)	110.5	(10.1)
Diastolic pressure (mmHg)	74.5	(8.9)	69.8	(8.6)
Insulin (mU/L)	6.33	(4.0)	5.96	(3.35)
Glucose (mmol/L)	5.14	(0.42)	4.84	(0.40)
HDL-cholesterol (mmol/L)	1.26	(0.25)	1.51	(0.33)
LDL-cholesterol (mmol/L)	3.04	(0.84)	2.74	(0.74)
Triglycerides (mmol/L)	1.03	(0.65)	0.81	(0.42)
Young Finns (n=2175) [a]	45.8%	(996)	54.2%	(1179)
Age (year)	37.6	(5.1)	37.8	(4.9)
Body mass index (kg/m^2)	26.1	(4.0)	24.5	(4.3)
Average steps/day	6729	(2732)	7509	(2811)
Leisure-time, commuting activity (MET.hour/week)	9.9	(19.2)	12.1	(17.9)
Any vigorous leisure-time activity[a]	67.5%	(667)	76.7%	(895)

Carotid distensibility (%/10mmHg)	1.71 (0.62)	1.97 (0.72)
Stiffness index	5.71 (2.14)	5.28 (1.95)
Young's elastic modulus (mmHg.mm)	372 (168.9)	306.5 (135.5)
Heart rate at rest (bpm)	66.7 (9.9)	68.9 (9.2)
Systolic pressure (mmHg)	125.2 (12.8)	115.2 (13.5)
Diastolic pressure (mmHg)	78.8 (10.9)	73.0 (10.9)
Insulin (mU/L)	7.54 (6.24)	7.00 (5.69)
Glucose (mmol/L)	5.38 (0.54)	5.08 (0.51)
HDL-cholesterol (mmol/L)	1.18 (0.28)	1.41 (0.32)
LDL-cholesterol (mmol/L)	3.22 (0.82)	2.89 (0.72)
Triglycerides (mmol/L)	1.33 (0.77)	1.01 (0.47)

Abbreviations: CDAH, the Childhood Determinants of Adult Health study; Young Finns, the Cardiovascular Risk in Young Finns study.

[a]Data are percentage (number).

[b]Data are reported only for participants who reported some vigorous physical activity of the corresponding subdomain.

Table 6.2 shows Spearman correlations of steps/day, and of self-reported PA, with CD and other cardiovascular risk factors. Steps/day and total PA in both studies, and total vigorous PA in CDAH, were negatively associated with RHR, insulin and triglycerides and positively associated with HDL-C, but not with CD. Among CDAH participants, self-reported time spent on walking was also not associated with CD (men p=0.431, women p=0.968). In each sample, although the associations of outcomes with total PA or total vigorous PA remained significant, they were largely reduced after adjustment for the vigorous leisure-time component of PA (not shown). Only vigorous leisure-time PA was positively associated with CD.

Because only vigorous leisure-time PA was associated with CD, we further investigated this association. Additional Table 6.A.1 shows that, other than CDAH women, participants with greater vigorous leisure-time PA had greater mean values of CD. Whereas light-to-moderate PA was not associated with CD, participants spending at least one hour/week in vigorous leisure-time PA had a lower vascular age of approximately 6.6 years (CDAH men), 1.0 year (CDAH women), 2.7 years (Young Finns men), and 3.2 years (Young Finns women) than those who did not. Based on consistent findings from parallel analyses, Table 6.3 shows pooled-data analyses adjusting for cohort and age, which presents associations of greater levels of vigorous leisure-time PA with lower risk of having low arterial distensibility (see Methods). In contrast, greater steps/day was not associated with risk of having low arterial distensibility (CDAH men p=0.868, women p=0.254; Young Finns men p=0.883, women p=0.161). Adjustment for socio-economic status, smoking and alcohol consumption, and muscular strength (CDAH only), did not change our findings (not shown).

Compared with BMI, MAP and blood biomarkers, RHR was most strongly correlated with CD (CDAH men r=−0.33 women r=−0.24; Young Finns men r=−0.30 women r=−0.30; p<0.001). To investigate the possible pathways by which participation in vigorous leisure-time PA may influence CD, Table 6.4 presents the estimated effects of participation in vigorous leisure-time PA on CD with adjustment for RHR and other relevant factors. While adjustment for MAP, BMI or insulin, HDL-C, LDL-C and triglycerides reduced slight-to-moderately the estimated effect of vigorous leisure-time PA on CD, adjustment for RHR substantially reduced this association by 88% (CDAH men), 100% (CDAH women, Young Finns men) or 80% (Young Finns women). Additional adjustment for MAP, BMI or blood biomarkers after adjustment for RHR provided small additional changes to the regression coefficients produced by adjustment for RHR.

Table 6.2. Spearman correlation of different measures of physical activity with carotid artery distensibility and other cardiovascular risk factors

	CD	HR	MAP	Insulin	Glucose	HDL-C	LDL-C	Triglycerides
CDAH								
Men								
Steps/day	−0.02	−0.10 **	0.01	−0.17 ***	0.06	0.09 **	0.04	−0.06
Total PA[a]	−0.04	−0.09 **	0.02	−0.15 ***	0.03	0.12 ***	0.05	−0.05
Total vig. PA[b]	0.01	−0.12 ***	−0.03	−0.14 ***	0.01	0.10 **	0.01	−0.05
Leisure vig. PA[b]	0.07 *	−0.23 ***	−0.06	−0.17 ***	−0.03	0.11 ***	−0.12 ***	−0.08 *
Women								
Steps/day	0.03	−0.14 ***	−0.02	−0.13 ***	−0.01	0.12 ***	−0.07 *	−0.09 **
Total PA[a]	−0.02	−0.05	−0.01	−0.00	0.03	−0.02	0.04	−0.00
Total vig. PA[b]	0.02	−0.16 ***	0.04	−0.04	0.02	0.07 *	−0.04	−0.03
Leisure vig. PA[b]	0.02	−0.19 ***	0.05	−0.09 **	0.02	0.11 ***	−0.05	−0.04
Young Finns								
Men								
Steps/day	0.04	−0.15 ***	−0.05	−0.22 ***	−0.04	0.15 ***	−0.02	−0.23 ***
Total PA[a]	0.04	−0.14 ***	−0.02	−0.18 ***	−0.17 ***	0.11 ***	−0.10**	−0.15 ***
Leisure vig. PA[c]	0.07 *	−0.20 ***	0.00	−0.17 ***	−0.17 ***	0.09 **	−0.08*	−0.10 **
Women								
Steps/day	0.05	−0.11 ***	0.01	−0.14 ***	−0.04	0.06 *	−0.03	−0.09 **

Total PA[a]	0.04	−0.12 ***	0.01	−0.15 ***	−0.09 **	0.06 *	0.00	−0.09 **
Leisure vig. PA[c]	0.08 **	−0.13 ***	0.00	−0.16 ***	−0.09 **	0.06 *	−0.05	−0.10 **

Abbreviations: CD, carotid distensibility; HR, heart rate; MAP, mean arterial pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CDAH, the Childhood Determinants of Adult Health study; Young Finns, the Cardiovascular Risk in Young Finns study; and PA, physical activity.

*p<0.05; **p<0.01; ***p<0.001.

[a]Total MET.hour/week.

[b]Minutes/week spent on different types of vigorous physical activities.

[c]Levels of participation in vigorous leisure-time physical activities.

Table 6.3. Relative risks of having low arterial distensibility by levels of participation in vigorous leisure-time physical activity in the two samples (pooled-data analysis).

	Men		Women	
	n/N	RR (95% CI)	n/N	RR (95% CI)
Vigorous leisure-time PA				
None	93/744	1.00 Ref	103/881	1.00 Ref
Any	83/1047	0.62 (0.46, 0.82)	115/1284	0.73 (0.56, 0.96)
Vigorous leisure-time PA				
None	93/744	1.00 Ref	103/881	1.00 Ref
<2 hours/week	33/351	0.73 (0.50, 1.07)	54/533	0.83 (0.60, 1.15)
2-3 hours/week	31/404	0.60 (0.40, 0.88)	36/486	0.60 (0.40, 0.87)
>3 hours/week	19/292	0.51 (0.32, 0.83)	25/265	0.73 (0.50, 1.06)
		P_{trend}=0.003		P_{trend}=0.03

Abbreviations: RR, relative risk; PA, physical activity.

Low arterial distensibility was defined by having carotid distensibility<10^{th} percentile specific for each sample, each sex and each year of age.

All models were adjusted for age and cohort.

Table 6.4. Regression of carotid distensibility on levels of participation in vigorous physical activity during leisure time, with adjustment for heart rate and other relevant factors

	Carotid distensibility (%/100mmHg)	
	Men	Women
	β (95% CI)	β (95% CI)
CDAH		
Unadjusted	0.47 (0.07, 0.87)	0.24 (−0.29, 0.76)
Adjusted for		
Age	0.43 (0.03, 0.83)	0.16 (−0.36, 0.68)
Age, MAP	0.41 (0.02, 0.80)	0.20 (−0.32, 0.71)
Age, BMI	0.41 (0.01, 0.80)	0.05 (−0.48, 0.57)
Age, Biomarkers[a]	0.28 (−0.12, 0.69)	0.06 (−0.45, 0.58)
Age, RHR	0.05 (−0.32, 0.44)	−0.25 (−0.76, 0.26)
Age, RHR, MAP	0.07 (−0.31, 0.45)	−0.18 (−0.70, 0.33)
Age, RHR. BMI	0.06 (−0.32, 0.44)	−0.34 (−0.86, 0.18)
Age, RHR, Biomarkers[a]	−0.00 (−0.39, 0.38)	−0.28 (−0.79, 0.23)
Young Finns		
Unadjusted	0.31 (0.03, 0.59)	0.42 (0.09, 0.75)
Adjusted for		
Age	0.29 (0.02, 0.56)	0.35 (0.03, 0.67)
Age, MAP	0.29 (0.02, 0.56)	0.37 (0.06, 0.67)
Age, BMI	0.21 (−0.06, 0.48)	0.18 (−0.14, 0.50)
Age, Biomarkers[a]	0.15 (−0.12, 0.42)	0.22 (−0.09, 0.53)
Age, RHR	−0.03 (−0.30, 0.23)	0.07 (−0.22, 0.37)
Age, RHR, MAP	0.03 (−0.23, 0.29)	0.12 (−0.17, 0.41)
Age, RHR. BMI	−0.04 (−0.31, 0.21)	−0.03 (−0.33, 0.27)
Age, RHR, Biomarkers[a]	−0.09 (−0.36, 0.17)	0.03 (−0.27, 0.32)

Abbreviations: CI, confidence intervals; CDAH, the Childhood Determinants of Adult Health study; MAP, mean arterial pressure; BMI, body mass index; RHR, resting heart rate; Young Finns, the Cardiovascular Risk in Young Finns study.

[a]Including adjustment for insulin, HDL-cholesterol, LDL-cholesterol and triglycerides.

Discussion

Our principal findings were as follows. First, vigorous leisure-time PA, but not total PA or less intensive forms of PA, were associated with greater CD. Second, participation in vigorous leisure-time PA may increase CD (or delay age-related arterial stiffening) by reducing RHR. Third, greater steps/day was associated with lower risk factors such as RHR, insulin, HDL-C, LDL-C and triglycerides, but not with CD. These findings were independent of age, MAP, BMI, biochemical markers, socio-economic status, smoking, and alcohol consumption.

Our study included only young to mid-aged adults who did not have the low levels of arterial distensibility typically found among older people. Light-to-moderate PA has been found to increase arterial distensibility among old adults,[33] but more vigorous PA may be required to increase the higher levels of arterial distensibility among younger adults as shown in our study. This is consistent with a study by van de Laar et al.[13] showing an association of self-reported vigorous PA with arterial distensibility among 373 young adults. The same logic may explain the weaker association found for CDAH women in our study. Women in this age range have higher CD than men. This was observed in both the CDAH and Young Finns samples, and in another study.[34] In our study, CDAH women had the highest mean level of CD and, as shown in Additional Table 6.A.1, the CDAH women who did not do any vigorous leisure-time PA had greater CD than the CDAH men who spent more than three hours/week on vigorous leisure-time PA. Thus, participation in vigorous PA may benefit these young women by reducing other cardiovascular risk factors, but not by directly improving CD.

Current recommendations for PA[8] reflect the evidence that cardiovascular risk can be reduced by either vigorous PA or light-to-moderate PA such as walking but with longer time required for light-to-moderate PA to achieve the same benefits. In our study, the benefits of PA in respect of greater CD were confined to vigorous leisure-time PA, and improvements in RHR and cardiorespiratory fitness were greater for this type of PA as well. Whereas light-to-moderate PA was not associated with greater CD, participants who spent at least one hour/week on vigorous PA as described by the guideline[8] had younger vascular age than those who did not. Although our findings do not contradict the benefits of light-to-moderate PA such as walking for cardiovascular health, they suggest that an increase in arterial distensibility among young to mid-aged adults may be best achieved by participation in vigorous PA and, are consistent with other evidence of vigorous PA being associated with greater cardioprotective benefits.[12]

In this study, RHR clearly mediated the positive relationship of vigorous leisure-time PA with CD. This is consistent with findings on the positive relationship of cardiorespiratory fitness with CD, which was also mediated by RHR.[21] Though not completely understood, high RHR may increase mechanical load on the arterial wall by exposure to higher mean pressure and increase cyclic shear stress by shortening the diastolic period.[35] This might lead to greater arterial wall stiffness possibly by promoting vascular smooth muscle cell growth and collagen deposition.[35] Using the same data from CDAH, we found that stroke volume was negatively associated with RHR, but was not related to CD. This again suggests that the lower arterial distensibility associated with high RHR may be due to remodelling of the arterial wall.

This study used two large population-based samples of adults in Australia and Finland on whom standardized measurements were made of an extensive range of study factors. Despite many cultural and environmental differences in the two countries, the very consistent results from the two populations strengthened the external validity of our findings. Using similar standardized protocols for physical measurements (including CD) in the two cohorts was another strength of this study. Although transducers with different frequencies were used, the coefficients of variation between these methods were very similar,[15] suggesting comparable accuracy. Combining data on both self-reported and objectively-measured PA helps to clarify the beneficial effects of PA at different intensities for cardiovascular health. The validity of self-reported PA in our study was confirmed by its strong association with objectively-measured cardiorespiratory fitness. We were able to somewhat differentiate endurance training from strength training, which may have adverse effects on arterial distensibility,[36] by accounting for muscular strength (in the CDAH sample). A limitation of our study was the use of brachial, instead of carotid, pulse pressure to calculate CD. This is likely to have resulted in underestimation of the association between RHR and CD because the most physically-active people (with higher CD and lower RHR) would also be more likely to have the greatest systolic and pulse pressure amplification (higher brachial compared with central systolic and pulse pressure). The higher estimated values for SBP may therefore underestimate the calculated CD. The cross-sectional design of this study, however, limits the causal inferences concerning the relationship of vigorous PA with CD. We cannot rule out the possibility of reverse causation whereby participants with stiffer arteries might do less vigorous PA. However, our findings on these generally-healthy individuals who were unaware of their levels of arterial distensibility link well with previous findings to suggest that young and mid-aged adults may acquire additional benefits of increased arterial distensibility by participation in vigorous leisure-time PA; a benefit mediated via lower RHR.

Conclusions

In conclusion, our findings provide further evidence to support the recommendation of vigorous PA for cardiovascular health benefits beyond those achieved through light-to-moderate PA such as walking in young to mid-aged adults and, for the first time, suggest that participation in vigorous physical activity may increase arterial distensibility through lower RHR.

Postscript

The research in this chapter investigated the relationship of different types of PA with arterial stiffness, and showed that only vigorous PA at leisure time was associated with arterial stiffness. The next chapter aims to examine the relationship of sedentary behaviour with arterial stiffness and to determine whether this relationship (if any) is independent of PA.

References

1. Avolio AP, Deng FQ, Li WQ, Luo YF, Huang ZD, Xing LF, O'Rourke MF. Effects of aging on arterial distensibility in populations with high and low prevalence of hypertension: comparison between urban and rural communities in China. *Circulation*. 1985;71(2):202-10.

2. Blacher J, Pannier B, Guerin AP, Marchais SJ, Safar ME, London GM. Carotid arterial stiffness as a predictor of cardiovascular and all-cause mortality in end-stage renal disease. *Hypertension*. 1998;32(3):570-4.

3. Barenbrock M, Kosch M, Joster E, Kisters K, Rahn KH, Hausberg M. Reduced arterial distensibility is a predictor of cardiovascular disease in patients after renal transplantation. *J Hypertens*. 2002;20(1):79-84.

4. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;55(13):1318-27.

5. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part I: aging arteries: a "set up" for vascular disease. *Circulation*. 2003;107(1):139-46.

6. Tanaka H, Dinenno FA, Monahan KD, Clevenger CM, DeSouza CA, Seals DR. Aging, habitual exercise, and dynamic arterial compliance. *Circulation*. 2000;102(11):1270-5.

7. Sugawara J, Otsuki T, Tanabe T, Hayashi K, Maeda S, Matsuda M. Physical activity duration, intensity, and arterial stiffening in postmenopausal women. *Am J Hypertens*. 2006;19(10):1032-6.

8. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, *et al.* Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation*. 2007;116(9):1081-93.

9. Cleland VJ, Schmidt MD, Salmon J, Dwyer T, Venn A. Correlates of pedometer-measured and self-reported physical activity among young Australian adults. *J Sci Med Sport*. 2011;14(6):496-503.

10. Dwyer T, Ponsonby AL, Ukoumunne OC, Pezic A, Venn A, Dunstan D, *et al.* Association of change in daily step count over five years with insulin sensitivity and adiposity: population based cohort study. *BMJ*. 2011;342:c7249.

11. Schmidt MD, Cleland VJ, Shaw K, Dwyer T, Venn AJ. Cardiometabolic risk in younger and older adults across an index of ambulatory activity. *Am J Prev Med*. 2009;37(4):278-84.

12. Swain DP, Franklin BA. Comparison of cardioprotective benefits of vigorous versus moderate intensity aerobic exercise. *Am J Cardiol*. 2006;97(1):141-7.

13. van de Laar RJ, Ferreira I, van Mechelen W, Prins MH, Twisk JW, Stehouwer CD. Lifetime vigorous but not light-to-moderate habitual physical activity impacts favorably on carotid stiffness in young adults: the amsterdam growth and health longitudinal study. *Hypertension*. 2010;55(1):33-9.

14. Dwyer T, Gibbons LE. The Australian Schools Health and Fitness Survey. Physical fitness related to blood pressure but not lipoproteins. *Circulation*. 1994;89(4):1539-44.

15. Huynh Q, Blizzard L, Sharman J, Magnussen C, Schmidt M, Dwyer T, Venn A. Relative contributions of adiposity in childhood and adulthood to vascular health of young adults. *Atherosclerosis*. 2013;228(1):259-64.

16. Schmidt MD, Blizzard CL, Venn AJ, Cochrane JA, Dwyer T. Practical considerations when using pedometers to assess physical activity in population studies: lessons from the Burnie Take Heart Study. *Res Q Exerc Sport*. 2007;78(3):162-70.

17. Tudor-Locke CE, Myers AM. Methodological considerations for researchers and practitioners using pedometers to measure physical (ambulatory) activity. *Res Q Exerc Sport*. 2001;72(1):1-12.

18. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, *et al.* International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc*. 2003;35(8):1381-95.

19. Juonala M, Jarvisalo MJ, Maki-Torkko N, Kahonen M, Viikari JS, Raitakari OT. Risk factors identified in childhood and decreased carotid artery elasticity in adulthood: the Cardiovascular Risk in Young Finns Study. *Circulation*. 2005;112(10):1486-93.

20. Magnussen CG, Fryer J, Venn A, Laakkonen M, Raitakari OT. Evaluating the use of a portable ultrasound machine to quantify intima-media thickness and flow-mediated dilation: agreement between measurements from two ultrasound machines. *Ultrasound Med Biol*. 2006;32(9):1323-9.

21. Quan HL, Blizzard CL, Sharman JE, Magnussen CG, Dwyer T, Raitakari O, Cheung M, Venn AJ. Resting Heart Rate and the Association of Physical Fitness With Carotid Artery Stiffness. *Am J Hypertens*. 2013 (doi: 10.1093/ajh/hpt161).

22. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18(6):499-502.

23. Buskirk E, Taylor HL. Maximal oxygen intake and its relation to body composition, with special reference to chronic physical activity and obesity. *J Appl Physiol*. 1957;11(1):72-8.

24. Withers RT, Davies GJ, Crouch RG. A comparison of three W170 protocols. *Eur J Appl Physiol Occup Physiol*. 1977;37(2):123-8.

25. Hotelling H. Analysis of a complex of statistical variables into principal components. *J Educ Psychol*. 1933;24(6):417-41.

26. Koskinen J, Magnussen CG, Taittonen L, Rasanen L, Mikkila V, Laitinen T, *et al.* Arterial structure and function after recovery from the metabolic syndrome: the cardiovascular risk in Young Finns Study. *Circulation*. 2010;121(3):392-400.

27. Hirvensalo M, Telama R, Schmidt MD, Tammelin TH, Xiaolin Y, Magnussen CG, Vkari JS, Raitakari OT. Daily steps among Finnish adults: variation by age, sex, and socioeconomic position. *Scand J Public Health*. 2011;39(7):669-77.

28. Mansikkaniemi K, Juonala M, Taimela S, Hirvensalo M, Telama R, Huupponen R, *et al.* Cross-sectional associations between physical activity and selected coronary heart disease risk factors in young adults. The Cardiovascular Risk in Young Finns Study. *Ann Med*. 2012;44(7):733-44.

29. Aatola H, Koivistoinen T, Hutri-Kahonen N, Juonala M, Mikkila V, Lehtimaki T, *et al.* Lifetime fruit and vegetable consumption and arterial pulse wave velocity in adulthood: the Cardiovascular Risk in Young Finns Study. *Circulation*. 2010;122(24):2521-8.

30. Arstila M, Impivaara O, Maki J. New ergometric reference values for clinical exercise tests. *Scand J Clin Lab Invest*. 1990;50(7):747-55.

31. Hosmer D, Blizzard L. Estimating effects for non-linearly scaled covariates in regression models Part I - Linear link function models. *Australasian Epidemiologist*. 2004;11(1):40-7.

32. Stein JH, Fraizer MC, Aeschlimann SE, Nelson-Worel J, McBride PE, Douglas PS. Vascular age: integrating carotid intima-media thickness measurements with global coronary risk assessment. *Clin Cardiol*. 2004;27(7):388-92.

33. Gando Y, Yamamoto K, Murakami H, Ohmori Y, Kawakami R, Sanada K, *et al.* Longer time spent in light physical activity is associated with reduced arterial stiffness in older adults. *Hypertension*. 2010;56(3):540-6.

34. Ferreira I, Twisk JW, van Mechelen W, Kemper HC, Seidell JC, Stehouwer CD. Current and adolescent body fatness and fat distribution: relationships with carotid intima-media thickness and large artery stiffness at the age of 36 years. *J Hypertens*. 2004;22(1):145-55.

35. Giannoglou GD, Chatzizisis YS, Zamboulis C, Parcharidis GE, Mikhailidis DP, Louridas GE. Elevated heart rate and atherosclerosis: an overview of the pathogenetic mechanisms. *Int J Cardiol*. 2008;126(3):302-12.

36. Miyachi M, Kawano H, Sugawara J, Takahashi K, Hayashi K, Yamazaki K, Tabata I, Tanaka H. Unfavorable effects of resistance training on central arterial compliance: a randomized intervention study. *Circulation*. 2004;110(18):2858-63.

Appendix 6.A. Additional Table

Additional Table 6.A.1. Mean values of carotid distensibility by levels of participation in vigorous physical activity during leisure time

	Men		Women	
	n	Mean (SD)	n	Mean (SD)
CDAH				
None	427	1.89 (0.65)	601	2.32 (0.78)
<2 hours/week	110	1.98 (0.61)	178	2.33 (0.81)
2-3 hours/week	156	2.00 (0.57)	105	2.38 (0.85)
>3 hours/week	124	2.00 (0.60)	86	2.36 (0.74)
		P_{trend}=0.036		P_{trend}=0.439
Young Finns				
None	317	1.66 (0.60)	280	1.89 (0.73)
<2 hours/week	241	1.70 (0.63)	355	1.98 (0.74)
2-3 hours/week	248	1.74 (0.63)	381	2.05 (0.68)
>3 hours/week	168	1.77 (0.58)	179	2.03 (0.76)
		P_{trend}=0.045		P_{trend}=0.013

Abbreviations: CDAH (the Childhood Determinants of Adult Health study), Young Finns (the Cardiovascular Risk in Young Finns study).

All models were adjusted for age.

Chapter 7

The association of sitting time with carotid artery stiffness in young adults

Currently under consideration with the journal

BMJ Open

(Revised manuscript submitted in 01/11/2013)

Huynh L. Quan, Christopher L. Blizzard, James E. Sharman, Costan G. Magnussen, Terence Dwyer, and Alison J. Venn

Chapter 7. The association of sitting time with carotid artery stiffness in young adults

Preface

Chapter 5 and 6 of this thesis show negative associations of cardiorespiratory fitness and vigorous physical activity with arterial stiffness and, for the first time, shed light on the possible mechanisms involved in these relationships. This chapter aims to investigate the association of sedentary behaviour with arterial stiffness and the possible mechanisms involved in any association, and to determine whether the relationship of sedentary behaviour with arterial stiffness (if any) is independent of physical activity and cardiorespiratory fitness.

Introduction

Physical activity is widely accepted as an important means to improve cardiovascular health. Indeed, lack of physical activity is the second leading behavioural cause of death in the United States, following tobacco use.[1] Many studies have reported participation in physical activity to be negatively associated with cardio-metabolic risk factors including arterial stiffness.[2, 3] Although the benefits of physical activity are well-known, recent data show that levels of participation in moderate-to-vigorous physical activity decline from childhood to adulthood and are low for adults.[4]

Sedentary behaviour such as sitting, watching television and computer use are ubiquitous in contemporary society and have become a new focus for research in health and physical activity. They are defined by both their posture (sitting or reclining) and their low levels of energy expenditure (typically in the range of 1.0 to 1.5 multiples of the basal metabolic rate).[5, 6] Recent findings suggest such activities should not be viewed as a replacement for moderate-to-vigorous physical activity but as a distinct cardiovascular risk factor.[7] Indeed, several studies have reported sedentary behaviour to independently predict greater cardio-metabolic[8-10] and mortality risk.[11-15] That is, even for individuals who meet guideline recommendation on physical activity, being sedentary for prolonged periods may still compromise their health.

The relationship between sedentary behaviour and arterial stiffness, which is considered as one of the most important contributors to the increased cardiovascular risk associated with ageing,[16] is however poorly understood. In this study of young adults, we examined the

association of sedentary behaviour with arterial stiffness and with other cardio-metabolic risk factors as a means to investigate the possible mechanisms. We hypothesised that sedentary behaviour is positively associated with arterial stiffness.

Methods

Study population

This cross-sectional study used data from the Childhood Determinants of Adult Health (CDAH) study, which collected baseline data in 1985 on a nationally-representative sample of 8498 Australian schoolchildren aged 7–15 years.[17] In this study, we included 2328 non-pregnant participants aged 26–36 years (49.4% male) who attended one of 34 study clinics across Australia at follow-up during May 2004–May 2006.[18] The CDAH study was approved by the local ethics committees.

Sedentariness, physical activity and physical fitness

Participants reported how much time (hours and minutes) they spent sitting on a weekday (Monday to Friday) and weekend day (Saturday and Sunday) during the last seven days using the long version of the International Physical Activity Questionnaire (IPAQ).[19] Time spent watching television, using computers and playing video games were also recorded in the same manner. Physical activity during the last seven days was also reported using the long version of the IPAQ.[19] Specifically, minutes/week spent on work-related, domestic and leisure physical activity at moderate and vigorous intensity were recorded together with time spent on active transport (classified as moderate intensity). These were summed to obtain total minutes of moderate-to-vigorous physical activity, and moderate and vigorous activities were weighted by their energy cost – by assigning metabolic equivalent of task (MET) values of four and eight respectively – to obtain total energy expenditure. The associations of self-reported measures of sedentary behaviour and physical activity with a range of demographic and cardio-metabolic factors in our study have been reported elsewhere.[20, 21] Daily steps were recorded by Yamax Digiwalker SW-200 pedometers for seven days as previously described.[21] Cardiorespiratory fitness was estimated as physical work capacity at a heart rate of 170bpm (PWC_{170}) by bicycle ergometry.[22] Because the absolute workload achieved is partly a function of muscle mass,[23] PWC_{170} was adjusted for lean body mass[24] to create an index of cardiorespiratory fitness that is uncorrelated with lean body mass.[25] For participants who were currently involved in strength training, total time spent on strength training was calculated

from self-reported information on average duration of each workout, number of workouts per week, and the total years and months of training.

Arterial stiffness and other cardio-metabolic risk factors

Arterial stiffness was measured in the left common carotid artery using a portable Acuson Cypress (Siemens Medical Solutions USA Inc., Mountainview, CA) platform with a 7.0MHz linear-array transducer by a single technician.[26] Brachial systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured during the ultrasound study with a mean of two readings used in this study.[18] Three indices of carotid artery stiffness[18, 25] were calculated as follows:

$$CD = ([D_{sbp} - D_{dbp}]/D_{dbp})/(SBP - DBP)$$
$$SI = \ln(SBP/DBP)/([D_{sbp} - D_{dbp}]/D_{dbp})$$
$$YEM = ([SBP - DBP) \times D_{dbp})/([D_{sbp} - D_{dbp}]/IMT)$$

where D_{sbp} and D_{dbp} are the end-systolic and end-diastolic diameters respectively, and IMT is carotid intima-media thickness. Carotid distensibility (CD), the inverse of stiffness, measures the passive expansion and contraction of the arterial wall with changes in blood pressure. Stiffness index (SI) is a measure of stiffness that is relatively independent of pressure. Young's elastic modulus (YEM) is an estimate of stiffness per mm of IMT.

Resting heart rate (RHR) was measured while sitting after at least a five-minute rest. Weight, height and waist circumference were measured.[18] Body mass index (BMI) was calculated as weight(kg)/height(m)^2. Sum of skinfolds at biceps, triceps, iliac crest and supraspinale was used.[27] Glucose, high-density lipoprotein cholesterol (HDL-C), triglyceride and insulin concentrations were measured in 12-hour overnight fasting blood samples.[18] Low-density lipoprotein cholesterol (LDL-C) concentration was calculated using the Friedewald formula.[28] Metabolic syndrome status was determined by using the 2009 harmonized definition proposed jointly by the International Diabetes Federation, National Heart, Lung and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society, and the International Association for the Study of Obesity.[29] A continuous metabolic syndrome score was calculated using the method described by Wijndaele *et al*[30] as previously reported.[27] Briefly, the score was calculated by applying sex-specific principal component analysis to the normalized metabolic syndrome risk factors (including waist circumference, SBP, DBP, HDL-C, triglycerides and glucose). Two principal components that explained

34% and 26% of the variance in men and 31% and 25% of the variance in women were identified. These principal components were then summed, weighted according to the relative proportion of variance explained, to compute the continuous metabolic syndrome score.

Covariates

Data on smoking (never-smoker, ex-smoker and current-smoker), alcohol consumption (g/week), diet (whether dietary guidelines on various types of food were met), highest education and parity were obtained by questionnaire.[18, 31]

Statistical analyses

Right-skewed outcome data were appropriately transformed before estimation of means. The rank correlations were estimated by applying Pearson's correlation to the rank of variables. The associations of time spent watching television, and of time using a computer or playing video games, per weekday and weekend day with the outcomes were similar to, but somewhat weaker than those of total sitting time per weekday and weekend day with the outcomes (not shown). For brevity, we reported the associations of total sitting time. Because only leisure-time vigorous physical activity but not less intensive forms of physical activity were associated with arterial stiffness among the young participants included in our study (not shown), the correlations presented in Table 7.3 were adjusted for leisure-time vigorous physical activity. Adjustment for total physical activity provided similar results (not shown). There was no difference in self-reported moderate-to-vigorous physical activity in childhood between the participants at follow-up and the non-participants who dropped out from the baseline sample ($p=0.62$). However, the non-participants had lower socio-economic status, lower levels of school academic performance, higher BMI, greater waist circumference and lower cardiorespiratory fitness in childhood in 1985 than the participants included in this study (all $p<0.05$). Using these characteristics, we calculated the probability of participation at follow-up for each subject at baseline. We then weighted the associations of sitting time with the outcomes among the participants using inverse probability weighting; this gave estimates of the association of interest with the inclusion of non-participants at follow-up represented by those similar to them at baseline in terms of socio-economic status, school performance, BMI, waist and fitness. The weighted results were very similar to those presented in this manuscript (not shown), and thus give us confidence that the drop-outs did not influence our results. STATA 12 (Statacorp, College Station, Texas, USA) was used for analyses.

Results

Characteristics of participants are shown in Table 7.1. Of the 2328 participants included in the analysis, 1246 (54%) of them spent at least five hours sitting per weekday whereas 900 (39%) of them spent at least five hours sitting per weekend day. On average, the male participants spent more time sitting and watching television or using computers or video games (all $p<0.05$), but had greater steps/day and greater self-reported moderate-to-vigorous physical activity, than their female counterparts ($p<0.05$). Computer use in this study included time using a computer at work and home. 91% (2122/2328) of our participants had a job or were students, and were likely to use a computer frequently. This may explain the large proportion of total sitting time in our study attributed to watching television, using computers and playing video games. The men had lower mean value of CD and higher mean values of SI and YEM (that is, stiffer arteries) than the women (all $p<0.001$). With the exception of RHR and skinfolds, all other cardio-metabolic risk factors were greater among the men than the women (all $p<0.001$).

Table 7.1. Characteristics of participants

	Men (n=1150)	Women (n=1178)
	Mean (SD)	Mean (SD)
Age (year)	31.6 (2.6)	31.3 (2.6)
Sitting time		
Per week (hour)	39.9 (21.1)	37.1 (18.7)
Per weekday (hour)	6.1 (3.6)	5.7 (3.2)
Per weekend day (hour)	4.9 (2.7)	4.5 (2.6)
Television, computer, video games		
Per week (hour)	32.4 (22.1)	27.1 (18.8)
Per weekday (hour)	4.9 (3.8)	4.3 (3.4)
Per weekend day (hour)	4.0 (3.1)	2.8 (2.1)
Average steps per day	8819 (3426)	8575 (2932)
Total active hours/week‡	11.3 (8.7)	10.8 (7.9)
Total MET.hour/week‡	52.6 (44.1)	42.2 (33.3)
Vigorous leisure-time activity (hour/week)	1.5 (2.5)	1.0 (1.9)
Carotid distensibility (%/10mmHg)	1.94 (0.64)	2.35 (0.79)
Stiffness index	5.29 (1.82)	4.83 (1.68)

Young's elastic modulus (mmHg.mm)	293.3 (111.5)	230.3 (87.4)
Resting heart rate (bpm)	68.3 (9.9)	73.2 (9.7)
PWC_{170} (watts)	193.7(45.1)	127.9 (30.5)
Total time of strength training* (hour)	205.0 (614.9)	52.8 (153.4)
Body mass index (kg/m^2)	25.9 (3.9)	23.9 (4.2)
Waist circumference (cm)	88.0 (9.8)	75.7 (9.6)
Skinfolds (mm)	61.7 (25.9)	73.4 (30.8)
Systolic pressure (mmHg)	124.6 (10.7)	110.5 (10.1)
Diastolic pressure (mmHg)	74.5 (8.9)	69.8 (8.6)
Insulin (mU/l)	6.33 (4.0)	5.96 (3.35)
Glucose (mmol/l)	5.14 (0.42)	4.84 (0.40)
HDL-cholesterol (mmol/l)	1.26 (0.25)	1.51 (0.33)
LDL-cholesterol (mmol/l)	3.04 (0.84)	2.74 (0.74)
Triglycerides (mmol/l)	1.03 (0.65)	0.81 (0.42)
Continuous metabolic syndrome score	0.00 (0.71)	0.00 (0.71)
Metabolic syndrome†	11.8% (136)	5.1% (60)

Abbreviations: PWC170 (physical work capacity at a heart rate of 170 beats per minute).

*Data are for those who were doing strength training only (men n=256, women n=245).

†Data are percentage (number).

‡Including moderate-to-vigorous physical activity.

Levels of education were positively correlated with sitting time per weekday, and with time using a computer per weekday and weekend day, but was negatively associated with time watching television per weekday and weekend day (all $p<0.001$ for each sex). Among women, both sitting time per weekday and per weekend day were negatively correlated with parity ($p<0.001$). Sitting time was strongly correlated with time spent watching television or using computers or video games per week (men r=0.50, women r=0.56), per weekday (men r=0.50, women r=0.57) and per weekend day (men r=0.49, women r=0.39) respectively (all $p<0.001$).

Table 7.2 shows rank correlations of sitting time with cardiorespiratory fitness, self-reported physical activity and average steps/day. While total MET.hour/week and average steps/day were negatively correlated with sitting time per weekday and per weekend day, cardiorespiratory fitness and self-reported time spent on vigorous physical activity were negatively correlated with sitting time per weekend day only. Among men and women who were currently doing strength training, sitting time per weekend day but not per weekday was negatively correlated with total training time ($p<0.05$). Similarly to sitting time, time spent watching television, using computers and playing video games per weekend day, but not per weekday, was inversely correlated with cardiorespiratory fitness (men r=−0.15, women r=−0.15) and self-reported leisure-time vigorous physical activity (men r=−0.08, women r=−0.05).

Table 7.3 shows rank correlations of sitting time with arterial stiffness, RHR, skinfolds and continuous metabolic syndrome scores. In general, sitting time per weekend day was more strongly correlated with arterial stiffness and other cardio-metabolic risk factors than sitting time per weekday. These correlations, with an exception of the correlation between sitting time and continuous metabolic syndrome scores among women, were not substantially altered after adjusting for either self-reported physical activity or objectively-measured steps/day, and for other potential confounders ($p<0.05$). Further adjustment for cardiorespiratory fitness did not change our findings either (not shown). The change in the correlations between sitting time and continuous metabolic syndrome score among women was due to adjustment for parity that was negatively correlated with sitting time and positively correlated with metabolic syndrome scores. In these cross-sectional data, one additional sitting hour per weekend day was associated with 5.6% (men $p=0.046$) and 8.6% (women $p=0.05$) higher risk of metabolic syndrome. Adjusting for RHR moderately reduced the correlation of sitting time with arterial stiffness among men ($p<0.05$), and adjusting for fatness (BMI or waist or skinfolds), and either the continuous metabolic syndrome score or individual components of metabolic

syndrome, only slightly reduced the correlation of sitting time with arterial stiffness (not shown).

Table 7.2. Rank correlations of sitting time with measures of cardiorespiratory fitness and physical activity

Sitting time	CRF	VLPA	Total PA†	Average steps/day
Men				
Per week	−0.07 *	−0.01	−0.42 ***	−0.37 ***
Per weekday	−0.05	0.01	−0.43 ***	−0.38 ***
Per weekend day	−0.14 ***	−0.10 **	−0.19 ***	−0.21 ***
Women				
Per week	0.03	0.03	−0.29 ***	−0.20 ***
Per weekday	0.05	0.04	−0.31 ***	−0.19 ***
Per weekend day	−0.08 *	−0.07 *	−0.13 ***	−0.18 ***

Abbreviations: CRF (cardiorespiratory fitness), VLPA (vigorous leisure-time physical activity, hour/week), Total PA (total MET.hour/week).

*p<0.05; **p<0.01; ***p<0.001

†Including moderate-to-vigorous physical activity.

Table 7.3. Rank correlations of sitting time with arterial stiffness and other cardio-metabolic risk factors

Sitting time	CD	SI	YEM	RHR	Skinfolds	cMetS
Men						
Un-adjusted correlation						
Per weekday	−0.05	0.08 *	0.02	0.08 **	0.05	−0.00
Per weekend day	−0.12 **	0.12 ***	0.09 **	0.13 ***	0.06	0.08 **
Adjusted correlation[a]						
Per weekday	−0.05	0.08 *	0.03	0.08 **	0.05	0.01
Per weekend day	−0.11 **	0.11 **	0.10 **	0.11 ***	0.06 *	0.07 *
Women						
Un-adjusted correlation						
Per weekday	−0.01	−0.01	0.01	−0.03	0.04	−0.00
Per weekend day	−0.07 *	0.06	0.05	0.00	0.10 **	0.08 *
Adjusted correlation[a]						
Per weekday	−0.01	0.00	0.03	0.01	0.06	0.04
Per weekend day	−0.09 *	0.08 *	0.08 *	0.02	0.11 **	0.12 **

Abbreviations: CD (carotid distensibility), SI (stiffness index), YEM (Young's elastic modulus), RHR (resting heart rate) and cMetS (continuous metabolic syndrome score).

*p<0.5; **p<0.01; ***p<0.001

[a]Adjusted for vigorous leisure-time physical activity, time spent on strength training, age, education, smoking, diet and alcohol, and for parity (women only).

Discussion

This study showed positive associations of sitting time per weekend day, but not per weekday, with arterial stiffness and other cardio-metabolic risk factors. These associations were independent of self-reported and objectively-measured physical activity, cardiorespiratory fitness and other potential confounders. The association of sitting time with arterial stiffness was not fully explained by RHR, fatness or metabolic syndrome, which are considered as potential mediators in this association.

Confidence in the reliability of our measures of sedentary behaviour in our study is strengthened by their plausible associations with sex, levels of education, and self-reported and objectively-measured physical activity. The greater role of sitting time per weekend day in prediction of arterial stiffness and cardio-metabolic risks than that of sitting time per weekday may be due to better discrimination of discretionary sitting behaviour. Sedentary behaviours are ubiquitous in contemporary society, and many occupations require a person to remain sedentary during weekdays.[32] An obvious example is office-based workers who have to spend many hours sitting during weekdays, and have more freedom to be physically active during non-working days that are usually weekends. This is consistent with our results because 54% of the participants in our study reported sitting at least five hours per weekday whereas 39% of them reported sitting at least five hours per weekend day, and objectively-measured cardiorespiratory fitness was negatively associated with sitting time per weekend day but not with sitting time per weekday.

A recent review suggests that prolonged sitting may be an independent cardiovascular risk factor.[7] In this study, we have shown a positive association of sitting time with arterial stiffness and, consistently with previous findings of adverse health effects of being sedentary that were independent of physical activity,[7] adjusting for physical activity made little difference to the association of sitting time with arterial stiffness in our study. Because arterial stiffness independently predicts mortality,[33] this relationship between sitting time and arterial stiffness may be a possible pathway through which sedentary behaviours are associated with mortality as reported in other studies.[11, 12, 14] Although Moreau *et al*[34] have suggested the greater carotid artery compliance in habitually exercising than sedentary postmenopausal women is mediated by an absence of oxidative stress, the mechanisms through which sedentary behaviour may influence arterial stiffness remain poorly understood. Unlike associations of physical activity or cardiorespiratory fitness with arterial stiffness, which we found to be mediated by RHR in our study,[25] the association of sitting time with arterial

stiffness was not mediated by RHR, fatness, metabolic syndrome or individual components of metabolic syndrome. Future studies are needed to explore the physiological mechanisms underlying the association of sitting time with arterial stiffness.

This study used a large national sample of young Australians on whom standardised measurements were made of an extensive range of study factors. To our knowledge, this is the first study that shows a positive association of sitting time with arterial stiffness in such a large population-based sample. The use of sitting time from self-report, rather than from objective measurements by accelerometers, is a limitation of our study. However, the self-reported sitting time in our study was well correlated with physical activity objectively-measured by pedometers and cardiorespiratory fitness objectively-measured by bicycle ergometry. The cross-sectional design of this study limits the causal inferences concerning the relationships of sitting time with arterial stiffness. We cannot rule out the possibility of a reverse causation whereby participants with greater arterial stiffness might be more sedentary in consequence. However, our findings on these young, generally-healthy adults who were unaware of their levels of arterial stiffness link well with previous findings on the deleterious effects of sedentary behaviour on health, and may suggest a possible pathway through which too much sitting may lead to higher risk of mortality.

Conclusions

In conclusion, our study shows positive associations of sitting time with arterial stiffness and other cardio-metabolic risk factors, independently of physical activity, and attributes a greater predictive value of these health outcomes to sitting time per weekend day than sitting time per weekday among young adults. This may be due to greater capability of sitting time during weekends in reflecting discretionary sitting behaviour of an individual, whereas sitting time during weekdays is probably more determined by occupational requirements. The association of sitting time with arterial stiffness was not fully explained by RHR, fatness or metabolic syndrome.

Postscript

The findings presented in the current and previous chapters demonstrated the relationships of fatness, fitness, vigorous physical activity and sedentary behavior with vascular health. The next chapter will summarise all these findings, and discuss their public health implications and future directions of research.

References

1. Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Actual causes of death in the United States, 2000. *JAMA*. 2004;291(10):1238-45.

2. Tanaka H, Dinenno FA, Monahan KD, Clevenger CM, DeSouza CA, Seals DR. Aging, habitual exercise, and dynamic arterial compliance. *Circulation*. 2000;102(11):1270-5.

3. Sugawara J, Otsuki T, Tanabe T, Hayashi K, Maeda S, Matsuda M. Physical activity duration, intensity, and arterial stiffening in postmenopausal women. *Am J Hypertens*. 2006;19(10):1032-6.

4. Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. *Med Sci Sports Exerc*. 2008;40(1):181-8.

5. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, *et al.* Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc*. 2000;32(9 Suppl):S498-504.

6. Sedentary Behaviour Research N. Letter to the editor: standardized use of the terms "sedentary" and "sedentary behaviours". *Appl Physiol Nutr Metab*. 2012;37(3):540-2.

7. Dunstan DW, Thorp AA, Healy GN. Prolonged sitting: is it a distinct coronary heart disease risk factor? *Curr Opin Cardiol*. 2011;26(5):412-9.

8. Thorp AA, Healy GN, Owen N, Salmon J, Ball K, Shaw JE, Zimmet PZ, Dunstan DW. Deleterious associations of sitting time and television viewing time with cardiometabolic risk biomarkers: Australian Diabetes, Obesity and Lifestyle (AusDiab) study 2004-2005. *Diabetes Care*. 2010;33(2):327-34.

9. Wijndaele K, Healy GN, Dunstan DW, Barnett AG, Salmon J, Shaw JE, Zimmet PZ, Owen N. Increased cardiometabolic risk is associated with increased TV viewing time. *Med Sci Sports Exerc*. 2010;42(8):1511-8.

10. Healy GN, Matthews CE, Dunstan DW, Winkler EA, Owen N. Sedentary time and cardio-metabolic biomarkers in US adults: NHANES 2003-06. *Eur Heart J*. 2011;32(5):590-7.

11. Dunstan DW, Barr EL, Healy GN, Salmon J, Shaw JE, Balkau B, *et al.* Television viewing time and mortality: the Australian Diabetes, Obesity and Lifestyle Study (AusDiab). *Circulation*. 2010;121(3):384-91.

12. Patel AV, Bernstein L, Deka A, Feigelson HS, Campbell PT, Gapstur SM, Colditz GA, Thun MJ. Leisure time spent sitting in relation to total mortality in a prospective cohort of US adults. *Am J Epidemiol*. 2010;172(4):419-29.

13. Warren TY, Barry V, Hooker SP, Sui X, Church TS, Blair SN. Sedentary behaviors increase risk of cardiovascular disease mortality in men. *Med Sci Sports Exerc*. 2010;42(5):879-85.

14. Stamatakis E, Hamer M, Dunstan DW. Screen-based entertainment time, all-cause mortality, and cardiovascular events: population-based study with ongoing mortality and hospital events follow-up. *J Am Coll Cardiol*. 2011;57(3):292-9.

15. Wijndaele K, Brage S, Besson H, Khaw KT, Sharp SJ, Luben R, Wareham NJ, Ekelund U. Television viewing time independently predicts all-cause and cardiovascular mortality: the EPIC Norfolk study. *Int J Epidemiol*. 2011;40(1):150-9.

16. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part I: aging arteries: a "set up" for vascular disease. *Circulation*. 2003;107(1):139-46.

17. Dwyer T, Gibbons LE. The Australian Schools Health and Fitness Survey. Physical fitness related to blood pressure but not lipoproteins. *Circulation*. 1994;89(4):1539-44.

18. Huynh Q, Blizzard L, Sharman J, Magnussen C, Schmidt M, Dwyer T, Venn A. Relative contributions of adiposity in childhood and adulthood to vascular health of young adults. *Atherosclerosis*. 2013;228(1):259-64.

19. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, *et al.* International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc*. 2003;35(8):1381-95.

20. Schmidt MD, Cleland VJ, Thomson RJ, Dwyer T, Venn AJ. A comparison of subjective and objective measures of physical activity and fitness in identifying associations with cardiometabolic risk factors. *Ann Epidemiol*. 2008;18(5):378-86.

21. Cleland VJ, Schmidt MD, Salmon J, Dwyer T, Venn A. Correlates of pedometer-measured and self-reported physical activity among young Australian adults. *J Sci Med Sport*. 2011;14(6):496-503.

22. Withers RT, Davies GJ, Crouch RG. A comparison of three W170 protocols. *Eur J Appl Physiol Occup Physiol*. 1977;37(2):123-8.

23. Buskirk E, Taylor HL. Maximal oxygen intake and its relation to body composition, with special reference to chronic physical activity and obesity. *J Appl Physiol*. 1957;11(1):72-8.

24. Dwyer T, Magnussen CG, Schmidt MD, Ukoumunne OC, Ponsonby AL, Raitakari OT, *et al.* Decline in physical fitness from childhood to adulthood associated with increased obesity and insulin resistance in adults. *Diabetes Care*. 2009;32(4):683-7.

25. Quan HL, Blizzard CL, Sharman JE, Magnussen CG, Dwyer T, Raitakari O, Cheung M, Venn AJ. Resting Heart Rate and the Association of Physical Fitness With Carotid Artery Stiffness. *Am J Hypertens*. 2013 (doi: 10.1093/ajh/hpt161).

26. Magnussen CG, Fryer J, Venn A, Laakkonen M, Raitakari OT. Evaluating the use of a portable ultrasound machine to quantify intima-media thickness and flow-mediated dilation: agreement between measurements from two ultrasound machines. *Ultrasound Med Biol*. 2006;32(9):1323-9.

27. Schmidt MD, Dwyer T, Magnussen CG, Venn AJ. Predictive associations between alternative measures of childhood adiposity and adult cardio-metabolic health. *Int J Obes (Lond)*. 2011;35(1):38-45.

28. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18(6):499-502.

29. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, *et al.* Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120(16):1640-5.

30. Wijndaele K, Beunen G, Duvigneaud N, Matton L, Duquet W, Thomis M, Lefevre J, Philippaerts RM. A continuous metabolic syndrome risk score: utility for epidemiological analyses. *Diabetes Care*. 2006;29(10):2329.

31. Smith KJ, McNaughton SA, Gall SL, Blizzard L, Dwyer T, Venn AJ. Takeaway food consumption and its associations with diet quality and abdominal obesity: a cross-sectional study of young adults. *Int J Behav Nutr Phys Act*. 2009;6:29.

32. Matthews CE, Chen KY, Freedson PS, Buchowski MS, Beech BM, Pate RR, Troiano RP. Amount of time spent in sedentary behaviors in the United States, 2003-2004. *Am J Epidemiol*. 2008;167(7):875-81.

33. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, *et al.* Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J*. 2006;27(21):2588-605.

34. Moreau KL, Gavin KM, Plum AE, Seals DR. Oxidative stress explains differences in large elastic artery compliance between sedentary and habitually exercising postmenopausal women. *Menopause*. 2006;13(6):951-8.

Chapter 8

Summary, implications, future directions and conclusions

Chapter 8. Summary, implications, future directions and conclusions

Summary of background

Cardiovascular disease (CVD) is the leading cause of death worldwide,[1] and is predicted to remain so in the next couple of decades.[2] It is suggested that CVD has a long process of development through the life course and has origins from very early periods in life, and even from childhood.[3-5] This evidence implicates the need to understand the determinants of early stages of CVD for long-term reduction of CVD risk. Because cardiovascular events do not typically occur until older ages, studies of the early stages of CVD among young people previously had to rely on autopsy studies or required invasive methods. The advancement of novel non-invasive techniques such as ultrasound during the 1990s opened a new era of using subclinical markers of CVD among young and apparently healthy individuals for large population-based studies, which had not been possible before. These markers, including measures of the structure (intima-media thickness – IMT) and stiffness of the carotid artery, are strong predictors of major cardiovascular events and mortality,[6-9] and can be used to predict early stages of CVD. Improved understanding of the determinants of these measures among young people may therefore lead to targeted early interventions to reduce CVD risk. This research examined the associations of the lifestyle factors – including fatness, fitness, physical activity and sedentary behaviour – with arterial structure and stiffness among young and mid-aged adults, and aimed to shed light on the possible mechanisms involved. The novel findings from this research make important contributions to improved understanding of the lifestyle determinants of vascular health among young adults.

The following sections summarise the principal findings of the studies presented in this thesis and discuss their strengths and limitations, public health implications and directions for future research.

Summary of results

The key findings from this thesis are summarised as follows:

First, large artery stiffness appears to play a more prominent role in the pathophysiology of obesity-induced hypertension for Caucasians than for Asians. In a comparison of the relationship of body size and fatness with blood pressure in population-based samples of Australian and Vietnamese people, the positive association of body size and fatness with pulse pressure found in the Caucasian sample may be indicative of increased large artery stiffness. The positive associations of body size and fatness with both systolic and diastolic blood pressure in the Asian sample were more typical of essential hypertension. This is possibly due to increased circulatory volume and/or increased peripheral vascular resistance. These associations were independent of years of smoking, alcohol consumption, consumption of fruit and vegetables, self-reported physical activity, and fasting blood total cholesterol and glucose.

Second, carotid artery stiffness and carotid IMT (measured by carotid ultrasound) in adulthood were associated with body size and fatness in both childhood and adulthood. While arterial stiffness depended primarily on adult body size and fatness and was greatest for obese adults who were normal weight in childhood, carotid IMT appeared to be influenced by body size and fatness in both childhood and adulthood. These findings add to evidence suggesting that CVD has origins from obesity in childhood.

Third, carotid artery stiffness among young adults was negatively associated with cardiorespiratory fitness (CRF), but was positively associated with muscular strength, both independently of adult body size and fatness. While greater CRF may reduce arterial stiffness mainly through lower resting heart rate (RHR), greater muscular strength may have deleterious effects on arterial stiffness that are partially offset by lower RHR. These results, for the first time, attribute a key intermediary role to RHR in the association of physical fitness with arterial stiffness.

Fourth, carotid artery stiffness among young and mid-aged adults in samples of the Australian and Finnish populations was negatively associated with vigorous physical activity, but not with less intensive forms of physical activity or number of steps per day. Similar to the relationship between CRF and arterial stiffness, participation in vigorous physical activity may also reduce arterial stiffness through lower RHR, independently of body size and fatness.

These findings, for the first time, shed light on the possible mechanisms involved in the relationship between vigorous physical activity and arterial stiffness, and strengthen the evidence of the potential cardioprotective benefits of vigorous physical activity that are beyond those achieved by less intensive forms of physical activity.

Fifth, carotid artery stiffness was positively associated with sitting time per weekend day, but not with sitting time per weekday, independent of physical activity and CRF. For the first time, these findings show a detrimental association of sitting time with arterial stiffness, and suggest that sitting time during weekends rather than weekdays predict arterial stiffness and other cardio-metabolic risk factors in this population of young adults. This may be due to greater capacity of recollection of sitting time during weekends than weekdays to accurately reflect discretionary sedentary behaviour of young adults in this population. These novel findings advance our knowledge in relation to the possibly harmful effects of prolonged sitting periods on health. Unlike CRF and vigorous physical activity that may reduce arterial stiffness through lower RHR, the relationship of sitting time with arterial stiffness was not mediated by RHR, body size and fatness, and metabolic syndrome. Further research is needed to investigate the possible mechanisms involved.

Strengths and limitations of this research

This research has several strengths. First, all the participants included in the five studies were from large population-based samples that were each selected by multi-stage random sampling. Second, an extensive range of study factors were measured using standardised protocols in each study included in this research. These factors included potential mediators, effect modifiers and confounders that were able to be investigated in the analytical process. This approach not only contributed to shedding light, for the first time, on the possible mechanisms involved in the relationship of physical activity and fitness with arterial stiffness, but also made the findings from this research more likely to be free of confounding bias. Third, most of the participants included in this research were young adults. While many studies of vascular health have focused on adults at older age, less information is available for younger adults. Thus the findings of this research help to fill one of the evidence gaps, and improve our knowledge of the determinants of vascular health among younger adults. Fourth, the consistent findings on the relationship between vigorous physical activity and arterial stiffness among Australians and Finns, despite their cultural and environmental differences, strengthened the confidence that can be placed in the external validity of the results from this research.

There are also a number of limitations that need to be considered when interpreting the findings from this research. First, the cross-sectional analysis in four out of five studies included in this research is a limitation. This limits the causal inferences that can be drawn about the relationship between the exposures and the outcomes of those studies. For example, the possibility of a reverse causation in the relationship of physical activity and fitness, and of sedentary behaviours, with carotid artery stiffness (where individuals with higher arterial stiffness may tend to be less physically active and more sedentary) cannot be ruled out. However, the findings from this research link well to previous findings of intervention studies making the possibility of a reverse causation less likely.

Second, although the Burnie Take Heart project and the Can Tho survey had good response rates (69% and 74% respectively), the loss to follow-up in the Childhood Determinants of Adult Health study and the Cardiovascular Risk in Young Finns study is another limitation. This may have caused selection bias if the association of the exposure with the outcome was different among participants and non-participants. However, this research was an analytical investigation using large population-based samples from well-characterised study populations for which the distributional range of confounders and effect modifiers was not restricted by sampling or diminished by attrition. Threats to external validity are therefore less of an issue in these circumstances.[10] In addition, the probability of participation at follow-up was calculated for each subject at baseline. This information was used in sensitivity analyses to weight the association of interest by using inverse probability weighting. This estimated the association with non-participants at follow-up represented by participants who had similar characteristics to them at baseline. The results were very similar to those presented in this thesis. Therefore it is unlikely that the results were influenced by loss to follow-up. Reporting bias was also unlikely because the studies used data from large population-based samples, and included young and apparently healthy adults who were not aware of their levels of arterial stiffness.

Third, unmeasured potential confounders may be another potential limitation of this research. An example is sodium intake, which may influence arterial stiffness.[11, 12] Fourth, using accelerometers may have minimised measurement errors on participants' physical activity and sedentary behaviour compared with using pedometers and a self-reported questionnaire. However, the high cost of accelerometers greatly reduces their feasibility in such large population-based studies. In addition, confidence in the reliability of the self-reported measures of physical activity in this research is strengthened by their plausible associations

with demographic measures, socio-economic status, physical measures (including objectively-measured CRF, fatness, RHR and blood biomarkers) and pedometer-measured steps per day.

Public health implications

The research findings presented in this thesis show the associations of different lifestyle risk factors with vascular health. Given that there are currently no medications that are specifically targeted at improving arterial structure and stiffness, any lifestyle modifications that can do so may have heightened importance as potential targets of interventions to reduce cardiovascular risk. The findings from this research not only show the possible benefits of early lifestyle interventions to improve vascular health among young persons, but also, for the first time, shed light on the possible mechanisms involved. These findings have several important public health implications that are discussed in the following text.

A different pathophysiology related to obesity-induced hypertension has, for the first time, been suggested among Caucasians in comparison to Asians and is presented in Chapter 3 of this thesis. The findings suggest a pathway involving increased large artery stiffness among Caucasians, but increased circulatory volume and/or increased peripheral vascular resistance that may be related to higher salt intake among Asians.[13] These findings may suggest a possibility of different approaches to treatment of hypertension in the two populations, and underline the importance of interventions to reduce obesity (probably through diet and physical activity) in prevention of hypertension. Our findings are also consistent with evidence suggesting a restriction in salt intake, particularly among Asians, to prevent hypertension.

Using more direct measures of vascular health assessed by ultrasound examination, the findings from Chapter 4 of this thesis demonstrated that obesity in both childhood and adulthood may influence adult vascular health. While child obesity may influence adult carotid IMT independently of adult obesity, weight gain from childhood to adulthood may be important in determining arterial stiffness in adulthood because the obese adult participants who were normal weight in childhood had the greatest arterial stiffness. Our data show that children as young as seven years of age who have greater body size and fatness than their counterparts may have thicker carotid IMT and greater arterial stiffness in adulthood because they are more likely to become overweight or obese adults. These findings not only strengthen the evidence of childhood origins of adult CVD, but also emphasise that early interventions to

reduce obesity and maintain healthy weight from childhood to adulthood are needed to reduce CVD risk.

As discussed, reduction of obesity in both childhood and adulthood is needed to reduce CVD risk. However, obesity clearly has many behavioural and genetic determinants that are not easy to address. Although obesity is now widely accepted as a major CVD risk factor,[14] and despite actions that have been undertaken at individual and population levels to reduce obesity, many overweight or obese people remain overweight or obese for many years.[15] In the contemporary population-based sample of young Australians included in this research, of those who were classified as overweight or obese in childhood (7–15 years, n=259), 88% (n=227) remained overweight or obese as adults 20 years later when they were aged 26–36 years. It is therefore encouraging for these people that doing physical activity and improving CRF may reduce CVD mortality independently of the effects on weight loss.[16, 17] The findings presented in Chapter 5 strengthen this evidence by showing that, independently of body size and fatness, having greater CRF was negatively associated with arterial stiffness – which independently predicts mortality[18] – even among young and apparently healthy adults with low levels of arterial stiffness. In line with this, the findings presented in Chapter 6 point out that young and mid-aged adults who participate in vigorous physical activity have lower arterial stiffness. These findings are very consistent with each other because CRF was more strongly associated with vigorous physical activity than with light-to-moderate physical activity, and are consistent with findings from other studies showing greater reduction in blood pressure and glucose produced by vigorous physical activity than produced by light-to-moderate physical activity even when the total energy expenditure is held equivalent.[19] The evidence on the potential extra benefits of vigorous physical activity should be emphasised more strongly as it is in the National Physical Activity Guidelines for Australians.[20] This is necessary to encourage people to achieve greater health benefits from vigorous physical activity, and to change the thinking that similar benefits can be achieved by either vigorous or moderate physical activity, but with longer time required for moderate physical activity.[21]

For the first time, the findings from this research suggest the possible mechanisms involved in the associations of vigorous physical activity and CRF with arterial stiffness, and attribute a key intermediary role to RHR in these relationships. These findings contribute to filling the evidence gap in the relationship of exercise training with vascular health. They also strengthen the evidence on the positive association of high RHR with increased arterial stiffness.[22, 23] Because both high RHR and arterial stiffness are reported to independently

predict greater mortality,[18, 24] any future studies of arterial stiffness predicting mortality should take account of RHR, which has never been done before.

Muscular strength, on the other hand, was positively associated with arterial stiffness among young adults. This finding is consistent with those of many intervention studies that show detrimental effects of strength training on arterial stiffness.[25-28] It is nevertheless inconsistent with some other studies showing no change[29] or even a decrease in arterial stiffness[30] following strength training. For the first time, the findings from this research propose two offsetting pathways that may be involved in the relationship of muscular strength with arterial stiffness. They include one pathway with a positive association of muscular strength with arterial stiffness, and one pathway with a negative association of muscular strength with arterial stiffness that is mediated by lower RHR. The total effect of increased muscular strength on arterial stiffness is the net effect of these two pathways. These findings not only help to reconcile the previous inconsistent findings on the effect of strength training on arterial stiffness, but also strengthen the evidence for strength training to improve general health in physical activity guidelines.[22, 23]

The research reported in Chapter 7 of this thesis examined the relationship of a recently recognised lifestyle risk factor – sedentary behaviour – with arterial stiffness and, for the first time, shows a positive relationship of sitting time with arterial stiffness that was independent of physical activity, CRF, and body size and fatness. These findings advance our knowledge of the possible detrimental effects of sedentary behavior on health, and demonstrate the importance of minimising prolonged periods of being sedentary, in addition to doing physical activity and improving CRF, to reduce CVD risk.

Future directions

Longitudinal studies are needed to confirm the cross-sectional findings reported in this thesis, and to examine the long-term effects of doing vigorous physical activity and reducing sedentary time on vascular health. This will be possible with future follow-ups of the Childhood Determinants of Adult Health (CDAH) study and the Cardiovascular Risk Factor in Young Finns study.

Longitudinal studies with multiple follow-up time-points from childhood to adulthood are needed to investigate whether there are particularly sensitive periods of exposure to obesity that are associated with vascular health in adulthood. Reducing obesity and maintaining

healthy weight from childhood to adulthood are important but not easy to achieve. Thus understanding the most sensitive periods of exposure may help to set up more effective interventions to reduce CVD risk through reducing obesity. Having multiple follow-up time-points is also necessary to investigate the effects of changing lifestyles (for example, from being sedentary to being physically active or vice versa) on vascular health. This may be possible using data from the Cardiovascular Risk in Young Finns study that collected physical measurements at multiple time-points from childhood to adulthood and, together with the CDAH study, is a member cohort of the International Childhood Cardiovascular Cohort (i3C) consortium.

Longitudinal studies with follows-up into old ages are needed to investigate the relationship of childhood risk factors with major CVD events in late adulthood, and to confirm whether modifications of childhood risk factors to improve vascular health in young adulthood can translate to lower risk of major CVD events. Because CVD events are rare in young adulthood, it requires a long-term follow-up of the CDAH study before these findings can be confirmed. This research is possible using currently-held data from the i3C consortium that includes several cohort studies similar to the CDAH study and constitutes a very large number of participants that can be used to investigate rare events.

In addition to observational studies, intervention studies may be needed to confirm the effects of physical activity at different levels of intensity on vascular health among people of different age groups. This will be helpful in recommending physical activity for specific age groups of the population. Intervention studies are also needed to confirm the intermediary role of RHR in the relationship of exercise training to improve CRF with arterial stiffness. Novel indicators of arterial stiffness (such as arterial reservoir[31, 32]) may also be used to strengthen our findings on carotid artery stiffness.

Although the findings from this research suggest the associations of fatness and fitness with vascular health to be independent of each other, more research is needed to examine the vascular health of persons who are consistently obese but physically fit. As shown in this research, the majority of obese participants remain obese for many years. It is therefore important to confirm the effects of improving CRF on vascular health among people who are consistently obese from childhood to adulthood. Because the number of those who are obese but fit is apparently small, it will require either cohort studies with a very large sample (such as collectively the i3C consortium) or intervention studies to confirm the findings.

Conclusions

Taken together, the findings from this research highlight the importance of lifestyle risk factors in predicting vascular health among young to mid-aged adults. They suggest that efforts to improve vascular health, and thereby to reduce CVD risk, among these younger adults should be simultaneously targeted at reducing obesity, encouraging vigorous physical activity, improving CRF and reducing sedentary behaviour to maximise the total beneficial effects on vascular health.

References

1. The Global Burden of Disease: 2004 update. Geneva: World Health Organization; 2008.

2. World Health Statistics 2012. Geneva: World Health Organization; 2012.

3. McGill HC, Jr., Geer JC, Strong JP. Natural history of human atherosclerotic lesions. In: Sandler M, Bourne GH, editors. Atherosclerosis and its origin. New York: Academic Press; 1963. p. 39-65.

4. Berenson GS, Wattigney WA, Tracy RE, Newman WP, 3rd, Srinivasan SR, Webber LS, Dalferes ER, Jr., Strong JP. Atherosclerosis of the aorta and coronary arteries and cardiovascular risk factors in persons aged 6 to 30 years and studied at necropsy (The Bogalusa Heart Study). *Am J Cardiol*. 1992;70(9):851-8.

5. McGill HC, Jr., McMahan CA, Zieske AW, Tracy RE, Malcom GT, Herderick EE, Strong JP. Association of Coronary Heart Disease Risk Factors with microscopic qualities of coronary atherosclerosis in youth. *Circulation*. 2000;102(4):374-9.

6. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation*. 2007;115(4):459-67.

7. Blacher J, Pannier B, Guerin AP, Marchais SJ, Safar ME, London GM. Carotid arterial stiffness as a predictor of cardiovascular and all-cause mortality in end-stage renal disease. *Hypertension*. 1998;32(3):570-4.

8. Barenbrock M, Kosch M, Joster E, Kisters K, Rahn KH, Hausberg M. Reduced arterial distensibility is a predictor of cardiovascular disease in patients after renal transplantation. *J Hypertens*. 2002;20(1):79-84.

9. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;55(13):1318-27.

10. Miettinen O. Theoretical epidemiology. Principles of occurrence research in medicine. New York: Wiley; 1985.

11. Avolio AP, Clyde KM, Beard TC, Cooke HM, Ho KK, O'Rourke MF. Improved arterial distensibility in normotensive subjects on a low salt diet. *Arteriosclerosis*. 1986;6(2):166-9.

12. Gates PE, Tanaka H, Hiatt WR, Seals DR. Dietary sodium restriction rapidly improves large elastic artery compliance in older adults with systolic hypertension. *Hypertension*. 2004;44(1):35-41.

13. Brown IJ, Tzoulaki I, Candeias V, Elliott P. Salt intakes around the world: implications for public health. *Int J Epidemiol*. 2009;38(3):791-813.

14. Eckel RH. Obesity and heart disease: a statement for healthcare professionals from the Nutrition Committee, American Heart Association. *Circulation*. 1997;96(9):3248-50.

15. Singh AS, Mulder C, Twisk JW, van Mechelen W, Chinapaw MJ. Tracking of childhood overweight into adulthood: a systematic review of the literature. *Obes Rev*. 2008;9(5):474-88.

16. Gregg EW, Cauley JA, Stone K, Thompson TJ, Bauer DC, Cummings SR, Ensrud KE. Relationship of changes in physical activity and mortality among older women. *JAMA*. 2003;289(18):2379-86.

17. Lee DC, Sui X, Artero EG, Lee IM, Church TS, McAuley PA, *et al.* Long-term effects of changes in cardiorespiratory fitness and body mass index on all-cause and cardiovascular disease mortality in men: the aerobics center longitudinal study. *Circulation*. 2011;124(23):2483-90.

18. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, *et al.* Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J*. 2006;27(21):2588-605.

19. Swain DP, Franklin BA. Comparison of cardioprotective benefits of vigorous versus moderate intensity aerobic exercise. *Am J Cardiol*. 2006;97(1):141-7.

20. National physical activity guidelines for Australians. Canberra: Australian Government Department of Health and Ageing 1999.

21. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, *et al.* Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation*. 2007;116(9):1081-93.

22. Sa Cunha R, Pannier B, Benetos A, Siche JP, London GM, Mallion JM, Safar ME. Association between high heart rate and high arterial rigidity in normotensive and hypertensive subjects. *J Hypertens*. 1997;15(12 Pt 1):1423-30.

23. Tomiyama H, Hashimoto H, Tanaka H, Matsumoto C, Odaira M, Yamada J, *et al.* Synergistic relationship between changes in the pulse wave velocity and changes in the heart rate in middle-aged Japanese adults: a prospective study. *J Hypertens*. 2010;28(4):687-94.

24. Palatini P, Benetos A, Grassi G, Julius S, Kjeldsen SE, Mancia G, *et al.* Identification and management of the hypertensive patient with elevated heart rate: statement of a European Society of Hypertension Consensus Meeting. *J Hypertens*. 2006;24(4):603-10.

25. Miyachi M, Kawano H, Sugawara J, Takahashi K, Hayashi K, Yamazaki K, Tabata I, Tanaka H. Unfavorable effects of resistance training on central arterial compliance: a randomized intervention study. *Circulation*. 2004;110(18):2858-63.

26. Cortez-Cooper MY, DeVan AE, Anton MM, Farrar RP, Beckwith KA, Todd JS, Tanaka H. Effects of high intensity resistance training on arterial stiffness and wave reflection in women. *Am J Hypertens*. 2005;18(7):930-4.

27. DeVan AE, Anton MM, Cook JN, Neidre DB, Cortez-Cooper MY, Tanaka H. Acute effects of resistance exercise on arterial compliance. *J Appl Physiol*. 2005;98(6):2287-91.

28. Heffernan KS, Collier SR, Kelly EE, Jae SY, Fernhall B. Arterial stiffness and baroreflex sensitivity following bouts of aerobic and resistance exercise. *Int J Sports Med*. 2007;28(3):197-203.

29. Rakobowchuk M, McGowan CL, de Groot PC, Bruinsma D, Hartman JW, Phillips SM, MacDonald MJ. Effect of whole body resistance training on arterial compliance in young men. *Exp Physiol*. 2005;90(4):645-51.

30. Okamoto T, Masuhara M, Ikuta K. Home-based resistance training improves arterial stiffness in healthy premenopausal women. *Eur J Appl Physiol*. 2009;107(1):113-7.

31. Davies JE, Hadjiloizou N, Leibovich D, Malaweera A, Alastruey-Arimon J, Whinnett ZI, *et al.* Importance of the aortic reservoir in determining the shape of the arterial pressure waveform – the forgotten lessons of Frank. *Artery Research*. 2007;1:40-5.

32. Davies JE, Baksi J, Francis DP, Hadjiloizou N, Whinnett ZI, Manisty CH, *et al.* The arterial reservoir pressure increases with aging and is the major determinant of the aortic augmentation index. *Am J Physiol Heart Circ Physiol*. 2010;298(2):H580-6.

Appendix 9

The International Physical Activity Questionnaire

Appendix 9. The International Physical Activity Questionnaire

7394203480

OFFICE USE ONLY

SCAN	VERIFY	CHECK

☐☐☐☐ 1

OFFICE USE ONLY

(Clinic staff attach bar code here)

SECTION A: CURRENT ACTIVITIES

The following questions will ask you about the time you spent being physically active in the last 7 days. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Please answer each question even if you do not consider yourself to be an active person.

Think about all the **vigorous** and **moderate** activities that you have done **in the last 7 days.**

- **Vigorous** physical activities refer to activities that take **hard** physical effort and make you breathe much harder than normal.
- **Moderate** activities refer to activities that take moderate physical effort and make you breathe **somewhat** harder than normal

PART 1: WORK RELATED PHYSICAL ACTIVITY
The first section is about your work. This includes paid jobs, farming, volunteer work, course work, and any other unpaid work that you did outside your home.

Do not include unpaid work you might do around your home, like housework, yard work, general maintenance, and caring for your family. We ask about these in Part 3.

1. Do you currently have a job or do any unpaid work outside your home?

   No O --> **SKIP TO PART 2, TRANSPORTATION**

   Yes O

The next questions are about all the physical activity you did in the last 7 days as part of your paid or unpaid work. This does not include travelling to and from work.

2. During the **last 7 days**, on how many days did you do vigorous physical activities like heavy lifting, digging, heavy construction, or climbing up stairs **as part of your work**?
   Think about only those physical activities that you did for **at least 10 minutes** at a time.

   ☐ days per week

   O No vigorous job-related physical activity --> **SKIP TO Question 4**

3. How much time did you usually spend on one of those days doing vigorous physical activities as part of your work?

   ☐☐ hours ☐☐ minutes **Per day**

5971203489 ☐☐☐☐ 2

4. Again, think about only those physical activities that you did for **at least 10 minutes** at a time. During **the last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads as part of your work? Please DO NOT include walking.

☐ days per week

O No moderate job-related physical activity **--> SKIP TO Question 6**

5. How much time did you **usually** spend on **one** of those days doing **moderate** physical activities as part of your work?

☐☐ hours ☐☐ minutes **Per day**

6. During the last 7 days, on how many days did you walk for **at least 10 minutes** at a time as part of your work? Please do not count any walking you did to travel to, or from work.

☐ days per week

O No job-related walking**--> Skip to PART 2: TRANSPORTATION**

7. How much time did you usually spend on **one** of those days **walking** as part of your work?

☐☐ hours ☐☐ minutes **Per day**

PART 2: TRANSPORTATION PHYSICAL ACTIVITY
These questions are about how you travelled from place to place, including to places like work, stores, movies, and so on.

8. During the last 7 days, on how many days did you travel **in a motor vehicle** like a train, bus, car, or tram?

☐ days per week

O No motor transport **--> SKIP TO Question 10**

0547203483 ☐☐☐☐ 3

9. How much time did you **usually** spend in a motor vehicle on **one** of those days.

☐☐ hours ☐☐ minutes **Per day**

Now think only about the cycling and walking you might have done to travel to and from work, to do errands, or to go from place to place.

10. During **the last 7 days**, on how many days did you **cycle** for **at least 10 minutes** at a time to go from place to place?

☐ days per week

O No cycling from place to place **--> SKIP TO Question 12**

11. How much time did you usually spend on **one** of those days **cycling** from place to place?

☐☐ hours ☐☐ minutes **Per day**

12. During the last 7 days, on how many days did you **walk** for at **least 10 minutes** at a time to go from place to place?

☐ days per week

O No walking from place to place **--> SKIP TO PART 3: HOUSEWORK, MAINTENANCE AND CARING FOR FAMILY**

13. How much time did you usually spend on **one** of those days **walking** from place to place?

☐☐ hours ☐☐ minutes **Per day**

2201203482 ☐☐☐☐ 4

PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY
This section is about some of the physical activities you might have done in the last 7 days in and around your home, like housework, gardening, yard work, general maintenance work, and caring for your family

YARD WORK:

14. Think about only those physical activities that you did for **at least 10 minutes** at a time. During **the last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, chopping wood, shovelling snow, or digging in the garden or yard?

☐ days per week

O No vigorous yard activity **--> SKIP TO Question 16**

15. How much time did you usually spend on **one** of those days doing **vigorous** physical activities **in the garden or yard**?

☐☐ hours ☐☐ minutes **Per day**

16. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the last 7 days, on how many days did you do **moderate** activities like carrying light loads, sweeping, washing windows, and raking **in the garden or yard**?

☐ days per week

O No moderate yard activity **--> SKIP TO Question 18**

17. How much time did you usually spend on **one** of those days doing **moderate** physical activities **in the garden or yard**?

☐☐ hours ☐☐ minutes **Per day**

HOUSEWORK:

18. Once again, think about only those physical activities that you did for at least 10 minutes at a time. During the last 7 days, on how many days did you do **moderate** activities like carrying light loads, washing windows, scrubbing floors and sweeping **inside your home**?

☐ days per week

O No moderate activity at home **--> SKIP TO PART 4: RECREATION, SPORT, AND LEISURE-TIME PHYSICAL ACTIVITY**

19. How much time did you usually spend on **one** of those days doing **moderate** physical activities **inside your home**?

☐☐ hours ☐☐ minutes **Per day**

1515203489 ☐☐☐☐ 5

PART 4: RECREATION, SPORT, AND LEISURE-TIME PHYSICAL ACTIVITY
This section is about all the physical activities that you did in the last 7 days solely for recreation, sport, exercise or leisure. Please do not include any activities you have already mentioned.

20. Not counting any walking you have already mentioned, during **the last 7 days**, on how many days did you **walk** for **at least 10 minutes** at a time in your leisure time?

☐ days per week

O No leisure walking **--> SKIP TO Question 22**

21. How much time did you usually spend on **one** of those days **walking** in your leisure time?

☐☐ hours ☐☐ minutes **Per day**

22. Think about only those physical activities that you did for **at least 10 minutes** at a time. During **the last 7 days**, on how many days did you do **vigorous** physical activities like: aerobics, running, fast bicycling, or fast swimming in your leisure time?

☐ days per week

O No vigorous activity in leisure time **--> SKIP TO Question 24**

23. How much time did you usually spend on **one** of those days doing vigorous physical activities in your leisure time?

☐☐ hours ☐☐ minutes **Per day**

24. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the last 7 days, on how many days did you do **moderate** physical activities like: bicycling at a regular pace, swimming at a regular pace, and doubles tennis in your leisure time?

☐ days per week

O No moderate activity in leisure time **--> SKIP TO PART 5: TIME SPENT SITTING**

25. How much time did you usually spend on **one** of those days doing **moderate** physical activities in your leisure time?

☐☐ hours ☐☐ minutes **Per day**

9274203489 ☐☐☐☐ 6

PART 5: TIME SPENT SITTING
These last questions are about the time you spend sitting while at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television.
Do not include any time spent sitting in a motor vehicle that you have already told us about.

26. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekday**?

☐☐ hours ☐☐ minutes **Per day**

27. During the last 7 days, how much time did you usually spend **sitting** on a **weekend** day?

☐☐ hours ☐☐ minutes **Per day**

We are also interested in finding out about your television viewing and computer use habits

28. Please estimate the total time **during the last week** that you spent watching television, videos or DVD's when it was the **main** activity that you were doing.
For example, you should not include time when the television was switched on and you were preparing a meal or ironing.

Total time Monday to Friday ☐☐ hours ☐☐ minutes

Total time Saturday and Sunday ☐☐ hours ☐☐ minutes

29. Please estimate how often **in a usual week** you would have each of the following while watching television

	Always (every day)	Usually (5-6 times/week)	Sometimes (3-4 times/week)	Rarely (1-2 times/week)	Never
A Meal	O	O	O	O	O
A Snack	O	O	O	O	O
A soft drink	O	O	O	O	O
An alcoholic drink	O	O	O	O	O

I do not watch television O

30. Please estimate the total time **during the last week** that you spent using a computer during the week and on weekends (this might be a personal computer at home or work, Playstation, X-box, Gameboy, etc).

Total time Monday to Friday ☐☐ hours ☐☐ minutes

Total time Saturday and Sunday ☐☐ hours ☐☐ minutes