POOR GROWTH, SOCIAL INEQUALITIES AND CORONARY RISK

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DECLARATION OF ORIGINALITY

I, Claudia Langenberg, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that that this has been indicated in the thesis.

ABSTRACT

Data from 5 epidemiological studies, spanning an age range from childhood to late adult life, are used to investigate associations between components of height, used as markers of growth at different phases, and arterial stiffness, subclinical atherosclerosis and cardiovascular risk. The roles of prenatal growth and life course socioeconomic position are considered.

In the 1946 Birth Cohort, shorter leg, but not trunk length, was associated with greater pulse pressure, a measure of arterial stiffness, in adult men and women. Longitudinal analyses suggested that these effects were due to a steeper rise of blood pressure with age, independent of potential confounders and mediators considered. In the Whitehall II Study, shorter leg and trunk length were both associated with adverse levels of several cardiovascular risk factors and also lower distensibility and greater stiffness of the carotid arteries in men. In a cross-sectional examination of Filipino-American women, coronary disease was most strongly associated with leg length, while diabetes prevalence was not associated with measures of growth, but highest in women who were socioeconomically disadvantaged in childhood and adulthood. Higher blood pressure levels were observed in children with shorter leg length, relative to total body height, of a contemporary US birth cohort at age 3 years. The contribution of prenatal growth was considered in all studies where birthweight was available and found to be limited. Finally, results from the first Whitehall Study suggested that associations between stature and cardiovascular mortality may differ by socioeconomic position.

These findings lend some support to the hypothesis that factors limiting leg growth are associated with arterial stiffness, subclinical atherosclerosis and cardiovascular risk; these associations may originate in childhood and be amplified with age. The specificity of leg length as a marker of early influences on growth that alter cardiovascular risk is questioned.

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ABBREVIATIONS

BMI	Body Mass Index
CHD	Coronary Heart Disease
DBP	Diastolic Blood Pressure
DEXA	Dual-Energy X-Ray Absorptiometry
ER	Expected Range
FEV	Forced Expiratory Volume
HDL	High Density Lipoprotein
HR	Hazard Ratio
HRT	Hormone Replacement Therapy
IGF	Insulin-Like Growth Factor
IMT	Intima Media Thickness
LDL	Low Density Lipoprotein
MAP	Mean Arterial Pressure
NO	Nitric Oxide
NSHD	National Survey of Health and Development
PP	Pulse Pressure
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
WHR	Waist-Hip Ratio

95% CI95% Confidence Interval

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CHAPTER 1: INTRODUCTION

Atherosclerotic changes of the arterial wall are part of the pathophysiological basis of coronary heart disease (CHD) and stroke. Currently, preventive strategies focus on lowering the incidence of symptomatic disease, which rises with increasing age.

Early origins of atherosclerosis and cardiovascular disease

However, atherosclerotic changes leading to the thickening and hardening of the arterial walls have been observed as early as the prenatal period, and can be found in apparently healthy children and adolescents. (1;2) Aetiological studies investigating influences on the development of atherosclerosis may therefore provide important insights into the origins of cardiovascular disease.

Poor growth and cardiovascular disease

Recent evidence has suggested the importance of poor growth at different phases for cardiovascular morbidity and mortality, and this has led to speculations about growth limiting factors contributing to early atherogenesis and cardiovascular risk. The timing and nature of such factors remain unclear. To date, investigations have largely been restricted to white populations from Western Europe and North America and it remains unclear whether associations may differ in ethnic groups whose childhood conditions and determinants of their, on average, shorter height may differ from those born in industrialized and highly developed countries.

Phases of growth and subclinical vascular disease

Few studies have compared associations between markers of growth at different phases and specific measures of subclinical atherosclerosis, including vascular wall thickness, arterial distensibility and stiffness, or endothelial function. This may help to identify whether a specific phase of growth is particularly important and provide insights into aetiological mechanisms involved in the development of atherosclerosis before the onset of symptomatic coronary disease.

Tracking of cardiovascular risk

Factors that promote the early development of atherosclerosis persist over time and cluster both in childhood and adulthood, influencing subsequent subclinical and clinical cardiovascular disease. (3-6) This suggests that an early acquired risk tracks into adulthood, but the mechanisms involved remain unknown. Poor growth may contribute to the tracking of arterial stiffness, but few studies have repeated measures data, which are needed to assess influences on longitudinal change over the life course. To date, little is known regarding consequences of poor growth for the developing vascular system in childhood.

Social influences on growth and cardiovascular risk

Growth and cardiovascular disease are both socially patterned, and a study of the influence of growth on atherosclerosis and cardiovascular disease is complicated by accumulating and interacting biological, social and psychosocial processes, which have to be taken into account. (7) Adult measures of poor growth, such as short height, may, in addition to reflecting early influences on growth, be regarded as markers of socioeconomic disadvantage at different ages.

CHAPTER 2: AIMS AND OBJECTIVES

AIMS

Components of height will be used as markers of growth at different phases to investigate associations with arterial stiffness and its age related rise, atherosclerotic changes of the vasculature and cardiovascular disease risk. The role of prenatal growth and socioeconomic circumstances over the life course will be considered to gain insight into aetiological mechanisms potentially underlying these associations. Data from 5 prospective cohort studies, 4 of which collected information on components of height, will be used to address the following objectives:

OBJECTIVES

1st To identify which period of growth may be particularly important for the development of arterial stiffness in adult life, I will compare different markers of growth in their associations with arterial stiffness, as indicated by high peripheral pulse pressure in the National Survey of Health and Development (NSHD).

2nd To investigate whether poor growth contributes to the age related rise of pulse pressure, I will investigate associations between markers of growth and changes in arterial stiffness over time, using repeated measures of pulse pressure in the same cohort.

3rd To explore different pathways through which growth may influence the development of atherosclerosis and test whether associations are specific to pulse pressure, i.e. arterial stiffness, cross-sectional associations between markers of growth and a range of cardiovascular risk factors

available in the Whitehall II Study will be investigated; this will also allow to test associations between components of height and pulse pressure in another cohort.

4th To advance the understanding of the aetiological mechanisms involved, I will investigate associations between markers of growth, socioeconomic indicators and specific measures of vascular wall thickness (intima media thickness), arterial distensibility (distensibility coefficient) and stiffness (beta stiffness index).

5th To extend the investigation to metabolic and cardiovascular disease outcomes and advance our understanding of the influence of poor growth in a comparatively short and high risk population, with potentially different determinants of growth and disease, associations between components of height, diabetes and cardiovascular disease will be investigated in a study of Filipino-American women.

6th To investigate whether the detrimental effects of poor growth on the vasculature may originate early in life, I will investigate associations between markers of poor growth and pulse pressure and blood pressure in 3 year old girls and boys participating in Project Viva, a prospective cohort of pregnant women and their offspring.

7th Finally, mortality data from the first Whitehall study will help to answer questions that remain regarding the well documented association between short height and cardiovascular death; these include differences in associations according to prevalent CHD at baseline, differences by duration of follow-up and the exploration of any direct, mediated or interactive effects of growth and socioeconomic position.

CHAPTER 3: LITERATURE REVIEW

STRUCTURE OF THE LITERATURE REVIEW

Outcomes

This chapter will first review epidemiological trends of cardiovascular disease and introduce non-invasive measures of vascular wall thickness, arterial distensibility and stiffness, which assess the degree of atherosclerosis in asymptomatic individuals.

Exposures

Secondly, I will discuss the literature regarding the importance of markers of poor growth at different phases for measures of subclinical vascular disease and also cardiovascular morbidity and mortality outcomes.

Mediators

Thirdly, I will discuss potential explanations by which these exposures and outcomes may be linked.

CONTINUED IMPORTANCE OF CARDIOVASCULAR DISEASE

Coronary heart disease and stroke are among the leading causes of death worldwide. (8) This is despite a decline in cardiovascular mortality trends in most industrialized countries, with the exception of Eastern Europe, over the past decades. (9) While reductions in major risk factors, such as smoking, have contributed to these trends more recently, (10) improved early life circumstances may also be important. (11;12) The rate of decline has been faster in those living in higher

socioeconomic circumstances, and this has contributed to a widening of social inequalities in cardiovascular disease. (13;14)

ATHEROSCLEROSIS, ARTERIAL STRUCTURE AND FUNCTION

Atherosclerosis is a systemic process present throughout the vascular tree, and coronary heart disease and stroke are two of its clinical manifestations. Atherosclerosis particularly affects large elastic arteries, such as the aorta, carotid and iliac arteries, and large and medium-sized muscular arteries, such as the coronary and popliteal arteries. (15) Asymptomatic vessel disease could previously only be identified through invasive methods, such as cardiac catheterization, or after death through post mortem examination. (16) In order to understand aetiological processes that influence the development of atherosclerosis before the clinical manifestation of symptoms, measures of vascular structure and function that estimate the degree of systemic atherosclerosis are required. These, until recently, had to rely on invasive techniques that were neither feasible nor ethical in the context of long term prospective cohort studies.

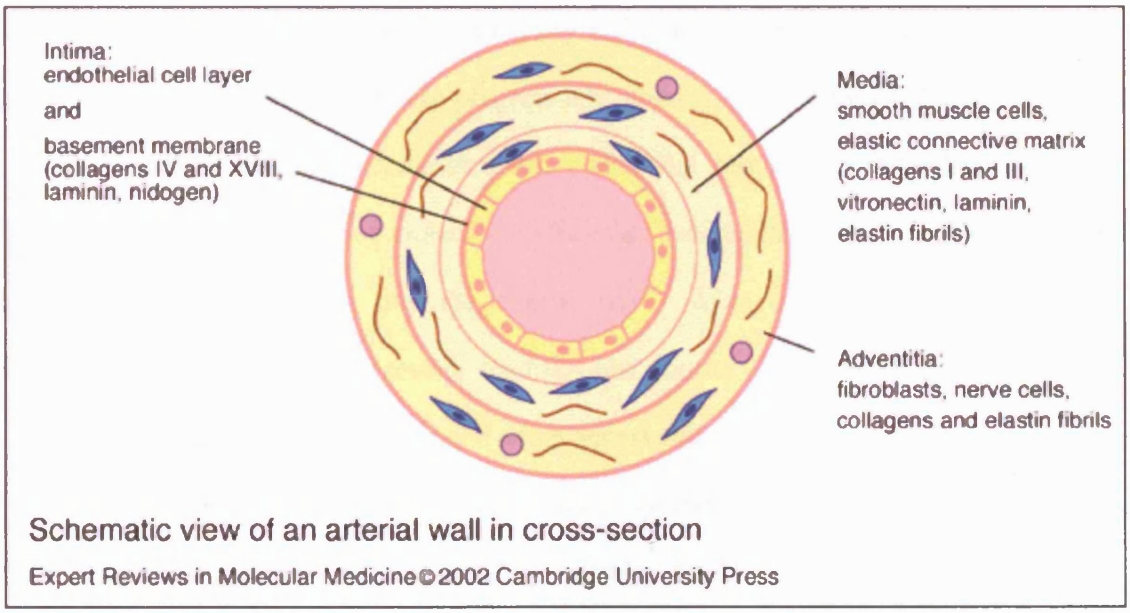
Over the last decade, non-invasive detection of early changes in vascular pathophysiology has become established, using high resolution ultrasound, and this offers several potential advantages. First, it is a measurement, which carries no risk for the research participant and is therefore suitable for population studies. Second, it helps to identify and understand factors that precipitate the onset of atherosclerosis or interact with vascular pathology on the development of clinical cardiovascular disease; also, repeated measures allow the investigation of the progression of preclinical disease. Third, objective measures of atherosclerosis have the potential to avoid some of the biases associated with clinical cardiovascular disease outcomes as assessed in prospective cohort studies. Outcome definition here often relies on symptom or medication reporting, physician diagnosis and referral, accuracy of death certificates or hospitalization records, which are prone to selection bias, and all of

which may lead to misclassification and biased estimates for the association between poor growth, socioeconomic disadvantage and atherosclerotic disease.

Further, ultrasound techniques used for vascular wall imaging are able to distinguish different pathophysiological aspects of disease: thickness of the arterial wall, arterial distensibility and stiffness.

The arterial wall consists of three concentric layers: the intima, media, and adventitia.

FIGURE 1 LAYERS OF THE ARTERIAL WALL



The media is separated from the intima and adventitia by an internal and external elastic lamina, and is made of muscle cells and elastic fibres in the elastic arteries. (15) The intima is the innermost layer, adjacent to the blood vessel lumen, consisting of a single layer of endothelial cells.

The endothelium is an important regulating organ, influencing vasomotor tone, platelet activity and blood flow through the secretion of vasodilatory, anticoagulant and fibrinolytic factors. (17) The

main dilating factor produced by endothelial cells is nitric oxide (NO), which is created from the amino acid l-arginine by the action of endothelial nitric oxide synthase (eNOS), a product of the NOS3 gene. (18) NO is responsible for the homeostasis between the endothelium and surrounding tissues, and agonists acting on endothelial cells as well as mechanical factors, such as shear stress, can modify eNOS activity. (19) NO is a vasodilator and regulates vascular tone; it has also been found to mediate many of the protective functions of the endothelium, (20) including regulation of vascular permeability, inhibition of platelet adhesion and aggregation and leukocyte-vessel wall interaction, and prevention of smooth muscle proliferation. (21;22)

Loss of endothelial function triggers compensatory inflammatory responses that represent the initial stage of the atherogenic process and can progress into atherosclerotic lesions and artery remodelling. (1) Early endothelial changes include increased endothelial permeability through up-regulation of leukocyte and endothelial adhesion molecules, which facilitate the migration of leukocytes, including monocytes and T-lymphocytes, into the arterial wall. After entering the intima, monocytes differentiate into macrophages, ingesting oxidized low density lipoprotein (LDL) cholesterol and forming foam cells. In addition to increased adhesiveness and permeability, functional impairment of the endothelium contributes to procoagulant effects, vasoconstriction, foam cell formation, T-cell activation, and proliferation and migration of vascular smooth muscle to the intima from the underlying media.

Over time, this contributes to the thickening of the intima and media and eventually to the development of plaque in large elastic arteries, and large and medium sized muscular arteries. Continuing endothelial dysfunction can lead to instability of the endothelial surface, erosion of the fibrous cap overlying plaque, subclinical plaque rupture, and vessel thrombosis. (1)

The following section briefly introduces the different non-invasive measures of vascular wall thickness, arterial distensibility and stiffness that are available, and discusses their properties for the prediction of symptomatic, clinically manifest cardiovascular disease.

MEASURES OF VASCULAR STRUCTURE AND FUNCTION

Arterial stiffness and compliance

Pulse pressure

Central pulse pressure is determined by large artery stiffness and is an estimate of arterial compliance. It represents the variation of blood pressure between systole and diastole and assesses the pulsatile component of blood pressure, which depends on the elasticity of the aorta. (23) After middle age, systolic blood pressure continues to rise, while diastolic pressure begins to decrease and consequently central pulse pressure increases. (24-26) Determinants of this age related increase of pulse pressure and systolic blood pressure are poorly understood; however, the absence of an age related increase of blood pressure and associated hypertension that has been observed in some rural populations has been interpreted as evidence for the importance of environmental influences. (27) Peripheral pulse pressure is the difference between systolic and diastolic blood pressure, as measured in the brachial artery, and is an estimate of central blood pressure variation.

Peripheral pulse pressure and central aortic pressure

Pulse pressure changes from central to peripheral arteries on account of the amplification of the pressure wave along the arterial tree with decreasing vessel diameter, and peripheral values tend to overestimate those in the aorta, particularly at younger ages. (28) In most studies investigating peripheral pulse pressure, no information is available to assess the degree to which higher peripheral pulse pressure corresponds to an increment in central aortic pressure and stiffness.

However, differences between central and peripheral pulse pressure may be important for the study of cardiovascular risk. (29) First, atherosclerosis does not occur in the brachial artery, where peripheral blood pressure is measured. Instead, it particularly affects large elastic arteries, and aortic pressure

and stiffness are therefore likely to be better indicators of systemic atherosclerosis, including the coronary arteries, compared to brachial measures. Secondly, high central pressure and stiffness represent atherosclerosis and modifications in the pressure waveform of the ascending aorta, which directly increase the pulsatile work of heart, leading to hypertrophy through left ventricular stress, and compromised perfusion of coronary and carotid arteries during diastole. (30-32) Thus pathophysiologically, measurements of aortic pressure and stiffness may be better predictors of cardiovascular outcomes, compared to brachial pressure. (33) As stated above, peripheral systolic and pulse pressure can overestimate central aortic values, particularly at younger ages. This may be less the case in the elderly, with loss of aortal elasticity and increased central pressure. (34) Thus with advancing age, central and peripheral pressure may more become more equal in their ability to accurately reflect aortic stiffness and predict the onset of cardiovascular events. Differences in pressure between central and peripheral arteries may also explain the importance of mean arterial pressure, (35) which does not vary across the arterial system and may therefore be more accurately be determined in the brachial artery.

Assessment of aortic haemodynamic parameters can be obtained non-invasively from peripheral recordings of the radial artery pressure waveform by using applanation tonometry. (28) Good inter- and intra-operator reproducibility of the measurement has been reported, (36;37) and recently guidelines have been published to help standardize the technique. (38) However, longitudinal variation has been shown in earlier studies, (39) and a recent review has highlighted a number of restrictions, including limited evidence for its prediction of future events. (29)

Despite evidence favouring the hypothesis that arterial stiffness develops as a consequence of chronic atherosclerosis, the nature and direction of associations still remains unclear; this is particularly true for the degree to which the observed relationship between arterial stiffness and atherosclerotic burden may be due to shared underlying risk factors. (40) Population based studies have shown that arterial

stiffness, as measured by pulse wave velocity and distensibility, is strongly associated with atherosclerosis at various sites in the vascular tree, (41) and that their relation is independent of major risk factors, (42) but others have yielded conflicting results. (43;44) Some of these discrepant results may originate from the differing assessment of atherosclerosis in these studies, (45) or the investigation of populations with varying degrees of existent vascular disease, which may influence the strength of the association. (46;47)

Peripheral pulse pressure and cardiovascular events

Whilst systolic and diastolic pressure are established predictors of cardiovascular morbidity and mortality, the importance of peripheral pulse pressure has only more recently been highlighted, particularly in middle aged or older, (48;49) or hypertensive persons. (50) There is an ongoing debate, whether it has predictive value beyond the information provided by systolic blood pressure and how its association with coronary heart disease mortality changes with age. While one study suggested that in middle aged and older subjects wider pulse pressure is the blood pressure component most strongly associated with coronary heart disease risk, (25) another study found that the risk associated with pulse pressure was entirely explained by higher systolic blood pressure. (51) The prospective studies collaboration found that pulse pressure is less informative than the average of systolic and diastolic blood pressure or either alone for predicting cardiovascular mortality. (35)

Central pulse pressure and cardiovascular events

Studies obtaining pulse pressure directly at cardiac catheterisation, (52-55) or from carotid pressure, (56-58) have supported the view that that central pulse pressure and its principal determinant, large artery stiffness, may be better predictors of cardiovascular risk and mortality than peripheral brachial pulse pressure. However, clinical studies of selected patient groups or of those undergoing catheterisation with a small number of events and composite end points encounter several methodological limitations and their generalizability is questionable.

The few longitudinal studies assessing the relationship between central arterial stiffness obtained by applanation tonometry and future cardiovascular events have mainly used measures of pulse wave augmentation and velocity. These were largely performed in different groups of patients, rather than the general population, and will be reviewed in the following section.

While the first part of this thesis is concerned with influences on peripheral pulse pressure, encountering limitations as outlined above, more specific measures of arterial stiffness and systemic atherosclerosis, such as arterial distensibility and compliance, will also be used to validate findings.

Arterial distensibility and compliance as measures of arterial stiffness

Arterial compliance, an index of vessel wall stiffness, represents the absolute change in vessel diameter or area for a given change in pressure and decreases with age. Arterial distensibility, the relative change in area for a given change in pressure, is a measure of vascular elastic behaviour, and loss of distensibility in adults is related to risk factors for clinical vascular disease. (59-61) Lower distension implies a stiffer artery; beta stiffness index describes the relation between arterial pressure and arterial diameter and characterizes the deformation behaviour of the vascular wall, independent of intraluminal pressure within the physiological range. (62)

Distensibility and compliance and cardiovascular events

While non-invasive assessment of distensibility and compliance represents an innovative way of studying influences on asymptomatic arterial disease, (63;64) relatively few data exist concerning the predictive value of distensibility and compliance for future cardiovascular events. (65)

Aortic pulse wave velocity is a measure of arterial stiffness and is inversely related to aortic distensibility. Longitudinal studies have shown its influence on cardiovascular outcomes in patients with hypertension, (66) diabetes, (67) end stage renal disease, (58;68) and older healthy individuals. (69)

In patients with manifest cardiovascular disease or cardiovascular risk factors, increased arterial stiffness, as assessed by carotid artery distension, has been shown to be associated with a higher risk of cerebrovascular disease and aneurysms of the abdominal aorta. (70)

Intima media thickness

Assessment of atherosclerosis by measurement of intima media thickness

Thickening of the intima and media of the vessel wall can be visualized by high-resolution ultrasound. The disturbance of endothelial function in atherogenesis that leads to the thickening of the intima and media is a generalized process, and carotid intima media thickening therefore provides an indirect assessment of atherosclerosis in other elastic or muscular arteries, such as the coronaries. (16;71-73)

Intima media thickness and cardiovascular events

Previous reports have shown that carotid intima media thickness (IMT) is related to unfavourable levels of cardiovascular risk factors in older, (74) as well as younger populations. (75) Intima media thickness predicts subsequent cardiovascular morbidity and mortality, (76-79) a recent review has highlighted its prognostic value. (80)

Endothelial function

Endothelial function can be evaluated by measuring changes in arterial diameter or cross-sectional area in response to specific stimuli. (16) Selective inhibitors of nitric oxide synthase prevent these changes in diameter or area, indicating that they provide an indirect assessment of nitric oxide production and function. The gold standard of assessing endothelial function involves measurement of vasomotor responses of epicardial arteries by quantitative coronary angiography; (21;81) an invasive method, which is restricted to patients undergoing cardiac catheterization and not suitable for population based research.

Flow mediated dilatation

Assessment of the vasodilator response to increased blood flow (flow mediated vasodilatation) provides a non-invasive approach to evaluating endothelial function. (21;82) Haemodynamic shear stress during reactive hyperaemia is used to stimulate NO release, and impairment of flow-mediated dilatation of the brachial artery has been shown to be associated with coronary artery endothelial dysfunction, (83) and the extent of coronary artery disease at angiography. (84) While this provides some evidence for the agreement between peripheral and systemic endothelial function, the intraindividual correlation between coronary and brachial endothelial responses is only modest. (83)

Assessment of non-endothelium dependent vasodilatation can be performed using nitroglycerin or nitroprusside, and this measures non-specific smooth muscle effects.

Relatively small changes in vessel diameter are being estimated, and although some studies have reported good within-scan and within-subject coefficients of variation, (85) other authors have expressed concern regarding the potential for interpretative error, especially between observers, (86) or reported large within-subject variability. (87) Different protocols have been used in previous studies, affecting the magnitude of flow mediated dilatation, and recently guidelines have been published to reduce variation between centres. (82)

Endothelial function and cardiovascular events

Clinical studies have demonstrated associations between endothelial function assessed invasively and future cardiovascular complications. (88-93) However, due to small numbers, selected symptomatic populations and use of composite endpoints these studies encounter some limitations and their generalizability is limited. (21)

Although flow mediated vasodilatation in the brachial artery is regarded as an indicator of cardiovascular disease risk, few studies have validated this with prospective events. These have so far demonstrated that persistent endothelial dysfunction is associated with an increased risk of clinical events in postmenopausal women, (94) and patients with peripheral arterial disease. (95;96) More evidence is needed to assess the value of this emerging technique for the screening for asymptomatic early stage disease and its ability to predict clinical events in unselected populations. (80)

ORIGINS OF CORONARY HEART DISEASE RISK

Research into early influences on adult chronic disease has grown rapidly over the past decade. (7) Many studies have focussed on cardiovascular disease, (97;98) whose aetiology lends itself to life course approach, since atherosclerotic changes of the arterial wall begin at an early age, (16) occurring in apparently healthy children and adolescents, and progress with age. (2) Prevalent atherosclerosis has been observed in fetal aortas and fatty streaks, the earliest type of atherosclerotic lesion, are common in infants and young children. (1;99) The clustering of adverse levels of different cardiovascular risk factors has been demonstrated in children, and early levels of risk factors are known to persist over time and influence later cardiovascular risk. (5;100) This suggests that an early acquired risk tracks into adulthood, but the origins of such risk remain unclear.

Poor growth, atherosclerosis and the risk of coronary heart disease and stroke

Cohort studies with long term follow-up have reported associations between poor growth at different ages and adverse levels of cardiovascular risk factors, cardiovascular events and mortality. (98) Studies of children and adolescents have also demonstrated inverse associations between growth, particularly during the prenatal period, and early signs of atherosclerosis. (101-103) This has stimulated debate about the contribution of growth limiting factors to early atherogenesis and the development of cardiovascular disease. (104-108)

However, growth and cardiovascular disease are both socially patterned, and studies of the influence of growth on atherosclerosis and cardiovascular disease are complicated by accumulating and interacting biological, social, and psychosocial processes. (7)

Social influences on growth and cardiovascular disease

Many important influences on growth are socially distributed, such as prenatal development, premature birth, maternal health, behaviour and care for the child, early nutrition, living conditions, infections and age at puberty. (109-113) All of these factors have the potential to contribute to the shorter height, and particularly leg length, of children growing up in disadvantageous social conditions. (106;112;114;115)

People growing up in disadvantaged childhood conditions have a higher risk of coronary heart disease, and a recent systematic review concluded that socioeconomic circumstances during childhood and adulthood both independently contribute to adult coronary heart disease mortality. (116) Most prospective studies with information on childhood social class, measured by father's occupational class or living conditions, have shown associations with total cardiovascular or coronary disease, (117-126). Few studies reported no association, (127;128) or associations with stroke, one aspect of cardiovascular disease, only. (129) Studies generally found that adult social position did not account for this effect of childhood social class, with few exceptions. (130)

Some authors suggested that a composite measure of lifetime socioeconomic position might be a better predictor of cardiovascular mortality than socioeconomic position estimated at one point in time, which only inadequately accounts for socioeconomic disadvantage over the life course or changing employment patterns, particularly in the case of women. (131;132)

Most, (121;133) but not all, (120) studies have also reported a higher risk of stroke among those who experienced less favourable childhood socioeconomic circumstances, independent of adult socioeconomic position, (129;134) or height. (135)

A detrimental effect of lower childhood socioeconomic position, independent of adult position, has also been shown for a number of cardiovascular risk factors, particularly obesity, (136-142) but also

hypertension, (136;137), dyslipidaemia, (136-138;140) and insulin resistance. (140) This supports the hypothesis that early environmental factors may have long term effects on specific biological processes influencing metabolic disturbances and cardiovascular disease in adult life. (143)

The question therefore remains, to what degree associations of poor growth with atherosclerosis and cardiovascular disease may simply reflect or also mediate and contribute to the risk associated with early or later socioeconomic deprivation. Also, the nature of such risk may manifest itself in different forms.

Critical periods, cumulative and interactive effects

First, growth limiting exposures restricted to a specific early period, such as those occurring during the prenatal phase or the first years of life, may have long-term influences on cardiovascular disease risk. This early elevation of risk may occur through metabolic adaptation to growth restriction during sensitive periods of growth, leading to risk factor clustering and tracking and to the initiation of vascular wall changes.

Secondly, children who fail to reach their growth potential through environmental disadvantage are also more likely to be less educated, exposed to health behaviours such as smoking, poor diet and insufficient exercise, remain in lower social classes and experience material and other socioeconomic disadvantage, which in turn are associated with an increased risk of coronary heart disease. (144) Thus an accumulation of risk may occur, through additive effects of adverse influences on coronary heart disease at early and later stages of the life course.

Thirdly, early and later life influences may interact in their effects on coronary heart disease risk. Such effect modification may establish itself in different ways. On the one hand, the risk associated with poor growth may be greater in those who have grown up and/ or continue to live in

disadvantaged socioeconomic circumstances, compared to their more advantaged counterparts. For example, if growth limiting factors contributed to the initial level and tracking of cardiovascular risk from an early age, then people with poor growth and consequently shorter height, reflecting their adverse childhood conditions, may be expected to have greater cardiovascular vulnerability. Thus continuing social disadvantage and/ or effects of aging on the arterial tree may amplify the initial risk associated with poor growth and result in a steeper increase of arterial stiffness over the life course of people susceptible to cardiovascular disease. (145) Alternatively, the influence of poor growth on cardiovascular risk may be weaker in more disadvantaged groups, who are at greater absolute risk of cardiovascular disease. For example, early occurring growth limiting influences with comparatively smaller effect sizes may be overridden or superseded by the comparatively stronger effects of adverse adult living conditions and health behaviours, such as smoking, which are more common among those in disadvantaged socioeconomic positions.

Fourthly, although many influences on growth are socially distributed, and their influence may explain part of the association between poor growth and cardiovascular disease, socioeconomic deprivation and growth limiting factors may also exert independent effects on adult disease. Hormonal regulation, through the insulin–like growth factor axis, may not differ between socioeconomic groups, but still contribute to an increased risk in cardiovascular disease, (146) for example.

Equally, while not all of the detrimental consequences of childhood disadvantage for adult disease establish themselves through an influence on growth, growth limiting factors influencing atherosclerosis and cardiovascular risk may mediate part of the long term effects of early and continuing social disadvantage.

EVIDENCE OF ASSOCIATIONS BETWEEN GROWTH, ATHEROSCLEROSIS AND CARDIOVASCULAR DISEASE

Human growth occurs in four distinct phases: fetal, infancy, childhood and pubertal growth, (147;148) and several anthropometric measures have been used as indicators of growth at these different ages. The term "growth" is generally used for changes in height as well as weight, and while changes in body weight, overweight and obesity are associated with levels of atherosclerosis and coronary heart disease, the focus of this study is to investigate the role of markers of linear bone growth rather than fat mass or adiposity.

Although different hormonal influences underlie the main phases of linear growth, (147) they are interdependent, such that growth in one phase influences subsequent phases. (149) With regard to the association between poor growth and adult cardiovascular disease, the majority of evidence has so far come from investigations of the most proximal and distal measures of growth: size at birth and adult height. Importantly, as Lucas et al. have argued, (150) the size of an individual at any point of the continuum between fetal and adult size is correlated with both earlier and later size, and without information on different phases and dimensions of growth, it is therefore difficult to establish which period or aspect of growth may be most important for future cardiovascular risk.

Poor growth and shorter height are more common in men and women growing up and living in adverse socioeconomic circumstances, and stature can thus be regarded as a marker of socioeconomic disadvantage over the life-course. (115;138;151;152) Differences in attained height between generations and countries largely arise during the childhood phase of growth between 6 and 18 months of age, when a divergence of growth curves can be observed that is not seen immediately before and after this phase. (153;154)

Increased gain in total body length occurring during this growth hormone dependent phase is largely (over 80%) localised in the lower segment of the body. (155) This is because the growth of the long bones, represented in the legs, is more sensitive to growth hormone than other bone structures, such as the short bones in the vertebral column. (156) Socioeconomic, environmental factors play an important role for the secular trend in height, as well linear growth retardation in developing countries. Relatively shorter leg length may therefore be a better indicator of early environmental influences operating during the childhood phase of growth that are socially patterned, compared to total height.

Thus, leg and trunk length may be used as markers of growth at different phases and the investigation of their associations with cardiovascular disease can help our understanding of whether influences on or during the childhood phase of growth, in comparison with prenatal or later growth, may underlie the link between short height and cardiovascular risk.

Growth can be observed in absolute and relative terms. Epidemiological investigations of associations between measures of growth at different ages and cardiovascular disease commonly use absolute measures of growth; these include weight and length at birth, reflecting the prenatal period, heights and weights in childhood and adulthood and components of height, namely leg and trunk length.

Relative growth describes the tempo of growth and includes measures of growth rate and maturation, such as age at peak height velocity. Assessment of relative growth requires measures to be obtained repeatedly, at frequent intervals for estimation of age at peak height velocity, for example, and has thus rarely been investigated, as such data are uncommon in long term prospective studies following participants into adulthood and until the onset of cardiovascular disease.

The following section reviews the literature linking growth to measures of atherosclerosis and cardiovascular disease, including coronary heart disease and stroke, as well as a short overview of

each of the anthropometric measures used. Initially, the different absolute measures of growth will be introduced, starting in adulthood, going back to childhood, infancy, and fetal life, followed by a short section on growth velocity.

Adult height

Height as measure of linear growth

The height that an individual has attained in early adult life indicates linear growth in absolute terms and reflects genetic and environmental influences on height up to the point it is measured.

Unlike body weight or obesity, adult height changes little until middle age, and may be used to reflect long-term influences of exposures during the growing years. However, growth impairment at several stages of development can lead to reduced height, and total body height does therefore not allow inference about specific phases of growth or growth limiting exposures. (157) Height reflects the length of the long bones of the limb (tibia and femur), the irregular bones of the vertebral column, and the skull; it also indicates the amount of lean body mass. (158) Adult height is inversely related to age, due to secular increases in height in many populations, (159-161) and because of age associated height loss through shrinkage after around the age of 40 years. (162;163)

Height and the risk of cardiovascular disease

Early case-control, (164-166) and cohort studies, (167-170) reported inverse associations between adult height and coronary heart disease.

Supporting evidence is now available from more recent cohort studies of men, (151;168;171-177) women, (178) or both. (179-183) Although some of these studies have been criticised (184) for using self reported height, (173;178;179) this is not the case for the majority of cohorts in which height was

measured. It therefore seems unlikely that differential recall of height with regard to disease has lead to biased results.

One large prospective cohort study found no significant association between short height and myocardial infarction after adjustment for age in men; however, such an association was observed in women, and this persisted after taking account of several cardiovascular risk factors. (185) Stronger associations between self reported height and cardiovascular death were also seen in women, compared to men, of another American cohort, and these again remained significant after adjustments. (186) In contrast, results from a third American cohort found a graded inverse association between stature and both coronary heart disease and stroke in men, but not women, before and after multiple adjustments. (187)

A nested case-control study among twins found that the shorter twin in a monozygotic or dizygotic twin pair was more likely to die of heart disease than the taller, (188) and this was interpreted as evidence of an environmental basis for the association between shortness and coronary heart disease risk. Likewise, recent evidence from a study of 35,000 twin pairs showed an inverse association between height and mortality from CHD within monozygotic discordant twin pairs, pointing towards environmental factors directly affecting growth and CHD. (189)

Only a few studies reported no association between height and coronary heart disease, (184;190-192) and two of those studies found such associations with one aspect of cardiovascular disease, stroke. (191;192) Only one of these studies included women, as well as men. (184) Another study, which reported its main results for combined cardiovascular mortality, (193) also suggested that associations may be stronger for non-coronary cardiovascular mortality, compared to CHD mortality, although findings were based on a small number of deaths. In contrast, some of the studies which observed significant relationships with coronary heart disease, failed to show this for stroke, (173;178) and although inverse associations with stroke were found in one of these studies, these did not reach

conventional levels of significance. (183) Results from a large British cohort of men found that the risk of stroke was increased only in the shortest group of men, suggesting a non-linear association. (176)

Whilst the evidence regarding stroke seems conflicting, early reports of an association between short height and non-fatal and fatal stroke (194;195) have recently been supported by results from prospective cohorts of both genders, (181;182;196) or men only. (197;198)

Subtypes of stroke

Discrepant results regarding stroke may be explained by the fact that aetiological studies of stroke are complicated by the different pathologies underlying its main subtypes, cerebral infarct and cerebral haemorrhage. These are clinically difficult to distinguish and information about stroke subtype in epidemiological studies, for example from death certificates, is limited, particularly using information from before the time of diagnostic brain imaging. The majority of strokes are ischemic; however, studies of the atherosclerotic process underlying this type of stroke are complicated by its differing vascular mechanisms, including large-artery atherosclerosis with occlusion and distal embolization and small penetrating arterial disease with lacunar infarction. The mechanism of ischemic stroke events often remains unclear and a number of infarcts are of undetermined cause. (199)

The few studies, which were able to analyze ischemic and hemorrhagic stroke separately, have provided limited evidence that the adverse effect of short height may be stronger for hemorrhagic stroke. (196;198) This may be surprising, as coronary heart disease and ischemic, rather than hemorrhagic stroke, share a similar underlying aetiology. (200)

Height and the prognosis of people with prevalent coronary heart disease

Few studies have explored the influence of height on mortality of patients with prevalent coronary heart disease, and these yielded conflicting results for prognosis after myocardial infarction, with

some, (201) but not all, (202;203) reporting inverse associations with survival after a coronary event. One case-control study found such an association in men, but not women, hospitalized after myocardial infarction. (204) However, much of this evidence has come from trial or hospital patients after an acute infarct, and it remains unclear whether height affects the prognosis of prevalent cardiovascular disease in the general population.

Height and measures of vascular structure and function

One study suggested that associations between height and dynamic properties of the arterial tree may contribute to the increased cardiovascular risk in those of shorter height. (205) As mentioned above, pulse pressure is determined by arterial compliance and wave reflection. (23;30;31) Pressure wave reflection during systole boosts systolic pressure in the ascending aorta and increases ventricular load, while reflection during diastole favours myocardial perfusion. The travel time of the arterial wave and timing of wave reflection depend on arterial stiffness and transmission path length. (51;206) Reflected waves in those with poor growth and shorter height may arrive early and during systole, resulting in increased central pressure augmentation, due to their greater levels of arterial stiffness and/ or shorter transmission path length, and this may contribute to increased pulse pressure and cardiovascular risk of shorter individuals. (32;205)

Childhood height

Linear growth during childhood

Childhood growth before puberty is divided into two partly superimposed phases. The infancy phase, beginning in the middle of gestation and tailing off at about 3-4 years of age, and the childhood phase, which usually starts during the second half of the first postnatal year, occurring on average earlier in girls than boys. The rapidly decelerating infancy component is regarded as the postnatal nutrition dependent continuation of fetal growth, during which the abrupt start of the childhood phase marks the age at which growth hormone begins to exert a significant influence. (147;153;207) Infancy and childhood are sensitive periods of growth, and interference with the growth process in early years has long term consequences for adult health. (149)

Size at birth is only weakly related to final adult height; (158) however, the correlation between early and adult height increases steeply during the childhood phase of growth in the first years of life, and children achieve their individual location on a particular height growth centile at around the second year of life. (158) During this time, between 6 and 18 months of age, delayed onset of the childhood phase of growth can lead to linear growth retardation and shorter final height, (149;153;208) independent of the timing of puberty. (149)

Malnutrition with inappropriate caloric intake as well as malabsorption and reduced appetite during illness can lead to down-regulated growth, and result in shorter stature. (209) Subsequent improved nutrition, remission and recovery may accelerate linear growth, (210;211) and this "catch-up" growth often exceeds the normal growth rate for age. Although such compensatory growth improves final height, it does not necessarily lead to complete recovery of adult stature. (209;212) Down-regulation of growth that reduces final height is not limited to children with chronic disease, endocrine abnormalities, poverty-related deprivation, or eating disorders; it can be the consequence of relatively small, but prolonged, calorie restriction or shortfall in dietary quality. (209)

The analysis of childhood height is further complicated by the fact that differences in childhood height, even in children of the same age, may reflect differences in the rate of growth and maturation, rather than growth potential or attained height. This will be discussed in more detail in the section regarding growth velocity.

Childhood height and cardiovascular disease

One study investigating components of height in boys and girls aged 2 to 14 years found that associations between shortness and adult coronary heart disease were weaker in children aged 8 years or older, compared to the younger group. (213) The authors suggested that this might be explained by the onset of the adolescent growth spurt in the older group, whose height may not reflect earlier growth or growth potential, but rather their degree of maturity, i.e. a certain stage during the pubertal growth spurt, at least in those children who had entered puberty.

Childhood height and measures of vascular structure and function

Shorter prepubertal stature, relative to adult height, and interpreted as poor growth in childhood, was also shown to be an important determinant of adult pulse pressure and blood pressure. (214) And although this study provided some evidence of the importance of early growth for the development of arterial stiffness, it included only 300 survivors of an originally large cohort, was unrepresentative of the general population and, due to small numbers, men and women could not be analysed separately.

A study of prepubertal children aged 9-11 years, designed to investigate the influence of cholesterol on arterial distensibility in childhood, found that of all risk factors under investigation, height was the second most important influence on distensibility (after diastolic blood pressure), and this was only partly explained by the association of increased height with lower cholesterol and greater vessel size. (6) Prenatal growth, estimated by ponderal index at birth, was not significantly associated with distensibility. Birthweight, but not ponderal index or childhood height, was associated with

endothelial function, as indicated by flow mediated dilatation, in these children. (102) A similar investigation of children aged 13-15 years showed no significant associations between height and distensibility at these older ages, when 70% of boys and girls were at Tanner stages 4 or 5, while adiposity and its metabolic consequences were strongly related with distensibility during teenage years. (215)

One study of girls and boys aged 10-18 years showed that augmentation index, an estimate of early pulse wave reflection and reduction in the elastic properties of arteries, was significantly higher in those of low birthweight, short stature, low heart rate and female gender, after mutual adjustments. (145)

Components of height

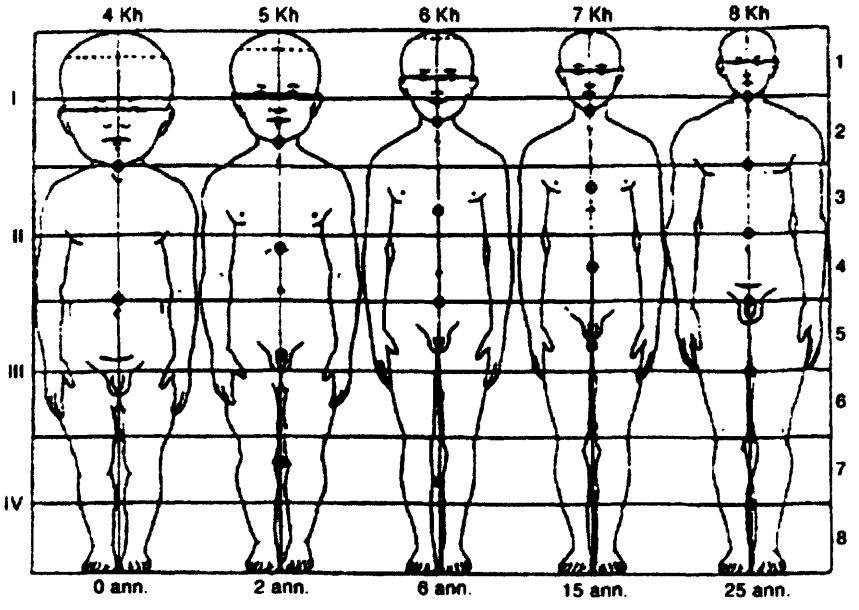
Leg and trunk length as markers of growth at different ages

The growth of the two main components of height, leg and trunk length, differs in timing and magnitude. (154) As mentioned above, a large amount of the dramatic changes in body proportions during the first years of life is due to the growth of the long bones of the leg (figure 3), and increases in total height before puberty are to a larger degree caused by gains in leg length, compared to trunk length. (157;216) This is illustrated by increases in the ratio of leg length to total height from birth to puberty (figure 2), (157) and is caused by the faster growth of the legs, which ceases at an earlier age, compared to the trunk. (159;217)

Growth hormone contributes to growth in length during infancy and childhood through influences on cartilage cells of the long bones, (218) and leg length can be regarded as a marker of early growth of the long bones at specific hormonally controlled phases of development. Leg growth is particularly sensitive to postnatal environmental influences, and short leg length has been suggested as a more

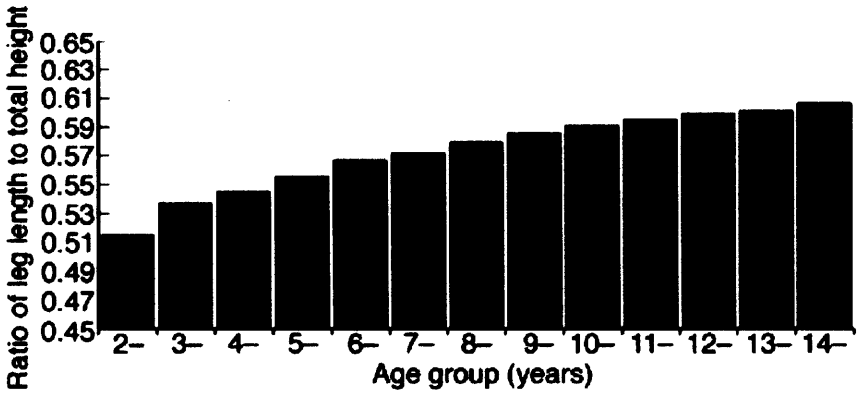
sensitive indicator of early environmental influences that limit growth, such as malnutrition, than total height. (106;115;219)

FIGURE 2 BODY PROPORTIONS AT DIFFERENT AGES



Reprinted in: Gunnell, D. Int. J. Epidemiol. 2002 31:390-394

FIGURE 3 CHANGES IN THE RATIO OF LEG LENGTH TO TOTAL HEIGHT



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Secular increases in height in industrialised countries over the past century have been attributed to greater leg length, rather than trunk length, (159) caused by earlier onset and/ or increases in growth tempo during the childhood phase of growth. (153) These secular increases in height and leg length have been more pronounced in children from low socioeconomic backgrounds, and this suggests the importance of environmental improvements for secular changes in leg length; decreased childhood infection rates, improved nutrition, social and living conditions seem to play an important role. (161) These early life factors may, through influences during the hormonally controlled childhood phase of growth, simultaneously influence growth spurts of long bones of the leg and changes in the structure and function of the developing vasculature, (220;221) and thereby increase the risk of coronary heart disease.

Components of adult height may therefore be used as markers of growth with different determinants and duration and recent studies have advanced research investigating the association between shortness and cardiovascular disease by exploring specific associations with components of height. In addition, studies analysing adult leg length, rather than total body height, also avoid measurement

bias introduced by age related shrinkage, which reduces total height mainly as a result of decreases in trunk length through the osteoporotic collapse of vertebrae.

Components of adult height and cardiovascular disease

To date, only a small number of studies have investigated associations between components of adult height and coronary heart disease, (222;223) including one study of middle aged men (222) and one study of postmenopausal women, (223) both of which suggested that leg length, rather than trunk length, is the component of height most strongly associated with coronary heart disease. Evidence from these studies of men, (222) and women, (224) also suggested that those with poor growth of the long bones of the leg show a higher prevalence of the metabolic syndrome, insulin resistance and non-insulin dependent diabetes, as well as other cardiovascular risk factors, which are components of the metabolic syndrome. (225;226) However, it has also been suggested that differences in insulin sensitivity and levels from early life on may influence stature through the growth promoting effects of insulin. (227) Associations between adult components of height and metabolic risk may therefore reflect insulin responses to glucose in earlier life influencing both growth and metabolic and cardiovascular risk.

Components of childhood height and cardiovascular disease

Childhood leg length, but not trunk length, was found to be inversely associated with CHD mortality over 52 years in one prospective cohort, which measured components of height in boys and girls of less than 14 years of age. (213)

Components of height and measures of vascular structure and function

Recent data from the ARIC cohort has provided some evidence of an inverse association between adult leg length and intima media thickness in 12254 middle aged participants. Differences in the magnitude of the inverse association between leg length and intima media thickness between ethnic groups and sexes were reported, being strongest in black men and positive and non-significant in black women, before and after multivariate adjustments. In univariate analyses, trunk length was inversely associated with intima media thickness in black and white men and women in this study; however, significant positive associations emerged in white men and women after adjustment for leg length, field centre and age, while estimates were attenuated to non-significance in black men and women.

No evidence exists regarding components of height and vascular structure and function in childhood; however, one previous study reported an association between fetal femur length and systolic blood pressure at age 6 years. (228)

Prenatal growth

Size at birth as a measure of prenatal growth and development

Information on size at birth with regard to length, but particularly weight, has been used in studies of prenatal growth and its consequences for adult disease.

Size at birth and cardiovascular disease

Many genetic and environmental factors affect size at birth, and since early suggestions of an association between poor growth in utero and increased coronary heart disease mortality, (11) an extensive amount of literature has been published investigating the role of prenatal influences on, or

markers of, growth and coronary heart disease and associated risk factors, particularly blood pressure. (229;230)

However, a recent systematic review, including a meta-analysis, concluded that reports of an inverse association between birthweight and subsequent blood pressure might reflect the impact of random error, publication bias and inappropriate adjustment for current weight and other confounding factors. (231) A systematic review of the association between birthweight and blood cholesterol level in adolescents also concluded that the importance of fetal nutrition for total cholesterol was weak and of limited public health importance compared to childhood obesity. (232) And although several studies investigating the association between size at birth and coronary heart disease have reported an inverse association, (128;233-243) no systematic review of the literature has yet been conducted. Some studies have found no or non-linear associations, (240;244-246) or interactions suggesting that the adverse effect of low birthweight may be restricted to those with high body mass index, (237) or lower social class in adult life. (124) Inverse associations of birthweight have been shown with stroke mortality in studies of men and women, (135;239;240;247;248) and differential associations with stroke subtypes have been suggested. (98)

In the light of this conflicting evidence, Barker's hypothesis that metabolic adaptation of the foetus to growth restriction programmes the risk of adult disease has not remained undisputed, and it is unclear which particular phase of growth is most important for the development of atherosclerosis and cardiovascular risk.

Size at birth and vascular structure and function

Few studies have investigated the influence of size at birth on arterial stiffness, and these have mostly used pulse wave velocity, which represents regional arterial visceroelastic properties and is inversely proportional to arterial compliance. In some of these studies decreased compliance in adult life was apparent in those with impairment of fetal growth, (101;249) and Martyn et al. hypothesized that this

may be caused by impaired elastin synthesis in blood vessels of children with poor prenatal growth, which – over their life course – could lead to increased left-ventricular mass and cardiovascular disease. (105) However, others have yielded conflicting results, reporting no associations, (250-252) or of opposite directions in men and women. (253)

One study investigating the association between birthweight and arterial stiffness using measures of distensibility and compliance at three different vascular beds found only weak positive associations between birthweight and arterial compliance, and these were accounted for by adult height. (103) Furthermore, birthweight was not associated with distensibility in any vascular bed and this was also observed in one study of prepubertal children aged 9-11 years, which found no association between prenatal growth, estimated by ponderal index at birth, and distensibility. (6) In contrast, birthweight was associated with endothelial function, as indicated by flow mediated dilatation, in these children; however, no relationship was observed when ponderal index was used as a measure of prenatal growth. (102) Associations between birthweight and endothelial function were described to be most marked in individuals with the lowest risk factor burden in one small study of young adults, and this was interpreted as early effects being "overwhelmed" by the presence of classic cardiovascular risk factors. (254) However, the relatively small sample and low response rate of this study require the reported interaction to be interpreted with some caution.

Another study, using ambulatory brachial pulse pressure as an indirect estimate of aortic compliance, found a significant inverse association with birthweight in girls and boys aged 10-18 years, independent of their height. (255) However, it remained unclear whether the increased peripheral pulse pressure was accompanied by an increment in central aortic pressure and/ or modifications in the waveform, and this was addressed by a subsequent study. This analysis showed that augmentation index, an estimate of early pulse wave reflection and reduction in the elastic properties of arteries, was significantly higher in those of low birthweight and short stature, as mentioned

earlier. (145) The authors hypothesized that these early alterations may be amplified throughout life and contribute to the increased cardiovascular risk associated with low birthweight, but this has not yet been investigated.

Studies assessing associations between prenatal growth and intima media thickness in adulthood have been inconclusive, (256) so far providing little evidence of a clinically significant relation between birthweight and carotid atherosclerosis. (257;258)

It has been suggested that an association between birthweight and endothelial function in neonates (259) may persist into childhood (102;260) and young adult life, (254;261;262). However studies have used a variety of measures to assess endothelial function, and some included only very few participants. Studies in infants have also yielded negative results, (263) and associations between birthweight and endothelial function in older adults remain to be shown.

Importance of prenatal versus postnatal growth

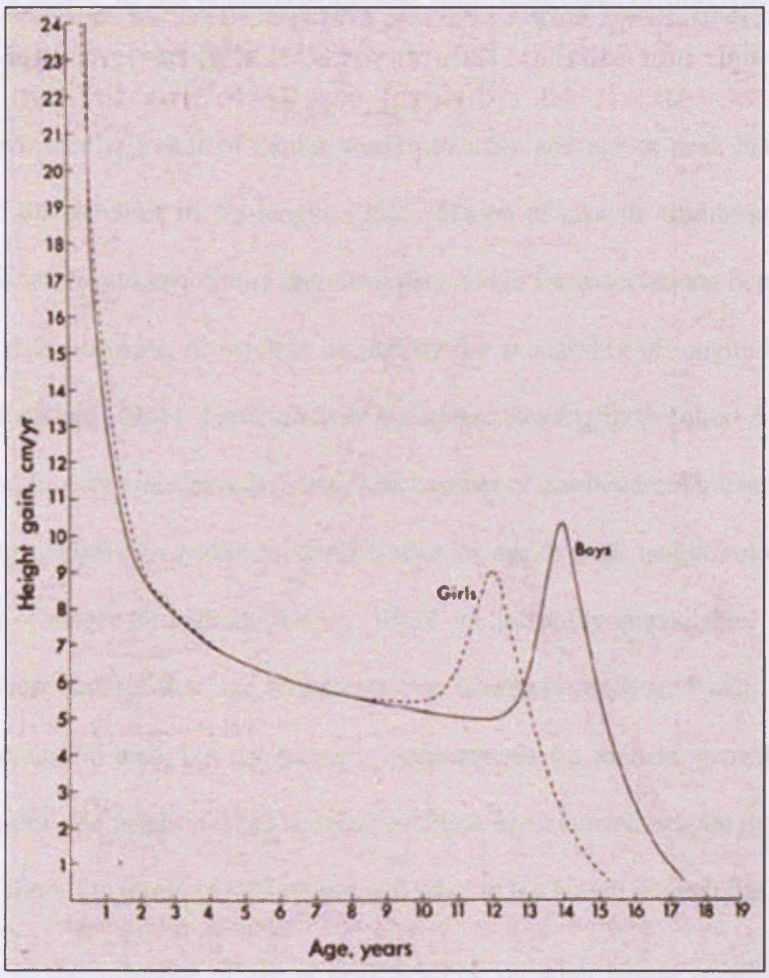
Several studies investigating whether poor prenatal growth may contribute to or explain the association between short height or leg length and coronary heart disease have not provided much support that poor prenatal growth may be responsible for the association between shortness and cardiovascular risk. First, studies with information on height as well as birthweight for either all or a subsample of participants, have found that the relationship between height and coronary heart disease was robust to adjustment for birthweight. (172;178;223) This supports the notion that size at birth and height, although weakly correlated, are markers of growth phases with different determinants and duration, and may represent separate influences on cardiovascular risk. Secondly, Gunnell et al. compared correlations between birthweight and components of stature in four different cohorts to test whether stronger associations between birthweight and leg length, compared to trunk length, may

explain the specific association observed between leg length and coronary heart disease. (264) No consistent evidence was found that birthweight might underlie the association.

Growth velocity: rate of growth and maturation

Although the evidence discussed so far points towards a distinct influence of prepubertal linear growth during childhood on cardiovascular risk, it remains to be shown that growth at a specific age or phase is of particular importance. Furthermore, the rate, i.e. speed, of growth changes substantially throughout the different growth phases and this can be visualized through the change of height with time: growth velocity (figure 4).

FIGURE 4 GROWTH VELOCITY IN BOYS AND GIRLS



From: Tanner JM (1962) Growth at adolescence. 2nd Ed, Blackwell Sci. Publ., Oxford

Two characteristic growth spurts occur, a small juvenile or mid-growth spurt at around six to eight years (not visible in figure 4), and a larger adolescent growth spurt. The latter is caused by the onset of puberty during the phase of childhood growth. The tempo of growth increases markedly, and accelerates up to peak height velocity, the age after which growth starts to decelerate until it finally ceases. Age at takeoff (acceleration) is highly variable and sex-dependent, occurring at a younger age in girls, who also experience earlier and lower peak height velocity, compared to boys. (265) A review of growth characteristics of boys and girls concluded that peak height velocity occurred at a

mean age of 11.5 years in girls and 13.5 years in boys. These gender differences in the timing and to a lesser degree the extent of the adolescent growth spurt contribute to differences in final height between men and women. (217;218)

As discussed above, secular trends of earlier sexual maturity and age at peak height velocity have been accompanied by increases in leg length. (266) Tempo of growth, timing and rate of skeletal maturation and sexual development may therefore play a role for associations between poor growth and adult disease risk; however, research is limited by the availability of longitudinal data required for the analysis of velocity. (267) Participants of the oldest ongoing birth cohort study with repeated measures of anthropometry were born in 1946, and number of cardiovascular events in this study is still insufficient for analysis; in addition, identification of age at peak height velocity requires very frequent measures of height throughout puberty, which are generally unavailable. One recent report from the 1946 cohort showed that age at puberty was inversely associated with adult systolic and diastolic blood pressure in men, but not women. Adjustments for prenatal growth, prepubertal and adult body mass index and height did not account for these associations, despite those maturing early being heavier and shorter in terms of total height and relative leg length in adult life. (268)

The interpretation of the influence of age at peak velocity on adult height is complex. On the one hand faster linear growth during infancy and childhood is associated with earlier peak height velocity, with short children entering puberty later than tall children. (147) On the other hand, earlier puberty leads to earlier cessation of growth, fusion of epiphysial growth plates and restricted acquisition of lean body mass. Extended growth prior to adolescence due to later maturity therefore increases final height; however, children with delayed maturation attain a height somewhat below their genetic target. (158) In summary, the importance of growth velocity for adult cardiovascular risk remains uncertain.

Attained versus expected height

The analysis of height at one point in time does not account for growth at different phases and rates, which may differ in their importance for cardiovascular risk. Moreover, in adults of similar height some will have fulfilled their genetic growth potential, but others will have experienced limited growth due to environmental restrictions, including malnutrition, infections and psychosocial deprivation. This fundamental difference is likely to be unequally distributed among the different socioeconomic strata. If higher rates of cardiovascular disease were only observed in people who fail to reach their expected height, this would be more consistent with an environmental exposure as the underlying cause, and recent evidence from twin studies has been in support of this. (189)

ALTERNATIVE EXPLANATIONS FOR THE ASSOCIATION BETWEEN POOR GROWTH AND CARDIOVASCULAR RISK

Several alternative explanations exist for the association between poor growth and cardiovascular disease.

Chance

As demonstrated above, a large number of studies have found highly statistically significant associations between different indicators of poor growth and coronary heart disease risk in adulthood, suggesting that observations are unlikely to have occurred by chance alone.

Bias

However, systematic errors in the design, collection and analysis of data, and the interpretation and publication of results may lead to biased estimates. These distortions are likely to influence findings from case-control studies more in comparison to those from prospective cohorts, which have provided the majority of evidence for the association between short stature and coronary heart disease. However, recent examples in the literature demonstrate that even findings that were consistent across a number of cohort studies could not be confirmed in randomised controlled trials, which are less prone to the effects of bias and confounding. (269-271) This highlights that results from cohort studies, even if carefully adjusted for potential confounding factors, have to be interpreted with caution, particularly when studying exposures that are socially patterned.

Publication bias

As mentioned above, publication bias of studies relating birthweight to adult blood pressure has been suggested. (231) This may also be the case investigating the effects of height, which is a routine measure in many studies of different designs, and only authors with significant findings may decide to report those. The lower number of smaller studies with negative findings that have been published

potentially reflect this. However, publication bias seems less likely for studies investigating components of height, as these are not commonly measured and results from cohort studies with this information may therefore be more systematically represented in the literature.

Survival bias

Studies have included non-fatal as well as fatal coronary heart disease and stroke events, and it is therefore unlikely that better survival of taller people plays a major role in findings of an association between shortness and cardiovascular mortality. A healthy survivor effect before recruitment into cohort studies is also unlikely to cause associations biased in favour of a protective height effect, as first, only a small proportion of people in developed countries die before adulthood, and secondly, early accidental or violent causes of death are more common in socially disadvantaged and shorter people, making taller people more likely to survive into adulthood and develop chronic disease.

Selection bias and reverse causality

Analyses of data from the original Whitehall study suggested an attenuation of height effects with increasing duration of follow-up. (272) This was attributed to differential height reduction before study entry. Impaired growth through childhood illness and shrinkage in adulthood owing to morbidity will result in shorter adult stature. Both situations may lead to selective premature mortality, and the apparent protective effect of taller stature would diminish with increasing follow-up time if the association between height and mortality was restricted to participants whose short height was a result of existing disease in childhood or adulthood. Although it has not been investigated whether this assumption holds with longer term follow-up of the Whitehall or other cohorts, evidence from analysis of leg length or height measured in childhood or young adulthood contradict the notion that bias introduced by shrinkage of ill participants and thus reverse causality play a major role in the association between height and coronary heart disease.

Confounding

Anatomical and physiological characteristics associated with tall stature may confound the association between poor growth and cardiovascular risk.

Small-calibre arteries

First, the vessel diameter of taller people is larger, and this has been associated with improved survival in studies of hospitalized patients after myocardial infarct. (273) The same absolute degree of atherosclerosis may result in clinical disease earlier or present with more severe symptoms in shorter people with relatively smaller vessel diameters. Although information on vessel size is not commonly available, studies using ultrasound measures of vascular function have found associations after accounting for vessel size. (6)

Lung function

Secondly, taller people have a larger lung volume, and thus for mechanical reasons better lung function, for example as measured in forced expiratory volume in one minute (FEV_1). Because of this strong relation, estimates of FEV_1 in clinical assessment or for research purposes commonly account for height. (274) Because lung function is an important predictor of cardiovascular risk, in both smokers and life long non-smokers, (275) it has been regarded as a confounder of the association between height and cardiovascular disease. In some, (171;172;181;275) but not all studies, (186) adjustment for lung function attenuated or explained differences in cardiovascular disease according to height.

It has been argued that the specific association between leg length and CVD mortality is unlikely to be explained by lung function, as trunk length would be expected to show a stronger association with lung volume and function. (222) Contrary to this, one recent study found that the association between leg length and FEV_1 was slightly greater than the association between trunk length and FEV_1. (223)

However, the same study also showed that although adjustment for both smoking and FEV_1 attenuated the observed effects, some association between leg length and CHD remained. This and previous studies have suggested that height and lung function may both act as indicators of adverse exposures in early life which in turn increase cardiovascular risk, (276;277) and that accounting for lung function in studies of height may represent overadjustment. (223;225)

Common genetic polymorphisms

It is possible that genetic factors that influence growth also have a role in early programming of CHD. However, there is little evidence of shared genetic determinants. (278) Gunnell et al. investigated associations between components of height and cardiovascular risk factors and found that controlling for parental stature had little effect on their findings, (225) and this was interpreted as evidence against underlying genetic influences. Data from the STANISLAS family study, investigating familial clustering between height and cardiovascular risk factors has provided further evidence that genetic influences do not seem to play a major role. (279)

Twin studies, leaving their own limitations aside, provide a more powerful way of disentangling genetic and environmental effects. For example, if in a twin study differences in height between monozygotic twins were associated with different rates of cardiovascular disease, this would strongly suggest pre- or postnatal environmental exposures as the cause. Indeed, one nested case-control study among twins found that the shorter twin in a monozygotic or dizygotic twin pair was more likely to die of heart disease than the taller, (188) and this was interpreted as evidence of an environmental basis for the association between shortness and coronary heart disease risk. In support of this, recent evidence from a study of 35,000 twin pairs showed an inverse association between height and mortality from CHD within monozygotic discordant twin pairs, also pointing towards environmental factors directly affecting growth and CHD, as discussed earlier. (189)

In summary, owing to the multifaceted aetiology of coronary heart disease, it seems likely that a combination of factors from different stages of the life course contributes to the association between poor growth and cardiovascular risk. The aim of this thesis is to shed light on which period of growth may be particularly important for atherosclerosis and cardiovascular risk. This may help to identify specific growth limiting factors that are important and understand aetiological mechanisms involved.

CHAPTER 4: FIRST OBJECTIVE

OBJECTIVE

To identify which specific period of growth is particularly important for the development of arterial stiffness, I will use components of adult height as markers of growth at different ages and compare their associations with arterial stiffness, as indicated by high peripheral pulse pressure.

STUDY DESIGN OF THE MRC NATIONAL SURVEY OF HEATH AND DEVELOPMENT

Participants

The Medical Research Council's National Survey of Health and Development is a prospective birth cohort study of a class stratified sample (5362 births; 2547 women, 2815 men) of all births that occurred in the first week of March 1946 in England, Scotland and Wales.

Follow up included 20 contacts with the whole cohort between birth and 53 years of age, when 3035 participants (1472 men, 1563 women) provided information. The majority of participants (n=2989) were then interviewed and measured at home by trained research nurses using a standardized protocol. Those not visited at home completed a postal questionnaire (n=46). The participation rate was 70.4 percent among survivors still resident in England, Wales or Scotland, and 89.6 percent for whom contact was attempted. Contact was not attempted for those previously refusing to take part (n=640), living abroad at time of interview (n=119), emigrated (n=461), or those who had already died (n=469).

The data collection received MREC approval, and respondents gave informed consent to each set of questions and measures. The sample is reasonably representative of the national population of the same or similar age. (280) Similar data collections occurred at ages 36 (n=3322) and 43 years (n=3262). (281)

Measurements

Anthropometry

At age 53 years measures of weight (kg), height (cm), trunk length (cm), waist (cm) and hip circumference (cm) were obtained. Weight was measured to the nearest 0.1 kg with participants wearing light indoor clothing and no shoes. Height was measured to the nearest 0.5 cm, using a portable stadiometer with participants standing without shoes and with heels against the wall as tall as possible with the head in the Frankfort plane. Sitting height, used to represent trunk length, was measured to the nearest 0.5 cm. Participants were asked to sit upright, with their back against the vertical stand of the stadiometer, on the base plate located on a hard, flat seat, with the head in the Frankfort plane and their feet on the floor. Leg length was calculated as the difference between standing and sitting heights. Waist-hip ratio (WHR, waist circumference (cm) divided by hip circumference (cm)) and body mass index (weight (kg) divided by height squared (m^2)) were considered as possible confounding factors of the associations between shortness and arterial pressure measures.

Blood pressure

At age 53 years, peripheral blood pressure was measured, in duplicate, in the brachial artery of the upper left arm with the validated Omron HEM-705 automated digital oscillometric sphygmomanometer after 5 minutes of rest, with the participant sitting. The second reading was used

in the analysis. Pulse pressure was calculated as the difference between systolic and diastolic blood pressures. For comparison purposes, all blood pressure outcomes were converted into internally derived sex specific standard deviation scores (z-scores).

Birthweight

Birthweight was used as an indicator of prenatal development. It was recorded by midwives or obstetricians at birth, and taken from records by health visitors.

Social class

Father's social class was based on his occupation when survey members were 4 years old, according to the Registrar General's Classification. If this information was unavailable, father's occupation when survey members were aged 11 years (n=125) was used instead. The six classes were collapsed to four groups for the analysis, the highest classes I and II (professional and intermediate occupations) were combined, as were the lowest classes IV and V (semi-skilled or unskilled occupations).

Smoking

At age 53 years participants provided information on smoking status, and "current" smokers were distinguished from "previous" and "never" smokers.

Medication

During the interview at age 53 years, the nurses recorded any information on participants' current medication. This information was coded according to the British National Formula (BNF) Number 40 (2000). In this analysis information on current use of antihypertensive medication (taking drug versus not taking any drug of the following BNF sections: 2.2 - Diuretics, 2.4 – Beta blockers, 2.5 – Drugs affecting the renin-angiotensin system and some other antihypertensive drugs, 2.6.2- Calcium-channel blockers) was used.

STATISTICAL ANALYSES

Means or percentages of selected characteristics of men and women participating at the 53 year follow-up visit were calculated; t-tests or Pearson chi-squared tests were performed to test differences between the sexes, respectively. Linear regression models were used to compare differences in pulse pressure, systolic and diastolic blood pressure according to adult trunk length, leg length and height at 53 years. For the purpose of this analysis sex specific quartiles were used as cut-points to obtain four equal sized categories for each component of stature; these are included in Table 2. Mean pulse pressure, systolic and diastolic blood pressure were calculated for each group, including participants using antihypertensive medication (14.7%), and tests for linear trend across categories carried out. Multiple regression models of standardized blood pressure outcomes were then used to test the associations of interest, adjusted for characteristics thought to confound the association. First, current use of antihypertensive medication body mass index, waist to hip ratio and smoking status were included (model A). Second, to investigate the separate and joint influences of components of height and early social conditions for adult blood pressure, childhood social class was additionally included in the model (model B). Finally, the role of prenatal growth, as indicated by weight at birth, was considered (model C).

All analyses were undertaken separately for men and women and were restricted to participants with complete information on all measures (1363 men, 1355 women). Analyses were repeated restricted to those without any antihypertensive medication to test the robustness of our findings in the untreated group. All analyses were performed using SPSS for Unix version 10 (SPSS Inc., Chicago, Illinois).

RESULTS

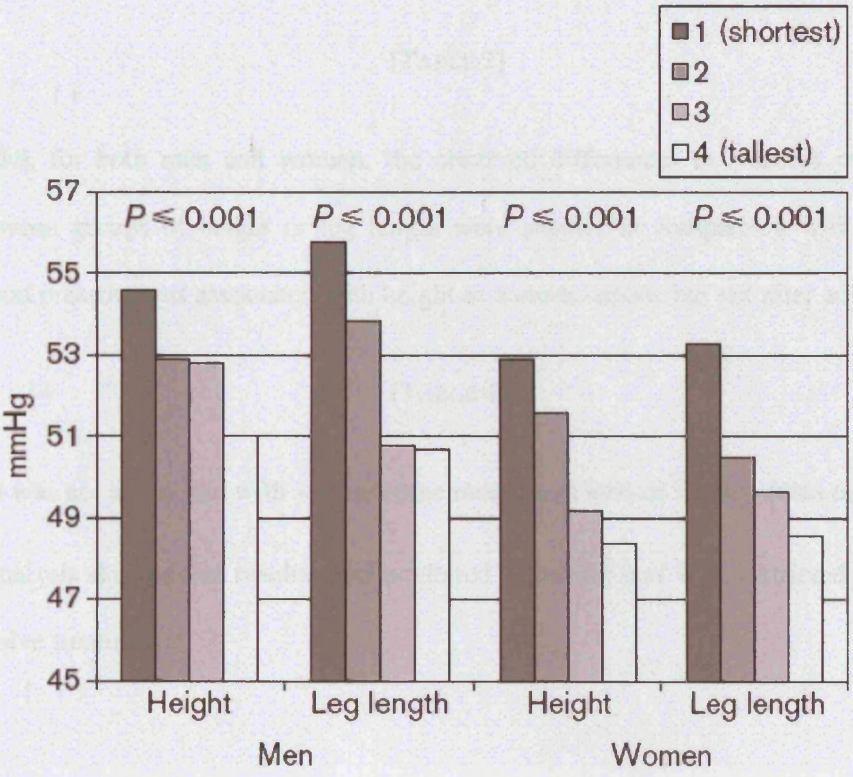
Information on contact and response rates at the most recent follow-up at 53 years of the National Survey of Health and Development at are shown in appendix 1; characteristics of the sample at age 53 years are shown in table 1. Men were heavier at birth and age 53 years, taller in terms of height, leg and trunk length, had larger waist circumferences, and higher pulse pressure, systolic and diastolic blood pressure, compared to women. On average, men were more likely to be educated at A levels or above, while women were more likely to currently be in non-manual occupations.

No significant differences were observed in terms of BMI, father's social class, antihypertensive drug use, current smoking and exercise levels.

[TABLE 1]

Pulse pressure increased linearly with decreasing height and leg length (figure 5, table 2) in men and women (shortest compared with the tallest height (leg length) group, men 54.6 versus 51.0 mmHg (55.8 versus 50.7 mmHg), women 52.9 versus 48.4 mmHg (53.3 versus 48.6 mmHg); p-value ≤ 0.001 in each case).

FIGURE 5 MEAN PULSE PRESSURE ACROSS GROUPS OF HEIGHT AND LEG LENGTH



Adjustment for adult confounding factors, current use of cardiovascular medication, central and total obesity and smoking status (model A) did not alter the results and levels of significance remained generally unchanged. Additional inclusion of either childhood social class (model B) or birthweight (model C) attenuated the effect of height on pulse pressure only slightly and in men only (p-value ≤ 0.01).

[TABLE 2]

Systolic blood pressure showed the same trends as pulse pressure for height and leg length in women and leg length in men (p-value ≤ 0.001 in each case). The association between height and systolic

pressure was slightly weaker in men (p-value=0.006) and lost statistical significance after inclusion of either birthweight or childhood social class in the model.

[TABLE 3]

In each model, for both men and women, the observed differences in z-scores of systolic blood pressure between groups of height or leg length were smaller in comparison with pulse pressure. Diastolic blood pressure was associated with height in women before, but not after adjustment.

[TABLE 4]

Trunk length was not associated with any outcome measure in men or women (data not shown).

Sensitivity analysis showed that results were unaltered when analyses were restricted to those without antihypertensive treatment.

CONCLUSIONS

Short height and leg length are associated with increased pulse pressure and systolic blood pressure, but not diastolic blood pressure, in middle aged men and women. Measures of differential prenatal growth or childhood social conditions contributed little to these associations. Greater levels of arterial stiffness and blood pressure in men and women with shorter height and leg length may be due to greater initial levels, a steeper increase in these measures as they rise with age, or a combination of both. This has not previously been investigated and will be addressed in the next chapter.

CHAPTER 5: SECOND OBJECTIVE

OBJECTIVE

To investigate whether poor growth contributes to the age related increase of pulse pressure and systolic blood pressure, I will investigate associations between components of height as markers of growth at different phases and the tracking of arterial stiffness, using repeated measures of pulse pressure and blood pressure.

STUDY DESIGN OF THE MRC NATIONAL SURVEY OF HEATH AND DEVELOPMENT

Participants

Data collections similar to those described in chapter 4 occurred at ages 36 (n=3322) and 43 years (n=3262) in the MRC National Survey of Health and Development. (281)

Measurements

Anthropometry

The measurement techniques of height, weight and components of height at 53 years are described in chapter 4; corresponding measures were obtained according to the same standardized protocol at age 43 years. Trunk length was not measured at 36 years and so leg length was also unavailable at this age. For all analyses, information on height, leg and trunk length as measured at 53 years, and only if not available, at 43 years (n=474), was therefore used, corresponding to analyses described in the

previous chapter. For descriptive purposes, sex specific tertiles were used as cut-offs, to divide these variables into three equally sized groups.

Blood pressure

In addition to blood pressure measures described in chapter 4, systolic and diastolic blood pressure was measured in duplicate by trained research nurses at 36 and 43 years, according to a standardized protocol. At these ages blood pressure was measured using the Hawksley random zero sphygmomanometer. At each age, the second blood pressure reading was used for analysis unless only the first measurement was available. Pulse pressure was calculated as the difference between systolic and diastolic pressure at each age.

Medication

In addition to participants' current medication at 53 years, as described in chapter 4, participants were asked at ages 43 and 36 years whether they had taken any prescribed medicines or tablets for high blood pressure in the last year.

Other variables

Measures of birthweight, social class, education, smoking and exercise are described in chapter 4.

STATISTICAL ANALYSES

To describe the sample and identify potential confounding factors, the mean or percentage of selected variables that have previously been suggested to influence blood pressure were calculated for each of three equally sized categories of height, leg and trunk length. Pearson chi-squared tests for trend across these categories were performed to investigate statistical associations. Linear regression analysis was used to estimate cross-sectional relationships between the explanatory variables and

blood pressure measures. Models were fitted including both men and women and an interaction term between sex and either height, leg or trunk length was used to investigate whether the effect of anthropometry on blood pressure differed significantly between the sexes. These analyses were performed using Stata 7.0 software (StatCorp. Stata Statistical Software: Release 7.0 College Station, Texas: Stata Corporation, 2002). (282)

Multilevel models were then used, (283) with blood pressure as a repeated outcome measure, using the package MLwiN. (284) In these models, repeated measures of blood pressure at different ages (level 1) are nested within individuals (levels 2), taking account of the correlation between repeated measures on the same individual and allow for incomplete outcome data as long as a missing at random process can be assumed. (283;285;286)

First, the change in blood pressure with age was modelled. The intercept (mean blood pressure at 36 years), and linear and quadratic terms for age were used to model the non-linear change in blood pressure over time. In all models, the variance of blood pressure was allowed to change with age (level 1 random variation), and both intercept and slope were allowed to vary between individual cohort members (level 2 random variation).

In all analyses, separate curves were modelled for men and women by including sex in the model and also interaction terms between sex and the linear effect of age, and sex and the quadratic effect of age.

Random effects

The level 2 variance parameters correspond to estimates of the population variance of the intercept (blood pressure at 36 years) and slope (change in blood pressure between 36 and 53 years). These variances were used to calculate expected ranges (95% ER) for the intercept and slope.

Examining residuals

Before developing this model further, the appropriateness of the model assumptions and evidence of outliers was examined. Normal scores plots of level 1 and 2 residuals, presence of outliers and heteroscedasticity were assessed graphically.

Effect of components of height on blood pressure

The intercept was then allowed to vary according to height, leg or trunk length, respectively. To test whether associations between components of height and blood pressure changed with increasing age, interaction terms between the anthropometric measures and age were added to each model.

Significance tests

Chi^2-tests based on $(\hat{\beta}/se(\hat{\beta}))^2$, where $\hat{\beta}$ is the regression coefficient, were carried out to assess levels of significance for the fixed effect parameters as suggested by Goldstein. (283)

Analyses were first performed with the maximum number of observations (9086) and repeated including only observations from participants with information on all covariates (7304), required for adjusted analyses.

Adjustments were performed introducing potential confounders (or groups of confounders representing similar underlying mechanisms) one at a time and all together, to investigate their separate and joint effects on the associations of interest. First, antihypertensive treatment status for each time point was considered. Interactions between components of height and treatment status

were also added to assess whether associations differed according to treatment status. Secondly, body mass index at each time point was added to the model, influencing both intercept and slope, as a time varying covariate, as separate analyses of this cohort had indicated the importance of body mass index on blood pressure and its change with age. (281) Thirdly, the influence of several other adult factors, including social class, smoking, exercise and educational attainment was considered. Fourthly, corresponding to earlier analyses, the impact of early life factors was investigated by introducing birthweight and father's social class into the model. Lastly, a model was fitted including all variables.

Additional analyses were carried out using sex-standardized measures of blood pressure (z-scores) to assess whether any change in the variance of blood pressure with age, potentially due to the different measurement instruments used, had an impact on the findings.

RESULTS

A total of 3414 participants (1721 men, 1693 women) had at least one measure of blood pressure (both systolic and diastolic blood pressure) and corresponding height and leg length measures.

Characteristics of the sample in relation to height, leg and trunk length

Participants' birthweight was found to be equally and positively associated with total height and both of its components, while body mass index at 36, 43 or 53 years was negatively associated with height and leg length, but not trunk length.

[TABLE 5]

In contrast, central obesity (waist-hip ratio) measured at the most recent home visit was related to upper body (trunk) length only. Higher proportions of participants with taller height, longer legs or trunks were found to have fathers from non-manual social classes, have education at A-level or above and to be working in non-manual occupations. They were also more likely to exercise regularly and not to be current smokers, when compared to those of shorter height, leg or trunk length. Chi-squared tests for trend across groups of height, leg and trunk length showed that associations were highly statistically significant (p-value ≤ 0.007 in all cases, except for the association between leg length and exercise, p-value=0.02), with the only non-significant association being between leg length and smoking (p-value=0.44).

Participants of taller height were also less likely to be treated for hypertension at each of the ages considered (p-value $\leq$ 0.002 in each case). Leg length was significantly associated with antihypertensive treatment at 43 and 53 years, and trunk length with treatment at 36 years. None of the significant associations showed deviation from linearity.

Associations between height, leg and trunk length and blood pressure at each age

As shown in the previous chapter, pulse pressure and systolic blood pressure at 53 years were significantly lower in men and women with greater height and leg length, but not trunk length; similar relationships were also observed at age 43 years.

[TABLE 6]

Regression estimates for all three measures of blood pressure were smaller at 43 years for both height and leg length, compared to those at age 53 years. Taller height was also significantly associated with lower systolic and diastolic blood pressure at 36 years, as was shorter leg length with lower diastolic blood pressure. Although regression coefficients for pulse pressure at this age were in the same direction, effects were smaller and not statistically significant.

Of 27 tests for interactions that were carried out to assess whether the effect of components of height differed between the genders, only 3 were statistically significant (p-value < 0.05). At 53 and 43 years, none of the tests for interaction reached conventional levels of statistical significance. Estimates for men and women are therefore presented combined, adjusted for sex, in all further analyses.

Multilevel modelling of the associations between components of height and repeated measures of blood pressure at 36, 43 and 53 years

Effect of age and sex on blood pressure (basic model)

A multilevel model was built successively, first in the sample with the maximum number of observations (9086). The basic model included the constant (intercept) and the effect of age (slope), both of which were allowed to vary randomly within and between individuals, as well as fixed terms for the quadratic effects of age, sex, and interaction terms between sex and age and sex and the quadratic effect of age. The random effect of the quadratic increase of blood pressure was also considered, but found to be non-significant and therefore not included in the model. Regression equations from each model and estimates obtained for all parameters included are given in appendix 2.

Examining residuals

Plotting standardized residuals from each basic model against their normal scores resulted in a nearly straight line, indicating that level 1 and 2 residuals were approximately normally distributed. There was no evidence of a non-linear trend of level 1 residuals with age (from a model excluding the level 1 random variation with age), thus no evidence of heteroscedasticity. Plotting standardized level 2 residuals for the intercept term against standardized level 2 residuals for the slope showed a negative correlation, as also seen from the negative covariance between the two terms in the regression equation (appendix 2). This indicates that participants with lower blood pressure at age 36 experienced a steeper increase of blood pressure over time, possibly representing the effect of regression to the mean. Plots of level 2 ranks with 1.39 standard error intervals around them, (283) indicated significant differences between person specific intercepts (blood pressure at 36 years) and, slightly less pronounced, person specific slopes.

Pulse pressure

Men's average pulse pressure at age 36 years (intercept) was significantly higher than women's pulse pressure at the same age (appendix 2 and figure 6).

FIGURE 6 PULSE PRESSURE OF MEN AND WOMEN BETWEEN THE AGES 36 AND 53 YEARS

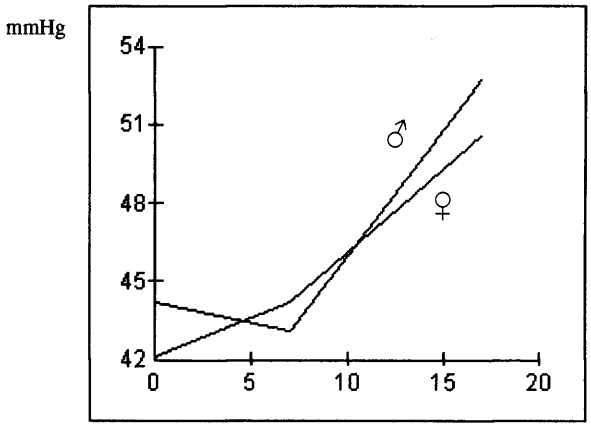


Figure 6 also shows that the effect of age on pulse pressure differed significantly between men and women. The greater linear and smaller quadratic increase in women compared to men, leads to lower pulse pressure at age 43 years in men compared to women, despite their higher levels at the previous measurement (36 years).

Random variation

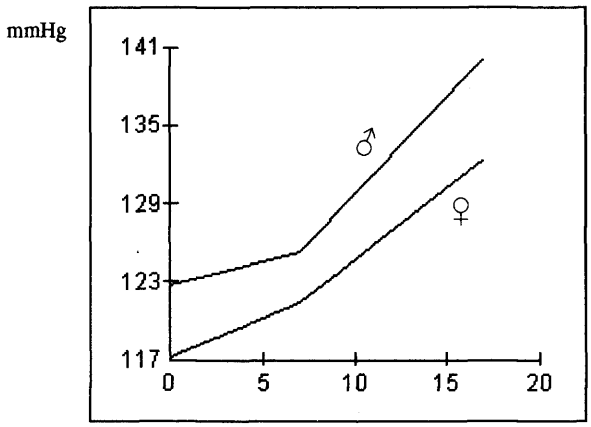
As all models include sex interactions, the following results are given here for the baseline group, in this case men, for easier comparisons with the corresponding equation in appendix 2. The between person variance in pulse pressure at age 36 years was 36.593. This gives a 95% expected range (ER)) in intercepts from 32.39 to 56.10 mmHg (44.25 +/- 1.96$\sqrt{}$ 36.593). The between person variance in slope was 0.146, indicating a 95% ER from –1.374 to 0.124 mmHg per year. The covariance (SE) of –0.711 (0.284) between individuals' intercepts and slopes implies that lower pulse pressure at age 36 years was associated with a steeper increase and vice versa, as previously indicated by the residuals. There was also significant variability of pulse pressure around person-specific predicted pulse pressure at age 36 (level 1 residual standard deviation of 9.28 mmHg ($\sqrt{}$ 86.036), which was allowed to vary with age.

Systolic blood pressure

Similarly to pulse pressure, systolic blood pressure at age 36 years was lower in women compared to men, and significant interactions were observed between sex and both the linear and quadratic increase of blood pressure with age (figure 7).

In contrast to pulse pressure, men's levels of systolic blood pressure were consistently higher compared to those in women. Estimates and more detailed information on the random variation in this model are presented in appendix 2.

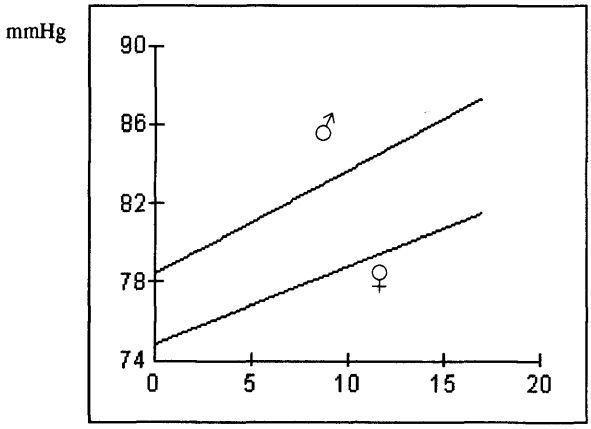
FIGURE 7 SYSTOLIC BLOOD PRESSURE OF MEN AND WOMEN BETWEEN THE AGES 36 AND 53 YEARS.



Diastolic blood pressure

In contrast, the change in diastolic blood pressure with age was found to be linear and the quadratic increase observed for pulse pressure and systolic blood pressure was non-significant. Again, the intercept (diastolic blood pressure at 36 years) was higher in men compared to women. The increase of diastolic blood pressure with age was steeper in men, compared to women. Results are displayed in figure 8 and more detail is presented in appendix 2.

FIGURE 8 DIASTOLIC BLOOD PRESSURE OF MEN AND WOMEN BETWEEN THE AGES 36 AND 53 YEARS



Effects of height, leg and trunk length on pulse pressure, systolic and diastolic blood pressure

Separate inclusion of height, leg or trunk length and interactions between each of the components of height and age in the basic multilevel model showed that the effects of both height and leg length on pulse pressure became significantly stronger with age.

[TABLE 7]

The linear change in pulse pressure (95% CI) was found to be –0.020 mmHg (-0.026; -0.014) per year lower for every centimeter increase in leg length. The change in systolic blood pressure was found to be –0.021 mmHg (-0.029; -0.013) per year lower for every centimeter increase in leg length. The model leads to an estimated effect of leg length on systolic blood pressure at 36 years of -0.086 mmHg (-0.18; 0.012) per centimeter increase in leg length and one of –0.44 mmHg per centimeter increase in leg length at 53 years. These estimates are of similar magnitude to those observed in the earlier cross-sectional analyses.

Diastolic blood pressure at 36 years (intercept) was significantly influenced by height and leg length, however, these effects did not appear to get stronger over time, as indicated by the non-significant results for the slope (p-value > 0.5 in both cases).

Trunk length was not related to any of the blood pressure measures at 36 years, and none of these associations changed with age. Trunk length was therefore omitted from all further analyses.

Adjusted analyses

Results from analyses of the restricted sample with complete information (7304 observations) showed that estimates for the amplification of the effect of height and leg length on pulse pressure and systolic blood pressure with age were of similar magnitude compared to previous analyses. Levels of significance remained identical.

[TABLE 8]

For pulse pressure, individual adjustment for confounders or groups of confounders had only a small effect on the estimates; coefficients were reduced only slightly more when all variables were included simultaneously in the same model and levels of significance remained unchanged (p-value ≤ 0.001 in all cases). For systolic blood pressure, body mass index and its increasing importance for blood pressure with age had the largest impact on the amplification of the effect of height or leg length. Full adjustment including all variables under consideration did not reduce estimates much further. Again, levels of significance remained high (p-value ≤ 0.01 in all cases). In addition, no evidence was found that the associations between either height or leg length and blood pressure were modified by treatment status (results not shown).

Sensitivity analysis

Replacing the blood pressure measures by their internally derived standard deviation scores did not alter associations between both height and leg length and pulse pressure or systolic blood pressure or the p-values.

CONCLUSIONS

These results support the hypothesis that greater levels of pulse pressure, a measure of arterial stiffness, and systolic blood pressure in men and women with shorter height and leg length are due to a steeper rise of these measures with age. Growth limiting factors may increase susceptibility to the effects of ageing on the arterial tree and thus contribute to the tracking of cardiovascular risk throughout life.

CHAPTER 6: THIRD OBJECTIVE

OBJECTIVE

To explore whether associations are specific to pulse pressure, i.e. arterial stiffness, cross-sectional associations between markers of growth and a range of cardiovascular risk factors available in the Whitehall II Study will be investigated; this will also allow to replicate (validate) associations between components of height and pulse pressure in another cohort.

STUDY DESIGN OF THE WHITEHALL II STUDY

Participants

The target population for the Whitehall II study was all the London-based office staff, aged 35–55, working in 20 Civil Service departments. With a response rate of 73%, the final cohort consisted of 10308 participants (6895 men, 3413 women) at the first phase of data collection in 1985-88. (287) However, the true response rate was higher as around 4% of those invited were not eligible for inclusion. Although mostly white collar, respondents covered a wide range of employment grades from office support to permanent secretary. Participants were predominantly white European 91.5%, 2.8 % were Afro-Caribbean, 4.3% South Asian, and 1.4% reported other ethnic origins. Ethical approval for the Whitehall II study was obtained from the University College London Medical School committee on the ethics of human research.

The screening at baseline (phase 1) involved a clinical examination, and a self-administered questionnaire containing sections on demographic characteristics, health, lifestyle factors, work characteristics, social support, and life events. Since the baseline screening, six more data

collection rounds have been completed; successive phases alternated between collecting data by self-administered questionnaire only and clinical screening in addition to questionnaire completion. Clinical examinations were carried out in 1992-3 (phase 3), 1997-9 (phase 5) and 2003-4 (phase 7). Of the 10308 participants at baseline in the Whitehall II study, 8354 (81%) responded at phase 3, 7824 (76%) at phase 5 (7269 attending the clinic examination) and 6944 (67%) at phase 7 (5743 attending the clinic examination, 741 having a home visit and 4112 with vascular measures).

Measurements

Anthropometry

Measurements of height and weight were carried out according to a standard protocol at each clinic examination; standardized assessment of waist and hip circumference were carried out at the phase 3 (1991-93), 5 (1997-99) and 7 (2003-4) examinations. (288) Body circumferences were measured with subjects in the standing position and unclothed, utilizing a fibreglass tape-measure at 600 g tension. The waist circumference was measured halfway between the costal margin and iliac crest and hip circumference at the level of the greater trochanter. BMI was calculated as weight divided by height squared (kg/m^2) at each phase. Waist to hip ratio was calculated as waist divided by hip circumference and expressed as a percentage.

At phase 5, sitting height, used to represent trunk length, was measured to the nearest 0.5 cm. Participants were asked to sit upright, with their back against the vertical stand of the stadiometer, on the base plate located on a hard, flat seat, with the head in the Frankfort plane and their feet on the floor. Leg length was calculated as the difference between standing and sitting heights. Self reported birthweight was obtained from questionnaires and data collected at phases 3 and 5 combined. For comparison purposes, all anthropometric measures were converted into internally derived sex specific standard deviation scores (z-scores).

Cardiovascular risk factors (phase 5)

Measurements cardiovascular risk factors were carried out according to a standard protocol at the phase 5 examinations (1997-99). (289) Systolic and diastolic blood pressures were measured twice in seated resting subjects; pulse pressure was calculated as the difference between systolic and diastolic blood pressures. Participants reported whether they ever received treatment for high blood pressure (men 12.4 %, women 15.9 %). A venous blood sample was obtained following an overnight fast in the morning or in the afternoon after no more than a light fat-free breakfast eaten before 8 am. Glucose was determined in fluoride plasma by an electrochemical glucose oxidase method. Cholesterol and triglycerides were measured in a centrifugal analyzer by enzymatic colorimetic methods. HDL cholesterol was determined after dextran sulfate-magnesium chloride precipitation of non-HDL cholesterol. An oral glucose tolerance test (75 g anhydrous glucose) was administered and post load glucose measured in citrated plasma after 2 hours. Diabetes was defined according to 1999 World Health Organization (WHO) criteria. (290) A person was regarded as having diabetes if the fasting plasma glucose was $\geq$ 7 mmol/l (126 mg/dl) or the 2-h glucose after the oral glucose tolerance test was $\geq$ 11.1 mmol/l (200 mg/dl), or if he or she was using diabetes medication (oral or insulin). People with missing information on the 2 hour glucose and/ or drug use were classified as having diabetes if they reported a history of diabetes, even in the absence of an abnormal fasting glucose.

Socioeconomic indicators and health-related behaviour

Childhood social class was based on father's occupation, and grouped according to the Registrar General's Classification; participants with the highest social classes (I/II) in childhood were distinguished from all others. On the basis of salary and work role, the civil service defines a hierarchy of employment grades, and participants were assigned to one of three levels: unified grades 1-7 (high employment grades), executive officers (middle grades), and clerical and support staff (lower grades). (127;291)

Health-related behaviours were reported at Phase 5. Alcohol intake was based on consumption during the week prior to the interview with high intake defined as 15 or more units per week for women and 22 or more units per week for men, based on sensible drinking recommendations. (289) Smoking status distinguished never-smokers from previous and current smokers.

STATISTICAL ANALYSES

Of the 7269 (5090 men, 2179 women) participants attending the phase 5 clinic examination, participants with missing data for any component of stature (2278 missing) were excluded from analyses of cross-sectional associations between anthropometry and cardiovascular risk factors, leaving a total of 4991 participants (1534 women, 3457 men).

Differences in means of continuous and proportions of binary characteristics between men and women included in the study were assessed using t-tests and chi-squared tests, respectively.

Pearson correlation coefficients were calculated for the anthropometric variables in both the NSHD and the Whitehall II Study (age adjusted), in order to compare correlations of components of height with birthweight obtained from hospital records at the time of birth (NSHD) versus recalled in adult life (Whitehall II Study).

Linear regression analysis was then used to assess cross-sectional associations of the anthropometric markers with continuous cardiovascular risk factors. The distribution of triglycerides was skewed and required transformation; the natural logarithm was used in

regression models. Coefficients from linear regression analyses represent the age adjusted absolute change in each continuous risk factor associated with one standard deviation increase in the anthropometric measure of interest; in the case of log transformed variables, 100 times the coefficient represents the percentage change in the risk factor of interest. Age adjusted analyses were conducted separately in women and men; first, using the complete sample and second, restricted to participants with complete information on covariates. Fully adjusted analyses of the restricted sample were then performed including adjustments for birthweight, childhood social class, adult grade, health behaviours (smoking, alcohol intake) and antihypertensive treatment for blood pressure outcomes.

RESULTS

Women and men differed significantly with respect to most measures; the most notable difference being the proportion in low employment grades. In participants attending both phases, mean height at phase 1 and 5 was similar in both men and women.

[TABLE 9]

Correlations between components of height and birthweight recorded at the time of birth (NSHD) versus recalled in adult life (Whitehall II Study) are presented in table 10. Overall, age adjusted correlations between height and both leg and trunk length were high, reflecting the fact that the latter two are components of the former. Correlations between birthweight and components of height were weaker and similar for leg and trunk length in men and women, ranging from 0.13-0.20 in both studies and sexes. While leg and trunk length were positively and moderately correlated in Whitehall II participants, they showed weak inverse correlations in the NSHD cohort.

[TABLE 10]

Anthropometry and cardiovascular risk factors

As expected, shorter height was associated with older age (table 11). Significant inverse associations were also observed between total body height and all blood pressure measures in women, and pulse pressure in men. In fully adjusted models, height was significantly associated with all blood pressure measures and waist-hip ratio in women, while it also showed inverse relationships with cholesterol, triglycerides and 2 hour glucose in men.

[TABLE 11]

Leg length was not associated with age at measurement in women, and only weakly in men. Strong inverse associations were observed between leg length and pulse pressure and systolic blood pressure in both sexes and diastolic blood pressure in women, before and after adjustments.

[TABLE 12]

Likewise, longer leg length was associated with lower levels of triglycerides in men and women, and lower cholesterol, 2 hour glucose and waist-hip ratio in men only, before and after adjustments. In contrast to results obtained for leg length, strong associations between age and trunk length were found in both sexes, such that shorter trunks were observed at older ages.

[TABLE 13]

Age and waist-hip ratio were the only measures significantly associated with trunk length in men and women before and after adjustments; a significant association was observed for 2 hour glucose in men, too. Associations that were initially found in age adjusted analyses between trunk length and the blood pressure measures, triglycerides and 2 hour glucose in women, were attenuated in the restricted sample and none remained statistically significant in fully adjusted models.

CONCLUSIONS

Correlations between components of height and birthweight were weak and comparable for leg and trunk length; similar results were observed in the Whitehall II Study, where birthweight was recalled in adult life, and the NSHD, where birthweight was recorded at the time of birth. Shorter leg length was strongly and inversely associated with higher pulse pressure and systolic blood pressure in both men and women of the Whitehall II cohort, before and after adjustment for several potentially confounding factors, in accordance with earlier findings from the NSHD. As suggested in previous studies, height and both of its components showed significant relationships with several other cardiovascular risk factors linked to lipid and glucose metabolism, indicating that associations are not restricted to blood pressure measures and are not entirely specific to leg length.

CHAPTER 7: FOURTH OBJECTIVE

OBJECTIVE

To advance the understanding of the aetiological mechanisms linking poor growth, arterial stiffness and coronary heat disease risk, and to avoid potential biases due to misclassification of CHD outcomes that rely on self report and routinely recorded information, I will investigate associations between adult markers of growth and objective measures of atherosclerosis, including specific non-invasive measures of vascular wall thickness (intima media thickness), arterial stiffness (beta stiffness index) and distensibility (distensibility coefficient).

STUDY DESIGN OF THE WHITEHALL II STUDY

Participants

Data collections similar to those described in chapter 6 occurred at phase 7 of the Whitehall II Study, when vascular measures were obtained.

Measurements

Ultrasound vascular measures

Ultrasound vascular measures were performed from July 2003 to October 2005 (phase 7) in the Vascular Physiology Unit, Institute of Child Health, London, United Kingdom. Measurements were taken in a quiet, temperature controlled (22-26 degrees centigrade) room, using a non-invasive, high- resolution ultrasound system, the Aloka 5500 with a 7.5 MHz transducer.

Participants were examined in a supine position, with the head turned at a 45 degree angle away from the side to be scanned.

Intima media thickness

Intima media thickness (IMT) was measured in the right and left common carotid arteries. Longitudinal images of the common carotid artery, triggered on the R-wave of the ECG, were magnified and recorded in DICOM format as a cine loop and saved on the hard drive of the ultrasound machine for later analysis. Common carotid artery IMT was measured at its thickest part 1 cm proximal to the bifurcation. A measurement was taken between the leading edge of the intima and the media-adventitia interface on 3 separate images on each side using electronic calipers and the mean of the 6 measures was used for analysis.

Arterial stiffness index and distensibility coefficient

Arterial wall movement was tracked and vessel diameter and distension determined on a beat-by-beat basis. Blood pressure was measured on the ipsilateral arm synchronous with the carotid distension measurement using an automatic oscillometric sphygmomanometer. The distensibility coefficient was calculated for each side and averaged.

The distensibility coefficient reflects intrinsic vascular wall elasticity and is expressed as mean percent change in cross-sectional area between diastole and systole relative to the area during diastole per unit change in blood pressure (kPa), it is calculated as DC=(2*dD)/(Dd*dP); dD denotes the change in arterial diameter during the heart cycle, Dd the arterial diameter during diastole, and dP the difference in blood pressure, i.e. pulse pressure.

Carotid artery stiffness was calculated by the pressure independent beta stiffness index and calculated as $\beta=\ln(SBP/DBP)/(dD/Dd)$.

Logarithmic transformations were performed for all three vascular outcomes to normalize their distributions.

Cardiovascular risk factors (phase 7)

Systolic and diastolic blood pressure were measured twice in seated resting subjects and hypertension defined as blood pressure ≥ 140/90 mmHg or use of antihypertensive medication. A 75-g oral glucose tolerance test was performed in the morning after a requested 8 hour fast; blood samples were obtained by venipuncture at 0 and 2 h, as described in the previous chapter. Diabetes was defined according to 1999 WHO criteria. (290) A person was regarded as having diabetes if the fasting plasma glucose was ≥ 7 mmol/l (126 mg/dl) or the 2-h glucose after the oral glucose tolerance test was ≥ 11.1mmol/l (200 mg/dl), or if he or she was using diabetes medication (oral or insulin). People with missing information on the 2 hour glucose or drug use were classified as having diabetes if they reported a history of diabetes, even in the absence of an abnormal fasting glucose (34 men, 32 women).

Fasting plasma lipids and lipoproteins were measured as described in the previous chapter. LDL cholesterol was calculated using the Friedewald formula. Dyslipidaemia was defined as either LDL cholesterol ≥ 160 mg/dl (4.14 mmol/l) or HDL cholesterol < 50 mg/dl (1.295 mmol/l) in women and < 40 mg/dl (1.036 mmol/l) in men, respectively, or statin use.

Coronary heart disease at phase 7

Potential cases of definite, non-fatal myocardial infarction were ascertained by questionnaire items on chest pain, (292) and doctor's diagnosis of heart attack at each phase. Details of physician diagnoses and investigation results were sought from clinical records for all potential cases of myocardial infarction. Twelve-lead resting electrocardiograms were performed at each clinic visit (Siemens Mingorec) and coded according to Minnesota criteria. (293) Based on all available data (questionnaires, study electrocardiograms, electrocardiogram and cardiac enzyme results from hospital records), non-fatal myocardial infarction was defined according to MONICA criteria. (294) Classification was carried out blind to other study data independently by two trained coders, with adjudication by a third in the (rare) event of disagreement. Definite angina was recorded for participants who reported symptoms of angina, (295) together with

corroboration in clinical records or abnormalities on a resting ECG, exercise ECG, or coronary angiogram.

Socioeconomic indicators and health-related behaviour

Information on demographic, socioeconomic and behavioural variables was obtained from the self completed questionnaires administered either at phase 1 (ethnic group, childhood social class, employment grade) or phase 7 (all other variables).

Childhood social class and employment grade were defined as described in the previous chapter. Education level was based on the highest educational qualification achieved and higher education distinguished from advanced secondary qualifications, ordinary secondary qualifications and no academic qualification. Financial indicators were derived from phase 7 questionnaires, using pre-coded categories. Annual personal income included the "amount received annually from salary or wages, pensions, benefits and allowances before deduction of tax"; annual household income included the "total annual household income from any source, including personal income" and household wealth included the "amount of money the respondent would have if s/he cashed in all household assets and paid off all debts".

Smoking status and high alcohol intake were defined as described in the previous chapter. Physical activity distinguished participants with $\geq$ 2.5 hours of vigorous physical activity per week ("sufficient") from those who were less physically active. (296) A healthy diet indicator (scored 0-3) was constructed as previously reported. (297)

STATISTICAL ANALYSES

Age adjusted means and proportions of cardiovascular risk factors, health behaviours, socioeconomic and anthropometric measures were calculated separately for men and women and differences assessed using t-tests or chi-squared tests, as appropriate.

Differences in cardiovascular risk factors, health behaviours and socioeconomic variables across quartiles of intima media thickness, arterial stiffness and distensibility were obtained, separately

for men and women, and adjusted for age; p-values are based on Mantel-Haenszel tests for trend. Associations between standardized scores (z-scores) of the anthropometric measures and the log transformed continuous vascular outcomes were examined using multiple regression analyses.

Adjustments were performed in several steps: a) adjusting for age, b) additionally including concurrent weight, and c) adding ethnic group and cardiovascular risk factors (prevalent CHD, diabetes, hypertension, dyslipidaemia, and smoking). Further adjustments for socioeconomic variables that emerged as potentially important mediators or confounders in earlier analyses (see above) were performed for associations significant in age- and multiple adjusted analyses.

Sensitivity analyses were performed repeating final models restricted to white Europeans. Results for intima media thickness, distensibility and stiffness are reported as percentage difference for a 1 standard deviation increase in the exposure variables in these and the following analyses. Estimates were obtained from regression coefficients using the formula $(\exp(\beta)-1)*100$. All analyses were performed using the SAS statistical program (SAS Institute, Cary, NC, USA).

RESULTS

Sex differences

Geometric means of intima media thickness (mm), beta stiffness index and distensibility coefficient ($10^{-3}*kPa^{-1}$) were 0.780, 10.90 and 13.92 in men and 0.766, 10.31 and 15.08 in women, respectively. Age adjusted geometric means of all three vascular measures and means and prevalences of cardiovascular risk factors differed significantly between men and women, with adverse levels generally observed in men, except for age (p-value=0.08), pulse pressure (p-value=0.56), diabetes (p-value=0.88), and hypertension (p-value=0.07), which showed borderline or non-significant differences.

[TABLE 14]

Women were more likely to have a history of CHD before (16.4% versus 20.5%, p=0.002), but not after excluding those with angina pectoris (10.8% versus 9.9%, p=0.40). Men were more likely than women to be white European (93.5% versus 85.3%) and were less likely to have never been a smoker (52.2% versus 62.7%); in contrast, more women reported current smoking (6.4% versus 8.3%).

There was strong evidence of sex differences in the distribution of all socioeconomic indicators (all p-values < 0.001), with higher proportions of women in the more disadvantaged groups, adjusting for age. Gender differences were also observed for measures of body size; men were heavier at birth and taller as adults, in terms of total height, leg and trunk length (all p-values < 0.0001). While on average, men were heavier and had larger waist circumferences, women had higher levels of BMI at each phase (all p-values < 0.0001).

Cardiovascular risk factors and vascular outcomes

White European men and women were significantly less likely to have adverse levels of carotid intima media thickness, distensibility and stiffness in age adjusted analyses.

[TABLE 15, TABLE 16, TABLE 17]

Women with a history of CHD had higher levels of intima media thickness (p-value=0.04), this trend was somewhat weaker after exclusion of those with angina pectoris (p-value=0.06); no significant associations were seen for distensibility and stiffness or any vascular measure in men. Men with diabetes, hypertension and dyslipidaemia were significantly more likely to have adverse levels of all three vascular outcomes, while in women this was observed for hypertension only. Associations between health behaviours (smoking, alcohol intake, diet and exercise) and the vascular outcomes were weak and inconsistent in both men and women, with only women reporting greater levels of exercise being significantly more likely to have lower levels of intima media thickness (p-value=0.002); however, no associations were found between exercise and distensibility and stiffness or any vascular measure in men.

Socioeconomic variables and vascular outcomes

The carotids of men with lower personal income, household income and wealth were significantly less distensible and showed greater levels of stiffness, while the opposite was true for men in the highest employment grades. Men with less wealth also had significantly greater levels of intima media thickness, but the association with household income was weaker (p-value=0.07) and non-significant for employment grade (p-value=0.47).

[TABLE 15, TABLE 16, TABLE 17]

Intima media thickness was the only measure that differed significantly according to father's social class in men (p-value=0.02); surprisingly, a positive association was found for greater educational attainment. Except for an associations between employment grade and intima media

thickness (p-value=0.05) and distensibility (p-value=0.07), associations between the socioeconomic markers and vascular outcomes were weak or absent in women.

Anthropometry and vascular outcomes

Birthweight was not associated with any vascular outcome in men, before or after adjustments. In contrast, men's height, leg and trunk length were each negatively associated with arterial stiffness and positively with distensibility; these associations were strengthened after adjustment for weight and remained strong and significant in multiple adjusted models.

[TABLE 18]

Estimates for total height were larger than those for its components, with stiffness and distensibility being 2.47% lower and 3.67% higher, respectively, for a 1 standard deviation (SD) increase in height. There was a suggestion of inverse relationships of height and leg length, but not trunk length, with intima media thickness in analyses adjusted for age and weight; however, both were attenuated and non-significant in fully adjusted models.

Women with greater birthweight showed greater levels of arterial stiffness (2.74% greater for a 1 SD increase in birthweight) and lower levels of distensibility (2.41% lower for an increase in 1 SD of birthweight); these associations remained strong and significant in fully adjusted models (p-value=0.001 and 0.004, respectively). Estimates were similar adjusting for BMI instead of weight, and no evidence was found for effect modification by current body size (normal weight versus overweight and obesity) for either stiffness or distensibility (interaction p=0.42 and 0.43, respectively). Women's trunk length was significantly and positively associated with distensibility in age or age and weight adjusted analyses; however, this association did not remain in fully adjusted models. Sensitivity analyses restricted to white Europeans showed results similar to those obtained including all participants (not shown).

Associations between men's height, leg and trunk length and arterial stiffness and distensibility were unaltered in final models additionally including separate and joint adjustment for the socioeconomic markers.

[TABLE 19]

In contrast, none of the socioeconomic variables was significantly associated with distensibility or stiffness in these fully adjusted models, the only exception being the greater levels of distensibility in men with the highest household income (p-value=0.04, data not shown).

CONCLUSIONS

These results provide some evidence that growth limiting factors, including, but not restricted to, determinants of long bone growth, contribute to arterial stiffness and distensibility in men. Prenatal growth and socioeconomic markers considered here do not account for the observed associations, despite evidence for adverse levels of vascular distensibility and stiffness in those in less advantaged socioeconomic positions. Conversely, adult measures of poor growth were shown to contribute to associations between socioeconomic factors and subclinical atherosclerosis.

CHAPTER 8: FIFTH OBJECTIVE

OBJECTIVE

To investigate whether socioeconomic disadvantage and poor infant growth, resulting in short leg length, may contribute to the dramatically increased risk of diabetes and coronary heart disease (CHD) in Filipino-American women, a comparatively short population.

STUDY DESIGN OF THE RANCHO BERNARDO FILIPINA STUDY

Participants

Self-identified Filipinas, ages 40-86 years, were recruited between October 1995 and February 1999 for a cross-sectional study designed to estimate the prevalence of several chronic diseases. Most lived in north San Diego County, primarily Mira Mesa, a middle-class community with a high proportion of Filipino residents; all except 4 women were born in the Philippines. Random sampling of the entire county was not feasible because Filipinos are not identified separately in the San Diego census and recruitment strategies have previously been described in detail. (298;299) Clinical evaluations took place at the University of California, San Diego Rancho Bernardo Research Clinic. All participants gave written informed consent.

Measurements

Standardized questionnaires were used and administered by a Philippine-born, native Tagalog-speaking female nurse. All participants spoke functional English. Demographic characteristics, including age, childhood and adult income, education, occupation, birthplace, marital and

employment status, years of U.S. residence, and ethnic identity, were elicited for each group. Cigarette smoking, alcohol use, physical activity, parity, menopausal status, medication history, family history of heart disease (in either parent) and diabetes (in either a parent or in siblings after age 40 years) and other selected chronic diseases were determined using structured questionnaires. Participants who were using medications (prescription or non-prescription) or nutritional supplements in the month before the clinic visit brought their pills and prescriptions to the clinic to be verified and recorded by a nurse. Systolic and diastolic blood pressure were measured twice in seated resting subjects using the Hypertension Detection and Follow–Up Program protocol, (300) and hypertension defined as blood pressure >140/90 mmHg or use of antihypertensive medication. (301)

Anthropometry

Weight was measured to the nearest 0.1 kg with participants wearing light indoor clothing and no shoes. Height was measured to the nearest 0.5 cm, using a portable stadiometer with participants standing without shoes and with heels against the wall as tall as possible with the head in the Frankfort plane. Participants were seated upright, with their back against the vertical stand of the stadiometer, on the base plate located on a hard, flat seat, with the head in the Frankfort plane and their feet on the floor to assess sitting height, a measure of trunk length. Leg length was quantified as the difference between standing and sitting heights. Waist circumference was measured in centimetres at the participant's natural waist, and hip measurements at the iliac crest. BMI was calculated as weight divided by height squared (kg/m^2). Waist-hip ratio was calculated by dividing waist by hip circumference and expressed as a percentage. Percentage of total body fat, truncal fat, and leg body fat (mean, right and left leg) was determined by dual-energy X-ray absorptiometry (DEXA; model QDR-2000 X-ray bone densitometers; Hologic, Waltham, MA).

Coronary heart disease, diabetes and plasma lipoproteins

Prevalence of CHD was defined as ECG abnormalities from a 12-lead resting electrocardiogram (Minnesota codes 1.1–1.2 (large Q and QS waves), 1.3 (small Q and QS), 4.1–4.4 (ST-T

depression), 5.1–5.3 (flattened or inverted T waves) or 7.1.1 (complete left bundle branch block)), (293;302) a positive Rose questionnaire for angina or prolonged chest pain, (292) hospitalization for coronary revascularization procedures or reported myocardial infarction. Rose angina was defined according to standard criteria as chest pain or discomfort that was brought on by exertion (walking on flat ground or uphill), was situated in the central or left anterior chest, forced the participant to slow down or stop and was relieved within 10 minutes if she did so.

A 75-g oral glucose tolerance test was performed in the morning after a minimum 8 hour fast; blood samples were obtained by venipuncture after 0 and 2 hours. Plasma glucose was measured by a glucose-oxidase method and insulin was determined by radioimmunoassay in a diabetes research laboratory. Diabetes was defined according to 1999 WHO criteria. (290) A person was regarded as having diabetes if the fasting plasma glucose was $\geq$ 7 mmol/l (126 mg/dl) or the 2-h glucose after the oral glucose tolerance test was $\geq$ 11.1mmol/l (200 mg/dl), or if he or she was using diabetes medication (oral or insulin).

Fasting plasma lipids and lipoproteins were measured in a Lipid Research Clinic Centre for Disease Control (CDC)-certified research laboratory, as previously described. (299) LDL cholesterol was calculated using the Friedewald formula. Dyslipidaemia was defined as LDL cholesterol $\geq$ 160 mg/dl, HDL cholesterol < 50 mg/dl or statin use.

Childhood and adult social conditions

Information on economic position in child and adulthood was obtained from questionnaires using pre-coded categories. Childhood financial circumstances (0-2) distinguished those who were "very poor", "average" and "well off". A total of 20 pre-coded categories of adult income were collapsed to form three equally sized groups (0-2) in ascending order (< 15k; 15-44.9k; $\geq$ 45k US dollars). A score of lifetime economic position (0-4) was calculated by adding up childhood financial circumstances to adult income, leading to a "social mobility" score with values between 0 (lowest group in both child and adulthood) up to 4 (highest category at both time points). For

sensitivity analyses, an alternative score (0-4) was calculated by adding childhood financial circumstances to attained education (< 12, 13-15 and ≥ 16 completed years).

World War II Birth Cohort

Food shortages and malnutrition were pervasive during the Japanese occupation (1941-45), and infant mortality rates were reportedly the highest in the world. (303) To assess the potential influence of wartime fetal and infant (up to age 2) malnutrition, participants were stratified into birth cohorts: born a) before 1938, b) 2 years prior to the Japanese occupation (1938-40), c) during up to two years after the occupation (1941-47) or d) more than 2 years post occupation (> 1947).

STATISTICAL ANALYSES

Analyses were restricted to women with complete information on components of height, weight, socioeconomic variables, diabetes and CHD. Means or proportions of population characteristics and their confidence intervals were calculated. Means of the anthropometric measures according to levels of the socioeconomic indicators were calculated and t-tests for trend performed. Logistic regression analysis was used to calculate age and multiple adjusted odds ratios for having diabetes or CHD across groups of all socioeconomic indicators and anthropometric measures, using the most disadvantaged or shortest group as the reference category; p-values are based on tests for trend across ordered categorical exposures.

Multiple adjusted models were constructed to additionally include BMI, waist circumference, family history of diabetes, smoking, exercise, employment status and household size for models with diabetes as the outcome. Corresponding models with CHD as the outcome included BMI, waist, family history of heart disease, menopausal status, hormone replacement therapy (HRT) use, hypertension, dyslipidaemia, smoking and exercise. The odds of diabetes from multiple adjusted models were plotted according to the score of economic position in childhood and

adulthood for graphic display. Correspondingly, multiple adjusted odds of CHD were plotted according to groups of leg length. Final models were performed simultaneously including all socioeconomic variables for diabetes models and leg length for CHD models plus all risk factors that were either significant at alpha < 0.20 in multiple adjusted earlier models or pre-specified covariates (biological age and age at immigration in all models and employment status and household size in diabetes models).

RESULTS

A total 389 women fulfilled the inclusion criteria, representing 85.7% of the total sample. Mean height, leg and trunk length were 153.2 cm, 70.7 cm and 82.4 cm; the average BMI was 25.3 kg/m^2. Approximately a third of women (31.4%) had diabetes, 22.4% had coronary heart disease, including 9% of women having both.

[TABLE 20]

Almost all (99%) were Philippine born, 84.6% were postmenopausal and 16.3% were currently taking oestrogen replacement therapy. Alcohol consumption was uncommon (1%) and 84% of women had never smoked. Half (51.6%) of the sample had been educated for 16 years or longer; however, a third were educated ≤ 12 years; 20.7% reported growing up in poor childhood circumstances and around a third reported a current total family income of less or equal to 15,000 US dollar. One-third was either born or a toddler during and up to two years post World War II (births in 1938-47). A positive family history of type 2 diabetes was present in 36% and 23.5% had a parent with heart disease. With regard to life-course social mobility, a total of 7.1% (n=22) of women were poor in childhood and were in the lowest income group in older adult life, compared to 5.9% being in the most advantaged group at both time points. The alternative score using education instead of adult income yielded corresponding figures of 11% and 6%, respectively (data not shown).

In age adjusted analyses, total body height, leg and trunk length differed according to education, childhood and adult income, life-course socioeconomic position and birth year category, with the most advantaged women and those born before the occupation being the tallest (tTable 21). For example, women who grew up in poor childhood economic circumstances in childhood were on average 1.52 meters tall, compared to 1.53 in those with average income or 1.55 in the well-off group (p-value=0.008). All differences were statistically significant except for leg length by birth year or education.

In contrast, education was the only measure that was strongly and significantly associated with BMI and waist circumference (p-value < 0.008 and 0.0004, respectively), with less educated women having a greater BMI and larger waist (tTable 21). Similar results were obtained using other measures of body size, including total percent body fat measured by bioelectric impedance and percent trunk fat measured by DEXA (data not shown).

[TABLE 21]

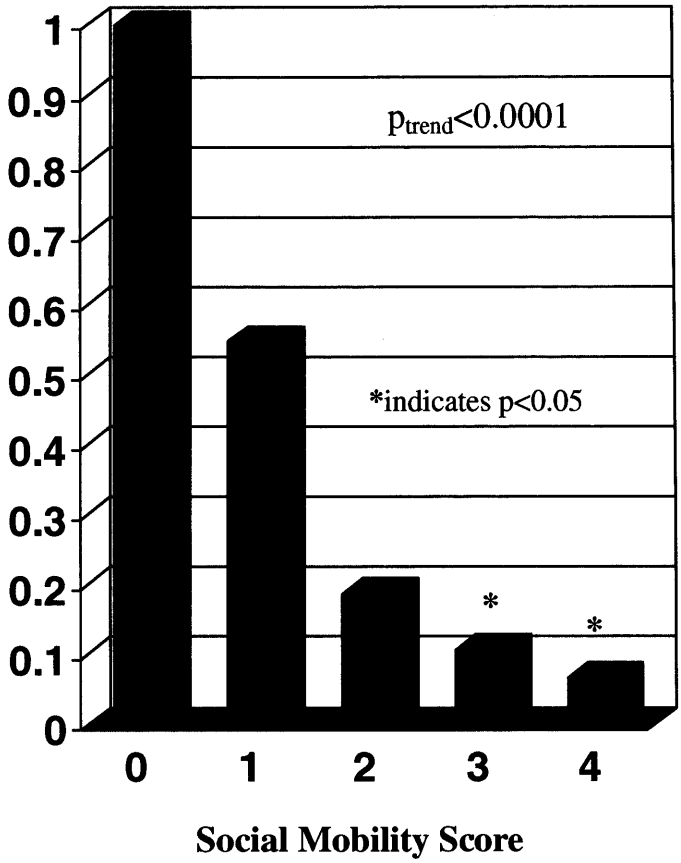
Diabetes

The odds of diabetes did not differ significantly according to height, leg or trunk length in age or multiple adjusted analyses, but were lower in women with better childhood financial conditions (p_{trend}=0.007), greater education (p_{trend}=0.01) and higher adult income (p_{trend}=0.0002) in age and multiple adjusted analyses including BMI, waist circumference, family history of diabetes, smoking, exercise, employment status and household size (tTable 22).

[TABLE 22]

Further, diabetes was significantly less common the higher the social mobility score; compared to Filipinas who were poor in childhood and remained in the lowest income group in older adult life, respective odds ratios (95% CI) for diabetes were 0.55 (0.18; 1.68), 0.19 (0.06; 0.62), 0.11 (0.03; 0.42) down to 0.07 (0.01; 0.51) in those who were most advantaged in childhood and in the highest income group in adult life, after adjustment for all variables mentioned above (p_{trend} < 0.0001). Similar results were obtained using the alternative score (data not shown).

FIGURE 9 MULTIPLE ADJUSTED ODDS RATIOS FOR DIABETES ACCORDING TO SOCIAL MOBILITY SCORE IN 305 FILIPINAS



The odds of diabetes were also associated with birth year category; however, this association was of borderline significance (p_{trend}=0.06) and reduced further in multiple adjusted models (p_{trend}=0.18).

In final models simultaneously including all socioeconomic variables and other risk factors, lower adult household income, a positive family history of diabetes and waist circumference were each significantly and independently associated with increased odds of diabetes (p-value < 0.001 in each case), while associations of childhood family income with diabetes did not remain statistically significant.

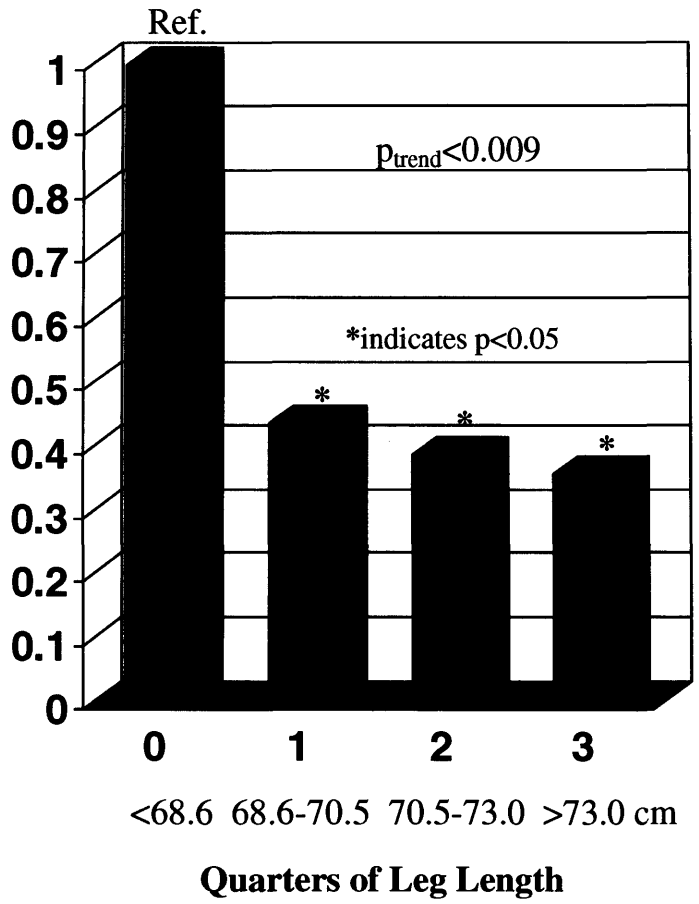
Coronary Heart Disease

CHD prevalence was not significantly associated with any of the socioeconomic indicators, and although the odds of CHD were lower the greater the social mobility score, with odds ratios (95% CI) ranging from 0.55 (0.20; 1.53), 0.46 (0.15; 1.37), 0.39 (0.12; 1.30) down to 0.19 (0.03; 1.15) in the most advantaged women, these differences were not statistically significant in age (p_{trend}=0.07) and multiple adjusted analyses (p_{trend}=0.13).

[TABLE 23]

In contrast, the odds of CHD differed significantly across quarters of leg, but not trunk length. Compared to those with the shortest legs, odds ratios for CHD were 0.60 (0.31; 1.19), 0.53 (0.26; 1.05) and 0.44 (0.22; 0.91) in the tallest group, in age (p_{trend}=0.02) and multiple adjusted models (p_{trend}=0.01). Total body height showed a comparable, but weaker association (p_{trend}=0.10).

FIGURE 10 MULTIPLE ADJUSTED ODDS RATIOS FOR CORONARY HEART DISEASE ACCORDING TO GROUPS OF LEG LENGTH IN 305 FILIPINAS



Final models showed similar results, with shorter leg length (p_{trend}=0.006), greater waist circumference (p_{trend}=0.01), hypertension (p-value=0.01) and exercise (p-value=0.01) being important predictors of CHD (Table 24). However, it should be noted that the estimate for exercise indicated a harmful, rather than a beneficial effect, potentially reflecting reverse causality, i.e. high risk women engaging in preventive behaviors.

[TABLE 24]

Adjusting for body size by including either BMI, total percent body fat, waist-hip ratio or waist circumference instead of weight, or excluding the 4 women not born in the Philippines did not materially change the results regarding diabetes or CHD (data not shown). Likewise, findings

remained unchanged in sensitivity analyses excluding 10 women with triglyceride levels > 400 (and thus potentially unreliable estimation of LDL cholesterol by the Friedewald formula) or adjusting for continuous measures of total cholesterol, HDL, LDL or triglycerides alone or in combination instead of dyslipidaemia. Sensitivity analyses excluding less specific ECG Minnesota codes (1.3, 4.1-4.3, 5.1-5.3) showed that despite a lower prevalence of CHD leading to small numbers in some of the cells, results remained unchanged, with leg length (multiple adjusted p=0.01) showing the strongest association.

CONCLUSIONS

Childhood and adult socioeconomic factors contribute to the high prevalence of diabetes in Filipina-American women, a comparatively short and non-obese population by Western standards. Results from this study support the hypothesis that factors limiting early growth of the legs increase the risk of CHD, but not diabetes; socioeconomic factors considered here do not seem to underlie this association, despite their strong associations with adult measures of growth.

CHAPTER 9: SIXTH OBJECTIVE

OBJECTIVE

To investigate whether associations between poor growth of the legs and higher levels of blood pressure and pulse pressure may originate early in life.

STUDY DESIGN OF PROJECT VIVA

Participants

Study subjects are Project Viva participants, a prospective cohort study of pregnant women and their offspring. Research assistants recruited women attending their initial prenatal visit at one of eight urban and suburban offices of a multispecialty group practice in eastern Massachusetts. (304) Exclusion criteria include multiple gestation (twins, triplets, etc), inability to answer questions in English, plan to move out of the area before delivery, and gestational age > 22 completed weeks at initial prenatal clinical appointment. A total of 2670 pregnant women (64% of those eligible) were enrolled between April 22, 1999, and July 31, 2002, of whom 329 subsequently became ineligible because of multiple gestation (n=19), transferring obstetric care to a non-study site (n=115), or because they were no longer pregnant (n=195). Of the 2341 remaining participants, 195 (8%) withdrew, and 18 (< 1%) were lost to follow-up, leaving 2128 who delivered a live infant. Of these, 1579 participants were eligible for 3-year follow-up at the time of analysis. Participants who refused 3-year follow-up (n=92), those who had not yet completed the 3-year assessment (n=118) or completed it by mail or phone but not in person (n=106), those with missing data on blood pressure (n=92) or anthropometry (n=21), and 17 infants whose gestational age at birth was less than 34 weeks were excluded, resulting in 1133

mother-infant pairs for analysis (appendix 3). Participants included in this study were slightly more likely to be white (73 versus 66%) and college educated (35 versus 28%), but did not differ in terms of mean household income, maternal pre-pregnancy BMI or birthweight compared to all 2083 participants who delivered a non-premature child.

All mothers gave informed consent and institutional review boards of participating institutions approved the study. All procedures were in accordance with the ethical standards established by the Declaration of Helsinki. (305)

Measurements

Details of examinations before age 3 years have previously been reported in detail. (304;306) In brief, information about maternal ethnicity, age, education, parity, and household income was obtained using a combination of questionnaires and interviews. Information on maternal blood pressure, glucose tolerance test results, serial pregnancy weights, and infant birthweight and delivery date were collected from prenatal medical records. Mothers reported their pre-pregnancy weight and height and paternal weight and height. Gestational weight gain was calculated as the difference between pre-pregnancy weight and the last clinically recorded weight before delivery; gestational age was derived from the last menstrual period or from the second trimester ultrasound if the two estimates differed by more than 10 days. Sex-specific birthweight for gestational age percentile and z-value based on U.S. national natality data was determined. (307) On the 6-month and 1-year questionnaires, mothers reported on infant diet including breast and formula feeding and complementary food intake.

Age 3 examinations were carried out in 2003-06 and anthropometry and blood pressure measured as described below.

Anthropometry (3 years)

Children's heights and weights were measured using a calibrated stadiometer (Shorr Productions, Olney, MD) and scale (Seca model 881; Seca Corp., Hanover, MD) and age- and sex-specific height, weight and BMI percentiles and z-scores calculated using U.S. national reference data (National Center for Health Statistics 2004, CDC Growth Charts, United States: http://www.cdc.gov/growthcharts). The Shorr board was placed on top of a hard, flat seat against a flat door or wall to assess sitting height, a measure of trunk length. Children were seated upright, as tall as possible, with their back against the board, the head in the Frankfort plane, knees directed straight ahead and feet hanging freely. Leg length was calculated as the difference between standing and sitting heights. Research assistants followed standardized techniques, (308) and participated in biannual in-service training to ensure measurement validity (IJ Shorr; Shorr Productions). Inter- and intra-rater measurement errors were within published reference ranges for all measurements. (309) The percentage of height contributed by leg length and the difference in sex-specific internally derived leg and trunk z-scores were calculated as measures of disproportion. (115;310)

Blood and pulse pressure (3 years)

Using biannually calibrated Dinamap Pro-100 oscillometric automated monitors (GE Medical Services, Tampa, FL), trained research assistants recorded child blood pressure up to five times at 1-minute intervals. Measurement conditions including order of readings, cuff size, limb, body position (sitting, semi-reclining, reclining, standing), and state (sleeping, quiet awake, active awake, crying) were recorded. Pulse pressure was calculated as the difference between averaged systolic and diastolic blood pressure measurements. Mean arterial pressure (MAP) was calculated as ((2*DBP) + SBP)/ 3 from averaged systolic and diastolic blood pressure measurements.

STATISTICAL ANALYSES

Means or proportions and standard deviations of maternal, family and child characteristics were calculated separately for girls and boys included in this study. Differences were compared using t-tests and chi-squared tests for continuous and categorical variables, respectively. Linear regression analysis was used to investigate associations of maternal, family and child characteristics with leg length, trunk length, percent leg length and the difference in leg and trunk z-scores, adjusting for age, sex and ethnic group. To investigate associations between the anthropometric measures and blood pressure, mixed effects regression models that incorporate up to 5 blood pressure measurements from each infant were used as repeated outcome measures (proc mixed, SAS version 8.02 (SAS Institute)). Simple models were adjusted for age, sex and measurement conditions (child's state, arm, cuff size, body position, and indicator for the measurement sequence number (1st through 5th). Current height and weight were then successively added to this model, as appropriate. Fully adjusted models were performed additionally including ethnic group and birthweight.

Sensitivity analyses were performed replacing measures of leg and trunk length with the proportion of height contributed by leg length and the differences in leg and trunk length z-scores.

RESULTS

A total of 1133 children attending the age 3 year examination were born at $\geq$ 34 weeks gestation and also had complete measures of anthropometry and blood pressure at age 3 years, reflecting 90% of all children attending this examination, 58% of children eligible for follow-up at birth and 54% of all live, non-premature births.

Average systolic, diastolic, pulse and mean arterial pressures (mean (SD)) were 92.1 (11.6), 58.1 (8.4), 34.0 (7.8), and 69.4 (8.9) mmHg in girls and 92.4 (9.6), 58.3 (7.8), 34.1 (7.3), and 69.7 (7.7) mmHg in boys, respectively. Maternal gestational weight gain, children's birthweight and length,

height, weight, BMI, leg and trunk length were all significantly greater in boys, compared to girls (p-value ≤ 0.003 in each case); however, the proportion of height contributed by leg length did not differ between the sexes.

[TABLE 25]

Leg length (mean (SD) 41.6 (2.5) cm in girls and 42.0 (2.8) cm in boys) and trunk length (55.2 (2.6) cm in girls and 56.1 (2.6) cm in boys) were both significantly greater in children who were heavier or longer at birth and at age 3 years and whose mothers or fathers were taller, adjusting for age, sex and ethnic group. Maternal pre-pregnancy BMI was positively and duration of breastfeeding was negatively associated with trunk, but not leg length. Leg length contributed a significantly greater proportion to body height in children with taller mothers and those with greater length at birth and age 3 years, while maternal age, children's weight, BMI and BMI z-score showed inverse associations with both, the proportion of height contributed by leg length and the differences in leg and trunk length z-scores. Despite the greater proportion of leg length contributed to the overall height of children who were taller at age 3 years, these showed smaller differences in leg and trunk length z-scores.

[TABLE 26]

In analyses adjusting for age, sex and measurement conditions, height, weight, leg and trunk length were each positively and significantly associated with systolic, diastolic and pulse pressure (p-value < 0.05 in each case), except for the association between leg length and DBP, which did not reach statistical significance.

[TABLE 27]

In models including both height and weight, only weight, but not height, remained significantly and strongly associated with all measures of blood pressure.

After accounting for differences in height, children with greater leg length had significantly lower SBP and PP (regression coefficient (95% CI) SBP -0.61 mmHg (-0.98; -0.24), PP -0.45 (-0.73; -0.17) for each centimeter increase in leg length. Analysis of the proportion of height contributed by leg length or the difference in leg and trunk z-scores yielded similar results and adjustment for weight did not explain these associations. Further adjustment for ethnic group and birthweight attenuated estimates of associations between leg length, leg length percent or difference in leg and trunk z-scores with systolic blood pressure only slightly, but associations were of borderline significance in these models (p-value ≤ 0.08 in each case). In contrast to the results for leg length, trunk length was positively associated with all blood pressure measures before and after adjustments.

CONCLUSIONS

Relatively shorter length of the lower body is associated with higher blood pressure in the first years of life. Other studies have shown that childhood blood pressure predicts adult hypertension. Therefore, factors limiting early growth of the long bones may contribute to an individual's blood pressure trajectory. Future studies may help identifying underlying growth limiting factors

CHAPTER 10: SEVENTH OBJECTIVE

OBJECTIVE

To investigate how associations between growth and mortality from coronary heart disease and stroke may be influenced by later socioeconomic position and to assess whether associations may differ according to prevalent CHD at baseline and duration of follow-up.

STUDY DESIGN OF THE ORIGINAL WHITEHALL STUDY

Participants

A total of 19019 civil servants aged 40-69 years attended the initial screening of the Whitehall study between September 1967 and January 1970, representing 74% of those invited. Participants completed a standard questionnaire, including age, self reported smoking habit, civil service employment grade, medical treatment and health status. (311-314)

Measurements

Anthropometry

Height was measured with the subject wearing shoes and standing with their back to a measuring rod; readings were taken to the nearest ½ inch (12.7 mm) below. (311) Body mass index was calculated by dividing weight by height squared (kg/m^2).

Cardiovascular risk factors

With the participant seated, a single reading of blood pressure was recorded on the left arm by specially trained observers using the London School of Hygiene random zero sphygmomanometer. Plasma cholesterol, two hour post-load glucose, weight, and forced expiratory volume in one second (FEV1), were determined in standardized fashion at baseline. (311) A regression analysis of FEV1 against height was used to adjust FEV1 measurements to a uniform height of 175 cm. (312)

Smoking

Smoking status was categorized into four levels as "never", "ex-", "current pipe or cigar only" or "current" cigarette smokers, with an additional variable to control for the number of cigarettes smoked per day.

Employment grade

The civil service grade of employment, an indicator of socioeconomic position, was coded into three categories: administrative and professional/ executive grades (high), clerical (middle) and other grades (low). Previous analyses have shown inverse associations between employment grade and mortality from a variety of causes, including CHD, independent of conventional risk factors. (313;314)

Assessment of existing coronary disease

Electrocardiography was undertaken with a Mingograph 31B, using "multipoint" electrodes. Five technically adequate complexes were recorded for each of the six limb leads and the middle three complexes were later analysed according to the Minnesota code. The six limb lead electrocardiography (ECG) removed the need for participants to undress. Coding was carried out independently in duplicate by trained and tested technicians.

Q (Minnesota codes 1:1–1:3), ST (4:1–4:4), T (5:1–5:3) and LBBB (7:1) abnormalities were chosen for defining CHD, since these are the strongest independent predictors of CHD events. (295)

Participants were defined as symptomatic if they reported angina, prolonged chest pain ("pain of possible myocardial infarction"), previous admission to hospital for CHD or being "under the general practitioner with heart disease or blood pressure". Prevalent CHD was defined by specific ECG abnormalities, or symptoms, or both. (315)

Ascertainment of mortality

Participants were flagged at the National Health Service Central Registry, which notified all deaths to the end of 2002. Causes were classified according to the International Classification of Disease, eighth revision (ICD-8), including mortality from CHD (ICD 410-414), stroke (ICD 430-438) and cardiovascular disease (ICD 390-458). Eight percent of deaths were coded using the corresponding codes of ICD 9 and 10.

STATISTICAL ANALYSES

Of the 19016 participants with known height and age, 167 men were excluded in the present analysis who were lost to follow-up, 44 for whom the cause of death was unknown, 863 men from the diplomatic service and the British Council for whom employment grading was not comparable, and a further 806 with missing information on any of the covariates.

In analyses of baseline characteristics according to three equally sized groups of height, the prevalence of these characteristics were adjusted for age (5 year age groups) by the direct standardization method. Trends in these proportions were tested for statistical significance using the Mantel-Haenszel test. For baseline characteristics expressed as continuous variables, least-squares means were used to present the age adjusted means, and tests for trend across height groups were computed by fitting a linear trend term.

Association between height and CVD mortality

Linear associations between height and the mortality outcomes were examined by fitting Cox's proportional hazards models. These models allowed hazard ratios and 95% confidence intervals associated with an increase in height of 15cm to be calculated. Separate models were fitted for participants with and without CHD at baseline. Models were initially adjusted for age and employment grade only and then, additionally, for potential confounding factors. Variables in the fully adjusted models included age, employment grade, smoking status, cholesterol, systolic and diastolic blood pressure, body mass index, height-adjusted forced expiratory volume in one second, glucose intolerance and diabetes. These were fitted as continuous variables, except for employment grade (3 levels), smoking status (4 levels with additional adjustment for number of cigarettes smoked per day for current smokers), glucose intolerance (2 levels) and diabetes (2 levels), which were fitted as categorical variables.

To investigate whether the effect of height on CVD, CHD or stroke mortality differed according to employment grade, separate height effects were fitted by grade and formal tests for interaction carried out by comparing the model fits, with and without the interaction terms, using likelihood ratio tests.

Additionally, to compare the magnitude of the association over different periods of follow-up and to test the proportional hazards assumption, the follow-up time was split into three intervals (0-9, 10-19, 20-29, 30+ years) and age adjusted hazard ratios for each interval computed. Differences in the effect of height on mortality between follow-up periods were tested formally by assessing the statistical significance of a height by time period interaction term in the models.

RESULTS

In age adjusted analyses, men of shorter stature were more likely to be in low grade employment, without a partner, have prevalent CHD at study entry, be a current smoker, glucose intolerant or suffer from diabetes, in comparison with taller men. Height was also significantly associated with

age, body mass index, total cholesterol, and forced expiratory volume in one second, such that the most favourable levels were seen in taller men. Diastolic blood pressure was positively associated with height, although differences between groups were only small.

[TABLE 28]

Height and cardiovascular outcomes

The 17139 men were followed up for at least 33 years and contributed a total of 5411 deaths from cardiovascular disease, including 3530 deaths from CHD and 952 deaths from stroke.

Associations between height and mortality from CVD, CHD and stroke in men who were free of coronary heart disease at study entry are presented first.

[TABLE 29]

In age and grade adjusted analyses, height was inversely related to mortality from total cardiovascular disease (HR associated with each 15 cm increase in height (95% CI) 0.89 (0.83; 0.95); p-value=0.001). This effect was stronger for CHD mortality (0.81 (0.74; 0.88); p-value $\leq$ 0.001), than for stroke (0.91 (0.78; 1.08); p-value=0.28). When the association between height and mortality was investigated separately for each employment grade, it became apparent that the beneficial effect of tall stature on subsequent CVD, CHD and stroke mortality was strongest in participants in high employment grades, but weaker and non-significant for middle and low grades.

The test for interaction was significant for mortality from CVD (p-value=0.02), but not CHD (p-value=0.09) or stroke (p-value=0.13). Further adjustments had only a small effect on these results.

Men with CHD at study entry

The pattern of results was similar in men with existing CHD, but none of the associations with stroke mortality reached conventional levels of statistical significance.

[TABLE 30]

Effect of duration of follow-up

In combined analysis of men with and without prevalent CHD at baseline, height was significantly and inversely associated with mortality from CHD, CHD and stroke, before and after adjustments. Associations between height and mortality did not differ significantly between periods of follow-up, suggesting that any observed differences between follow-up periods may have occurred by chance alone (all tests for interaction p-value > 0.22).

[TABLE 31]

CONCLUSIONS

Strong, inverse associations between height and CHD mortality in men with and without prevalent CHD indicate that short height is not only an important influence on the development of CHD in an asymptomatic healthy population, but also affects the prognosis in men with evident CHD. Differences in these associations between employment grades show the importance of bringing together studies of the influence of poor growth and socioeconomic position to consider their interactive effects. Associations between height and mortality do not differ according to duration of follow-up.

CHAPTER 11: DISCUSSION

SUMMARY OF FINDINGS

This body of research brings together evidence from 5 epidemiological studies, spanning an age range from childhood to late adult life. Each study was selected to address a specific aim designed to answer part of the underlying hypothesis concerning the relationships between poor growth, social inequalities and cardiovascular risk. The use of data from prospective cohort studies enabled me to investigate associations between markers of growth and long term changes in blood and pulse pressure, associations with future subclinical vascular disease, as well as incident events. Investigating different populations allowed replication and validation of associations in several data sets; including extrapolation to a comparatively short and non-obese population of Filipino-American women and to children as young as 3 years participating in Project Viva, a contemporary US birth cohort study.

In summary, results from these different studies showed the following:

First, findings from the oldest currently ongoing birth cohort study worldwide, the National Survey of Health and Development (NSHD - 1946 Birth Cohort Study), suggested that adult height and leg length, but not trunk length, are important determinants of pulse pressure, a measure of arterial stiffness, in adult men and women. Similar, but weaker associations were seen with systolic, but not diastolic blood pressure.

Second, longitudinal analyses of the same cohort showed strong evidence that the inverse associations between both height and leg length, and pulse pressure and systolic blood pressure are amplified with age, independently of a number of potential confounders and mediators from early and adult life that were considered.

Third, in the Whitehall II Study, an occupational cohort, associations between shorter leg length and greater pulse and blood pressure were replicated in both men and women; as in earlier analyses, prenatal growth, indicated by weight at birth, contributed little to these associations. Although birthweight was recalled in adult life in this cohort, correlations with leg and trunk length were similar to those observed in the NSHD, where weight was recorded at the time of birth. Results from the Whitehall II Study also showed associations of both components of height with several other cardiovascular risk factors, indicating that associations are not restricted to blood pressure measures and not specific to leg length.

Fourth, using specific measures of subclinical atherosclerosis in participants of the Whitehall II Study, men with greater height, leg and trunk length showed significantly greater distensibility and significantly lower stiffness of the carotid arteries in age and multiple adjusted analyses; this was not observed for intima media thickness or for any vascular outcome in women. Birthweight was not associated with adverse levels of vascular structure or function, and despite significant associations between several socioeconomic markers and arterial distensibility and stiffness in men, adjustment for these variables contributed little to associations between markers of poor growth and the vascular outcomes.

Fifth, in a cross-sectional examination of Filipino-American women, a comparatively short and non-obese population by Western Standards, who has a high prevalence of diabetes and cardiovascular disease, height, leg and trunk length were significantly and substantially lower in women who were socioeconomically disadvantaged in childhood and adulthood. Diabetes prevalence was not associated with measures of growth, but was significantly lower in women with greater education, childhood and adult income or life time economic score. In contrast, CHD prevalence was most strongly associated with leg length, but not trunk length, in age and multiple adjusted models.

Sixth, in Project Viva, a US observational cohort study of pregnant women and their offspring, children with shorter leg length, relative to total body height, showed higher levels of blood

pressure at age 3 years, providing some evidence that associations between poor lower body growth and high blood pressure may originate in childhood.

Lastly, results from the first Whitehall Study with a follow-up of over 33 years and 3893 cardiovascular deaths showed that short stature is not only an important influence on the development of CHD in an asymptomatic healthy population, but also affects the prognosis in men with prevalent CHD. No evidence was found that the adverse effect of short height is restricted to participants with differential shrinkage before study entry. Notably, the beneficial effect of tall stature on subsequent risk of cardiovascular mortality was strongest in participants in high employment grades, with significant inverse associations seen in this group, but weaker and non-significant associations in middle and lower grades.

The contributions of prenatal growth and socioeconomic circumstances were considered in all studies where birthweight and social position in childhood and/ or adulthood were available. While the influence of birthweight to the associations of interest was generally found to be only small, the role of social inequalities for growth and later cardiovascular risk appeared to be more complex. Social differences in height and its components were either observed or have previously been reported in all studies of adults that were included in this thesis. Yet, the different indicators of social position that were explored did not account for associations between components of height and cardiovascular risk, except for results obtained in the first Whitehall study. These suggested differential associations between growth and cardiovascular mortality according to adult socioeconomic position, with effects being strongest in the most privileged groups. The joint and separate contributions of components of height and the different socioeconomic indicators are discussed in more detailed in the context of each objective below.

INTERPRETATION AND CONTEXT

FIRST OBJECTIVE

Several factors may contribute to the associations observed between short height and leg length and greater blood pressure and arterial stiffness.

Prenatal growth

Impaired fetal development, reflected by low birthweight, might influence early growth and later disease simultaneously, but it seems to influence both components of height equally. (115;264) Consequently similar associations of trunk and leg length with blood pressure measures would be expected if birthweight was a joint underlying factor. In the 1946 Study, leg length, but not trunk length, was strongly associated with pulse pressure and systolic blood pressure and adjustment for birthweight did not alter these results.

Socioeconomic influences on growth and cardiovascular risk

Children who grow up under disadvantageous socioeconomic conditions have comparatively shorter height and legs in child and adulthood; similarly they have a higher risk of coronary heart disease and associated risk factors. (137;138;141;316;317)

In the NSHD, adjustment for childhood social class and potential confounding factors in adulthood, which are also more frequent among the lower social classes, such as smoking and obesity, did not change the observed associations between short leg length and pulse pressure or systolic blood pressure in either men and women. This indicates that early influences on growth that are important for development of arterial stiffness in later life may not (or only weakly) be socially distributed or not adequately be captured by the indicators of childhood social position used in this study.

Influences on early pre-pubertal growth

Leg growth is particularly marked during the growth hormone dependent childhood phase of growth in the first years of life, (153) and early endocrine control (hormonal levels and receptor expression) may simultaneously influence growth spurts of the long bones of the leg and arterial growth during these specific hormonally controlled phases of development before puberty. In contrast, many bones contribute to trunk length; their growth differs in timing and magnitude from that of the long bones. (318) Consequently, if hormonal factors affect leg length and arterial structure and function through arterial growth, attained leg length, rather than trunk length, may be more closely associated with adult pulse pressure.

In line with this, adult leg length has been suggested and used as a marker of early prepubertal childhood growth, and one previous study has found that rather than height per se, shorter prepubertal stature (at ages 5-8 years) relative to adult height, interpreted as poor childhood growth, is an important determinant of systolic blood pressure and pulse pressure, but not diastolic blood pressure. (214) A significant effect of adult height, after accounting for differences in earlier prepubertal height, would be expected, but was not observed, if changes in height between ages 5-8 years until adult life, i.e. largely pubertal growth, was the more important influence on adult blood pressure. However, these results may not be generalizable and/ or be biased, as this study selected 300 survivors (< 50 % response rate) from the Boyd Orr cohort, which originally included children from 1352 families. Participants were not representative in terms of social class, and due to small numbers, men and women could not be analysed separately; however, results from this study provide some evidence that childhood stature, rather than later growth rate, contributes to adult blood pressure and arterial stiffness, and thus corroborate findings from the 1946 Study.

Arterial wave reflection

Associations of height and leg length with dynamic properties of the arterial tree may contribute to the observed link between short stature and greater pressure. Pulse pressure is determined by arterial compliance and wave reflection and reflected waves in those of shorter height may be more likely to arrive early and during systole, due to their greater levels of arterial stiffness and/ or shorter transmission path length, resulting in increased central pressure augmentation and pulse pressure. (32;205)

In the 1946 Study, adult leg length, but not trunk length, was strongly associated with pulse pressure and systolic blood pressure. The functionally effective reflection site has been described as the "resultant or average" of all individual reflecting sites downstream of the ascending aorta. (32) While the influence of components of height on arterial haemodynamic remains unknown, one previous report has shown that correlations of aortic length with measures of arterial haemodynamics were equal or less than those observed with total height. (205) This suggests the importance of arterial path length beyond the aorta, and thus beyond sitting height, for haemodynamic properties such as early wave reflection. Arterial compliance and wave reflection may thus be mechanisms that contribute to some degree to the associations of short height and leg length with greater pulse pressure.

Strength and limitations

There are limitations in extrapolating results from the 1946 Birth Cohort Study to later generations. Levels of mean height as well as overweight and obesity have increased since the post war period, and the decline of coronary heart disease mortality rates over the past 30 years has been accompanied by decreases in systolic blood pressure, largely due to advances in treatment and changes in risk factor levels. (319-321) The observed gradient of pulse pressure

across groups of height and leg length may differ in younger generations with increased mean height, greater weight and altered burden of cardiovascular risk.

Avoidable loss to follow-up through participants' refusal or inability to trace was more common in those with adverse socioeconomic circumstances in childhood or those of shorter height at age 4 years. (280;322) However, after 53 years of follow-up, the sample was still reasonably representative of the national population of the same or similar age, taking account of the fact that immigration trends after the selection of the sampling frame and exclusion of multiple births and those born outside wedlock prohibit it from being completely representative. (280) Also, if loss to follow-up was non-differential with regard to blood pressure outcomes, i.e. participants lost to follow-up did not differ in terms of pulse pressure or blood pressure from those from a manual origin or shorter height who were examined at age 53 years, the influence on the results may only be small.

Adult leg and trunk length were used as markers of growth at different phases, rather than height measured during childhood, for two reasons. First, this approach is comparable with recent studies suggesting that leg length, as opposed to trunk length, is the component of height reflecting the childhood phase of growth and is most closely linked to cardiovascular risk in adult life. Second, the comparison of leg to trunk length distinguishes the growth of long bones occurring under the influence of growth hormone during the childhood phase of growth, (153) from the slower and later growth of the trunk. (154) Adult leg and trunk length were used, as components of height in childhood were not available in this cohort.

Using adult indicators of childhood growth has some disadvantages. Although leg length is regarded as a marker of environmental influences on childhood growth during the first years of life, later growth as well as genetic factors will also influence attained leg length, and their contribution to the observed associations cannot be excluded.

Shrinkage may introduce error in measures of adult height. However, previous studies have shown that loss of stature at these early ages (before 53 years) is only small. (162) In addition,

analysis of adult leg length avoids measurement bias introduced by age related shrinkage, which reduces total height mainly as a result of decreases in trunk length through the osteoporotic collapse of vertebrae. In this study, only total and sitting height (trunk length) were measured, and leg length calculated from them, resulting in greater measurement error in leg length (non-differential misclassification), which may bias results towards the null. Nevertheless, associations with blood pressure were observed for leg length, not trunk length, and the strength of the association may therefore be even greater if leg length was measured more accurately.

SECOND OBJECTIVE

Longitudinal analyses of the 1946 Study showed that leg length was the component of height associated with larger than average increases in pulse pressure and systolic blood pressure up to middle age. Early influences on changes in the structure and function of the developing vasculature may alter the susceptibility for arterial stiffness and hypertension in later life. (220)

Systolic blood pressure, pulse pressure and arterial stiffness increase with age; if poor early growth contributed to the tracking of these measures, its detrimental influence on vascular structure and function in the first years of life may amplify the vulnerability of those with shorter legs to the effects of ageing on the arterial tree. Our evidence supports this hypothesis by showing an amplification of the effect of leg length, as a marker of early growth, on pulse pressure and systolic blood pressure between 36 and 53 years.

Interestingly, as mentioned earlier, the one previous study suggesting that shorter prepubertal stature relative to adult height is an important determinant of adult blood pressure, also found associations with systolic blood pressure and pulse pressure, but not diastolic blood pressure. (214) In industrialized countries, systolic blood pressure increases progressively throughout adult life, while diastolic blood pressure increases less steeply and ceases to rise or even falls around 55 years, (27) resulting in a rise in pulse pressure throughout adult life. Accordingly, in this study of

blood pressure in the middle years of life, pulse pressure and systolic blood pressure show a greater rise with age, compared to diastolic blood pressure. If growth limiting factors influence the age-blood pressure relationship, then stronger associations may therefore be expected with those measures of blood pressure whose increase is more closely linked with ageing, as mentioned above.

The majority of cardiovascular risk associated with hypertension is due to blood pressure gradually increasing with age. The age specific rise, and therefore hypertension, is essentially absent in certain rural communities, and studies have shown that this protection is partly lost through migration to industrialized communities. (27) This suggests that a continuous influence of protective factors is necessary for maintaining low pressures into later life, and supports the hypothesis that environmental influences, some of which may operate through an effect on growth (e.g. nutrition or stress), can modify the age-blood pressure relationship.

It remains unclear, which influences on growth may contribute to the association with blood pressure and its age related rise, and it is likely that several pathways are involved, some of which have previously been discussed.

The quality of early nutrition, rather than simply energy intake, is a critical influence on growth (154) and may affect the individual age-blood pressure relationship. While dietary interventions have the potential to impact on the population burden of hypertension and associated cardiovascular disease, (323) evidence regarding associations between early life factors influencing growth, such as breastfeeding for example, and adult cardiovascular risk has been mixed. Systematically collected evidence suggested that selective publication of small studies with positive findings may have exaggerated claims that breastfeeding reduces systolic blood pressure in later life. (324) Heterogeneity of studies, with smaller and non-significant differences of systolic blood pressure in larger studies, was also reported in a more recent review. (325) Publication bias may therefore also apply to individual studies reporting associations between specific nutritional exposures and adult atherosclerosis. (325)

Growth limiting factors such as impaired fetal development and disadvantageous socioeconomic conditions have been associated with high blood pressure and cardiovascular risk and were considered as potential underlying or contributing factors here and in previous investigations. (326) Similar to earlier cross-sectional analyses, longitudinal associations remained unchanged after adjustment for birthweight. However, birthweight is only a crude marker of growth and development before birth, and this does not preclude the possibility of prenatal factors simultaneously influencing growth and later blood pressure. Adjustment for childhood social class, educational attainment, adult social class and potential confounding factors in adulthood (obesity, smoking, lack of exercise) slightly reduced the estimates for the age related rise associated with shorter height and leg length, but did not alter levels of significance. Some of these factors, particularly obesity, showed independent effects on blood pressure, and their importance for the development of cardiovascular disease should not be understated. Furthermore, a great variety of influences on growth are socially distributed, and these contribute to the shorter height, and particularly leg length, of children growing up in disadvantageous social conditions. (106;112;114;115) These influences include prenatal development, premature birth, maternal health, behaviour and care for the child, early nutrition, living conditions, infections and age at puberty. (109-113). Adjustment for childhood social conditions is unlikely to fully account for the diverse influences of these factors on early and later blood pressure and the importance of early socially patterned exposures underlying the observed associations cannot be excluded.

Earlier results from the 1946 Birth Cohort Study showed that birthweight, despite being negatively associated with systolic blood pressure at ages 36, 43 and 53 years, showed no significant influence on the age related rise of blood pressure. (281) In contrast, the association between lower childhood social class and systolic blood pressure was shown to increase with age, by 1.0 mm Hg (95% confidence interval: 0.1; 2.0; p=0·03) per decade, (281) highlighting the importance of childhood social class for changes in adult blood pressure. This effect was found to largely be mediated by body mass index, which was an increasingly strong determinant of blood

pressure, as also observed in the present analysis. In contrast, estimates for leg length remained strong and significant in fully adjusted analyses; however, the largest attenuation of the effect of leg length was also observed in models adjusting for body mass index. Leg length may be a marker of early growth patterns during the childhood phase that influence body weight trajectories from childhood to adulthood and thus adult blood pressure, and early weight gain and age at puberty may contribute to this. (268)

Short height and blood pressure regulation might be jointly genetically determined; however, as discussed earlier, the evidence of a genetically determined association between height and cardiovascular risk factors to date is weak. (278) Findings from a study with anthropometric data on two generations suggested that genetic factors contribute little to associations between components of height and cardiovascular risk factors, including blood pressure, as adjustment for parental height had only a small effect on these associations. (225) In addition, recent evidence from a study of 35,000 twin pairs also concluded that the association is due to environmental factors directly affecting growth and CHD. (189)

Strength and limitations

The 1946 Birth Cohort is the oldest ongoing birth cohort internationally, and no other birth cohort study is available with earlier measures of blood pressure and a follow-up till middle age.

Survivor bias is unlikely to have a great impact on our results, as only 4.8% of the whole cohort died in adulthood. (327) Potentially avoidable loss of participants in this cohort has been discussed earlier; an important advantage of repeated measures analyses is that sample size can be maximized as multilevel models allow for incomplete outcome data as long as a missing at random process can be assumed. (283;285;286)

Strength and limitations of using adult components of height as markers of growth have been discussed in more detail in the context of the first objective. In addition, for longitudinal analyses,

leg and trunk length were only available at 43 and 53 years and were therefore not used in conjunction with the three blood pressure measurements in the longitudinal multilevel models. This means that participants who attended the screening at age 36 years had to attend one of the next two examinations in order to have a valid measure of components of height to be included in this analysis, possibly resulting in selection bias. Previous studies have shown that loss of stature at these early ages (before 53 years), although present, is only small. (162) In addition, repeating the cross-sectional analyses using firstly measures of total height corresponding to the age of blood pressure measurement and secondly components of height at age 43, instead of 53 years, did not alter the results (not shown). This indicates a) that any potential loss of stature and b) selection bias at age 36 years were of little importance for the present analysis.

This study is restricted to an investigation of changes in blood pressure measured at three time points during the middle years of life. It may be that the observed associations will become stronger as the cohort ages and arterial stiffness and blood pressure increase further due to the continuing effects of ageing on the arterial tree. This could be investigated at future data collections. The availability of just three measures of blood pressure taken at fairly distant time points allows for only relatively simplistic modelling of changes in blood pressure, which may be unable to account for short term changes or more complex variations of blood pressure over time.

The increase in mean levels of blood pressure between 43 and 53 years may be influenced systematically by differences in sphygmomanometers used. However, readings between instruments are not likely to vary systematically by components of height. The variation in blood pressure reading might also vary between instruments or increase with age, as observed for pulse pressure and systolic blood pressure in this study. Using a standardized outcome measure, which accounts for the increase in the variation in blood pressure with age, a significant increase in the effect of height and leg length with age was observed for pulse pressure and systolic blood pressure, suggesting that the amplification of the effects of height and leg length were not simply due to increasing variance with age or change in measurement instrument.

THIRD OBJECTIVE

Assessment of a range of cardiovascular risk factors in the Whitehall II Study allowed detailed investigation of the specificity of cross-sectional associations with markers of growth. The inverse associations between height and CHD risk factors observed in men and women of the Whitehall II Study have previously been demonstrated in several other studies. (222;223;225;226) Findings of strong associations between leg length and CHD risk factors replicate earlier results from the 1946 birth cohort with regard to pulse and blood pressure and confirm results from the Caerphilly, Midspan, and British Women's Heart and Health cohorts, which suggested that leg length is the component of height more strongly and consistently associated with CHD risk factors in middle-aged and older men and women. (222;224;225) However, leg and trunk length both showed significant relationships with a number of cardiovascular risk factors, indicating that associations with arterial stiffness observed earlier may partly reflect adverse levels of risk factors for atherosclerosis other than blood pressure.

Associations between trunk length and cardiovascular risk factors question the specificity of factors limiting the growth of the long bones of the leg being solely responsible for the increased risk of cardiovascular disease; several aspects may explain or contribute to this. Even if influences during the growth hormone dependent childhood phase of growth largely underlie the link between poor growth and cardiovascular risk, associations with trunk length, albeit weaker, may still be expected. Although leg length is predominantly responsible for changes in height during this period, both components of height increase in length and may thus be restricted in their growth during this phase.

Associations with leg and trunk length may reflect more general influences on growth, and not necessarily one specific period, the childhood phase only. The degree to which socioeconomic and environmental influences on growth are reflected by shorter leg and trunk length are likely to

depend on which factors operate during sensitive periods of growth and differ according to the cohort or population under investigation.

Correlation between anthropometric measures

Previous work has shown that birthweight is similarly correlated with leg length and trunk length; (264) this has been interpreted as evidence that prenatal growth is unlikely to underlie differential associations of components of height with adult disease. Findings from other studies show the correlation between self-reported and recorded birthweight to be relatively good in younger people, but only moderate in elderly respondents. (328;329) Self-reported birthweights were not validated in the Whitehall II Study, and correlations between components of height and birthweight recorded at the time of birth (NSHD) versus recalled in adult life (Whitehall II Study) were therefore compared. These were found to be similar for leg and trunk length, as previously suggested, (264) for both studies alike.

While leg and trunk length were positively and moderately correlated in Whitehall II participants, they showed weak inverse correlations in the NSHD cohort. The reasons for this are unclear; however, despite age adjustment, the different age structure of the two studies, with all participants being the same age in the 1946 Birth Cohort (NSHD), may have contributed through differences in the degree of homogeneity of early life conditions between the two study populations.

Like analyses performed in the 1946 and Whitehall II cohorts, other recent investigations of associations between components of height and cardiovascular risk have also attempted to directly control for the effects of prenatal growth by means of adjustment. (223;225) Self-reported birthweights were available for less than a third of Midspan participants and adjustment in this subset slightly weakened inverse associations with blood pressure. (225)

Strength and limitations

Strength and limitations of the Whitehall II Study are also discussed in detail in relation to the findings of the following fourth objective, investigating associations between components of height and vascular structure and function in the Whitehall II cohort. In addition, some issues specific to the present analysis are discussed below.

Selection bias

Participants with missing information on components of height were excluded from the analyses and this may introduce selection bias, particularly as these data were missing for a large number of participants. Additional age adjusted analyses of associations between height and CHD risk factors were therefore performed using the maximum number of observations. Results were little different to those obtained for height using the restricted dataset. In addition, analyses were performed before and after excluding participants with missing information on covariates and estimates of associations were found to be broadly similar between the two samples.

Shrinkage and components of height

Although some shrinkage may commence around the age of 40 years, the degree of height loss is generally only small before middle age, but increases with advancing age. Because loss of height can be associated with pathological processes that influence the risk of cardiovascular disease, it has the potential to bias the observed associations. Leg length and trunk length are differently affected by shrinkage, as it predominantly affects the vertebral column, i.e. the trunk, and not the long bones of the leg. In line with this, results from the Whitehall II study showed that trunk, but not leg length, was negatively associated with age, particularly so in women. Although adjustment for age was performed in all analyses, residual confounding and reverse causality of associations with trunk length may play a role, due to metabolic disease processes underlying the risk for osteoporosis and cardiovascular disease that occur more commonly at older ages.

Age related differences in height or components of height may also be due to a cohort effect. Participants born from 1941 onwards, unlike those born before 1941, were recipients of war-time food supplements for expectant and nursing mothers, and young children. Mean differences in height at phase 1 and phase 5 was therefore compared between those born before and after 1941. While those born before 1941 were slightly shorter compared to those born after 1941, age adjusted differences were small and not statistically significant for height at phase 1, height at phase 5, or its components. Of those measures, the greatest difference between those born before

and after 1941 was observed for trunk length in women, with respective values of 85.4 versus 86.2 cm (p-value=0.06).

FOURTH OBJECTIVE

Findings of associations between adult markers of poor growth and distensibility and stiffness in men of the Whitehall II Study are in line with the earlier observed relationships between leg length and pulse pressure, a crude marker of arterial stiffness, and its age related rise. Estimates were greatest for total body height, largely owing to strong associations observed for both of its components, leg and trunk length. While inverse associations of height and leg length with intima media thickness were also observed in analyses adjusting for body weight, associations were significant in men only and reduced after accounting for differences in cardiovascular risk factors.

Considering the evidence presented so far, findings indicate that factors limiting growth predispose to atherosclerotic vascular changes before the development of symptomatic cardiovascular disease. Associations with distensibility and compliance, but not intima media thickness, were independent of cardiovascular risk factors and this may imply that functional impairment and absolute levels of arterial thickening are potentially affected via different mechanisms.

Associations between height, leg and trunk length and the arterial measures differed between the sexes and the reasons for this remain unclear, particularly as associations of leg length with blood and pulse pressure were shown to be similar in earlier analyses. The number of women in the Whitehall II study is substantially lower than that of men, reflecting the nature of this occupational cohort of civil servants. Also, men and women differed in the majority of characteristics that were compared; for example, women were less likely to report their ethnic origin as white European or to be in high employment grades and were more likely to have less personal income, household income and wealth, and a lower social class in childhood. While it is

unclear how these differences may have contributed to the lack of associations in women, the fact that women have lower levels of atherosclerosis for a given age, may have also contributed. Earlier reports have shown that a large proportion of women show no evidence of any calcified atherosclerotic lesions, as measured by electron beam computed tomography, before around age 60 years, (330;331) and women of the Whitehall Study may have been too young to detect differences according to stature.

One previous study using data from the ARIC cohort, found evidence of an inverse association between leg length and carotid artery intima media thickness in 12254 middle aged participants; measures of arterial function such as distensibility or stiffness were not available. (332) Estimates in the ARIC study were small in general, and differences in the magnitude and direction of associations between leg length and intima media thickness between ethnic groups and sexes were reported, being strongest and inverse in black men but positive and non-significant in black women. In univariate analyses, trunk length was also inversely associated with intima media thickness in black and white men and women; however, after adjustment for leg length, field centre and age, significant positive associations emerged in white men and women, while estimates were attenuated to non-significance in black men and women. Because adjustments were performed in groups, it is not possible to know which of the adjustment factors has lead to the reverse of associations for trunk length; however, as leg and trunk length are correlated and represent components of the same entity, adjustment for leg length is most likely to be responsible. It should be kept in mind that in models including both components of height simultaneously, effects sizes have to be interpreted as differences in leg length for a given trunk length and vice versa.

Contrary to results from the 1946 Study, associations with the arterial outcomes were observed in men only in the Whitehall II Study, and for both leg and trunk length. As mentioned above, trunk length showed weak inverse associations with intima media thickness in univariate analyses of the ARIC cohort; these did not withstand – or reversed – upon adjustments. In the Caerphilly study,

the inverse association between adult height and CHD was shown to be specific to leg length, and not seen for trunk length. Likewise, in the Boyd Orr study, leg length measured directly in childhood was found to be inversely associated with cardiovascular disease mortality over 52 years of follow-up, whereas there was no association between trunk length measured directly in childhood and cardiovascular disease mortality in later life. (213)

Results from the previous chapter have shown significant relationships between trunk length and several cardiovascular risk factors, questioning the specificity of leg length as an indicator of factors operating during the growth hormone dependent childhood phase of growth and influencing the risk of cardiovascular disease.

The growth hormone – insulin-like growth factor (IGF) axis plays a central role for the rapid period of postnatal childhood growth and levels of IGF 1 are strongly associated with childhood height. (333;334) Levels of IGF 1 and IGF-binding protein 1 in adulthood increase the risk of coronary heart disease, potentially through their effects on the endothelium and vascular smooth muscle cells. (146) Furthermore, recent studies have linked the IGF axis, particularly raised levels of IGF 1 and/ or reduced levels of its main binding protein (IGFBP3) with several cancers. (335-338)

While greater stature is associated with a reduced risk of cardiovascular disease, taller people and those with longer legs have an increased risk of developing cancer. (339-342) Because the directions of associations of height and leg length with cardiovascular disease, contrary to those with cancer, mirror those of the IGF axis, it has been speculated that IGF 1 may underlie leg length-disease associations. (343) However, recent results from the Avon Longitudinal Study of Parents and Children showed that although IGF 1 was strongly associated with subsequent growth, there was no evidence to support the hypothesis that leg length is a better biomarker of childhood IGF 1 levels than trunk length. (344)

Likewise, in the Whitehall II Study, associations between socioeconomic factors and components of stature were observed for both leg and trunk length. In summary, while these results question

the specificity of leg length as a marker of early influences on growth, they suggest that both components of height may be useful as markers of early social and/ or hormonal influences that potentially influence the risk of cardiovascular disease and cancer.

Strength and limitations

Strengths of this study include the standardized assessment of several vascular outcomes, the relatively large cohort size, and the wealth of data on potential confounding and mediating factors. Information on early life factors, such as birthweight and childhood social class, was reported in adulthood, and non-differential measurement error of recalled information and the smaller sample size due to missing data may weaken associations or result in residual confounding when controlling for the effect of birthweight or childhood social class. No validation of self-reported birthweights has been carried out in the Whitehall II study, as discussed in more detail in the previous chapter.

Earlier work using data from the Whitehall II Study has shown that height is more strongly associated with adult employment grade, compared to father's social class, (138) an observation that is generally not made in studies using prospective measures of early life social factors. (115;345) Although this is most likely due to greater measurement error of early life factors recalled in middle age, other explanations are possible. These include a narrower range of father's social classes in civil servants, upward social mobility (i.e. selection into employment grades) by height or factors associated with stature, and grade related shrinkage.

Vascular outcome measures

While vascular outcomes differed significantly by presence or absence of a range of traditional cardiovascular risk factors, differences according to presence or absence of coronary heart disease were weak and inconsistent and this may reflect treatment bias or reverse causality, for example smoking cessation in those with symptomatic disease or after treatment.

The same absolute degree of atherosclerosis may result in clinical disease earlier or present with more severe symptoms in shorter people with relatively smaller vessel diameters. Although information on vessel size is not commonly available, studies using ultrasound measures of vascular function have found associations after accounting for vessel size. (6) In this study, beta stiffness index and distensibility coefficient were used as measures of vascular function; these account for differences in baseline vessel diameter by estimating relative change and are expressed per unit change of blood pressure, i.e. are independent of blood pressure.

Sensitivity analysis

To test the influence of CHD history and ethnic group on the relationships between anthropometry and the vascular outcomes, sensitivity analyses were performed restricted to white Europeans and also stratified by presence or absence of CHD. These analyses yielded similar results and no evidence for significant effect modification was found.

Selection and survival bias

Survival and selection bias may have influenced our results, as components of height were not assessed before phase 5 and a total of 605 (400 men, 205 women) participants (5.9%) died before the end of phase 7 (107 deaths due to CHD; 86 men, 21 women), when vascular outcomes were measured. An inverse association between height and fatal and non-fatal CHD events, including all participants with data on height measured at phase 1 (n=10298) was observed in men (HR (95% CI) 0.83 (0.75; 0.91)) and women (0.88 (0.72; 1.08)). However, when the same association was investigated using height measured at phase 5, effectively restricting the analysis to those not dead or lost to follow-up at that phase (4027 men, 1693 women), and thus eligible for assessment of components of height, this estimate was weakened in men (0.89 (0.78; 1.01)), but strengthened in women (0.59 (0.45; 0.78)). The observed differences were due to selective survival/ loss to follow-up, but not shrinkage between phase 1 and 5, as results restricted to phase 5 attendees were virtually identical when height at phase 1 was used instead of phase 5 (HR 0.90 in men, 0.59 in women. This suggests that any associations between height or its components as measured at phase 5 and subsequent cardiovascular risk may be biased, potentially differentially with regard to sex. If the degree of under- or overestimation differentially affected associations with the two components of height, this may also bias their comparison.

Shrinkage and components of height

Limitations of leg and trunk length due to measurement error and also as markers of early growth have been discussed in detail earlier. It has been suggested that differential shrinkage of ill people before study entry may lead to artificial associations between shortness and increased future cardiovascular risk, particularly in the early years of follow-up, (272) and objective 7 will address this question in more detail. Evidence presented above has shown that shrinkage is unlikely to be a major problem in this study, particularly in comparison to the greater bias that may be introduced by selective mortality. Differential shrinkage of components of height has been discussed in detail in the previous and earlier chapters.

FIFTH OBJECTIVE

Little is known about associations between components of height and metabolic and cardiovascular risk in populations of comparatively short height.

Cross-sectional examination of Filipino-American women showed that the overall prevalence of diabetes in this, by Western Standards, comparatively short and non-obese population is greatly increased, (298) similar to other immigrant populations. (346) Unlike cohorts where diabetes prevalence is higher in migrant than native populations, the diabetes prevalence was similar to that of women in the Philippines, and longer term migrants and US born Filipinas in Hawaii. (347;348) Selective survival of undernutrition or starvation by those with efficient energy storage and greater body size may lead to increased susceptibility to diabetes when followed by a Western diet with an abundance of food. (349) Contrary to this "thrifty genotype" hypothesis stands the idea of a "thrifty phenotype", where early undernutrition may lead to impaired development of the endocrine pancreas and increased susceptibility to diabetes in later life. (350) Filipino women are less obese, compared to Caucasian American women, and earlier reports from the same population have shown that although Filipino women have more visceral adipose tissue (by

computed tomography) for a given level of body size, this does not explain their high prevalence of diabetes. (348) Adult body size is thus unlikely to underlie the observed associations; also, while education only was the only socioeconomic measure significantly associated with BMI and waist, income was most strongly associated with diabetes. These cross-sectional analyses cannot rule out the potential importance of weight trajectories from early to adult life contributing to associations with diabetes. However, the observed results suggest that factors associated with socioeconomic disadvantage during women's childhood that persist after migration to the US and into adult life may be important for the development of diabetes. In this context, the quality of the diet may be more important than absolute caloric intake or body size for the risk of diabetes in this non-obese population, i.e. the quality rather than quantity of fat and carbohydrate consumption. (351)

Although components of adult height differed significantly according to socioeconomic circumstances, no evidence was found for their association with diabetes or HOMA-IR (not shown). This is in contrast with two earlier studies of British men, (222) and women, (224) suggesting that those with poor growth of the long bones of the leg show a higher prevalence of insulin resistance and non-insulin dependent diabetes, as well as other cardiovascular risk factors. (225;352) Likewise, the most recently published study using NHANES III data reported significant associations between leg length and leg length to height ratio with adiposity (women only), insulin resistance and type 2 diabetes; diabetes associations remained significant in fully adjusted models. Ethnic differences were reported, but not shown, with associations being observed in Non-Hispanic Whites and Mexican Americans, but not non-Hispanic Blacks. (226)

Socioeconomic indicators available in this sample of Filipino-American women did not appear to be the main factors underlying the inverse associations between leg length and CHD observed in this and previous studies. (222;223) However, it should be noted that indicators such as childhood family income may be poor measures of early malnutrition not only during times of

war and occupation in the Philippines, but also considering that access to food may have been easier for families with low income but living or working on farms, for example.

Strength and limitations

An important advantage of the investigation of Filipina women is that potential residual confounding of health behaviours is unlikely to play a major role, as few Filipinas engaged in unhealthy behaviours, such as excess alcohol consumption, smoking or sedentary lifestyle. Some limitations of the present study should be noted. This is a cross-sectional study which used opportunistic sampling to recruit. Reverse causation and selection bias may have influenced our results, and prospective studies are warranted to validate these cross-sectional findings. Although the sample size was small, a significant association between leg length and CHD was observed. However, CHD was not significantly associated with any of the socioeconomic indicators, despite directions and magnitudes of associations with childhood and adult income and life-course socioeconomic position being similar compared to diabetes. The smaller number of CHD cases and thus low power may have contributed to the lack of statistical significance.

Childhood and adult income and education were self reported and may not reflect sustained income, particularly when migration occurred in mid-life. Adult income referred to current income, and many women (48%) reported to not currently be employed. Although 52% had 16 years of education or more, and as such, were presumably college graduates, the lower adult income might reflect underemployment if their Philippine college degrees were not transferable to the US, or they elected not to join the labour force due to concerns about adjusting to a foreign culture and language at an older age (half migrated to the US after age 45 years). Previous studies have shown that immigrants who previously held professional occupations, particularly those who migrate in middle age, lose status. (353) A total of 67% of our cohort with 16 years or more of education held jobs as professionals, managers etc. when residing in the Philippines. Of these, half (55%) held similar positions in the US, the remainder were housewives (10%), worked in

skilled manual (12%), semi-skilled (6%) or unskilled occupations (17%) in the US. As a consequence, the potential misclassification of the socioeconomic variables may have lead to an attenuation of associations if it was non-differential with regard to diabetes and CHD. However, underestimation as well as exaggerated effects may have occurred if participants with diabetes or CHD were selectively overrepresented in the higher or lower economic or educational groups, respectively.

Generalizability of the sample

Census data did not report Asian nationalities separately in 1995; population-based sampling of all Filipinos in San Diego County was therefore not possible. Because the sampling frame is unknown, it was not possible to calculate response rates and discuss the representativeness of the study population in detail. However, comparisons with 2000 United States Census data suggest that this cohort is representative of all Filipino-Americans with regard to education (where 43.8% of all Filipino-Americans $\geq$25 years of age are college graduates compared to 52% in this cohort). Median household income in this cohort ($25,000-29,999) is lower than national statistics ($65,189) for all Filipino-Americans; (24) this discrepancy likely reflects underemployment or retired status in this older cohort.

SIXTH OBJECTIVE

In 3 year old children of Project Viva, a prospective U.S. birth cohort study of pregnant women and their offspring, poor linear growth of the lower body, i.e. shorter leg length, relative to total body height, was associated with higher blood pressure.

Leg length was positively associated with blood pressure in analyses adjusted for age, sex and measurement conditions, but inverse associations emerged after additional inclusion of height in the model. While such reversal of associations may occur as a statistical artefact due to multicollinearity (between height and leg length), this is unlikely to be the case here for several

reasons. Correlations between height and leg length versus trunk length are generally both high (0.85 in both cases in this study) and it thus seems unlikely that collinearity differentially affects models including leg, but not trunk length. Also, analyses of leg percent or difference in leg and trunk z-scores, which are not subject to this problem, yielded similar results.

The inverse association between leg length and blood pressure in Project Viva replicates earlier findings in adults and suggests that the association between poor growth of the lower body and high blood pressure may have its origins early in life and develop during the childhood phase of growth.

Associations were observed for all four blood pressure outcomes, but were slightly stronger and remained significant in fully adjusted analyses for pulse pressure and systolic blood pressure, as observed in the 1946 Study. Although not the case for adults, greater measurement error of diastolic blood pressure may contribute to differential associations in childhood. (354) In studies investigating the role of prenatal growth, as indicated by birthweight, an effect on diastolic blood pressure has also less frequently been reported, potentially due to a lack of significant findings. (281) The reasons for this remain unclear; however, as hypothesized in chapter 5, associations between growth limiting factors and blood pressure may be strongest for those measures that show a greater rise with age, i.e. systolic blood pressure and pulse pressure.

Of all childhood predictors of adult blood pressure, blood pressure levels in childhood are most important. (354;355) Evidence comes from longitudinal studies showing that blood pressure tracks from childhood to adulthood. Blood pressure rises with age, particularly in childhood, but while children with initially high levels of blood pressure are more likely to become adults with high blood pressure, not all children maintain their ranks. (356) Factors that influence the level at which blood pressure tracks during childhood include growth, obesity and the degree of maturation acquired. (357) Height and weight are each positively associated with blood pressure during childhood, and this was seen in children of Project Viva, too. In analyses including height

and weight simultaneously, weight emerged as the more important (or stronger) influence, and this has previously been reported. (358)

Although no previous studies are available investigating associations between components of height and blood pressure in childhood, one earlier report has shown an association between fetal femur length and systolic blood pressure at age 6 years, adjusting for current height. (228) In that study, the authors obtained similar results after adjustment for current weight or BMI instead of height, and this was also observed in Project Viva (not shown).

Results from the Muscatine Study examining children aged 5 to 18 years showed that while having high levels of blood pressure for age was associated with excessive body weight or precocious height, having high blood pressure for height but not for age was associated with being short for age. (359) This pattern suggests that the positive association between height and blood pressure reflects greater weight and obesity, also supported by results from adjusted analyses in this study, where weight emerged as the stronger predictor, as mentioned above.

Positive associations between trunk length and blood pressure mirror those observed for height and the notion that these reflect the effects of greater weight and obesity are supported by the fact that weight and BMI showed stronger correlations with trunk length (correlation coefficients 0.71 and 0.23, respectively), compared to leg length (0.56 and 0.01, respectively) in these 3 year old children.

Shorter leg length, for a given height, may indicate that growth potential has not been achieved during the childhood phase. Relatively shorter childhood leg length may as such be a measure of being short for age, and thus be associated with lower levels of blood pressure in accordance with results from The Muscatine Study.

Predictors of components of height

Of all predictors that were considered, only few showed significant associations that differentially affected components of height; these consisted largely of parental and children's anthropometry. Leg length contributed a significantly greater proportion to body height in children with taller mothers and those with greater length, but not weight, at birth and at age 3 years; while maternal age, children's weight and BMI showed inverse associations with both, the proportion of height contributed by leg length and the differences in leg and trunk length z-scores.

In contrast to results from Project Viva, data from NSHD showed that diet in early childhood (breastfeeding and greater energy intake at age 4 years) was associated with greater adult leg length. (115) Data from the Boyd-Orr cohort showed similar results, with breastfeeding, high energy diets at age 2 years, and advantaged childhood social circumstances each being specifically associated with longer leg length in childhood. (106;360) Results of this study were also indicative of the association between breastfeeding and leg length being stronger at older ages, and this may suggests that associations may emerge in Project Viva as its children grow older. However, differences between this and previous studies may also be explained by changes in early life conditions of children of the earlier cohorts born 1918-39 and 1946, respectively, compared to contemporary and socially relatively homogenous children of Project Viva. These secular changes in early life conditions may also underlie the overall lack of associations observed between markers of socioeconomic position and components of height in this study, which is in contrast with the notion of leg length being a sensitive marker of early environmental influences on growth. (310)

Strength and limitations

Important strength of the Project Viva Study include prospectively collected longitudinal data beginning in early pregnancy, detailed assessment of demographic, socioeconomic and biological family and child characteristics, availability of components of height, in addition to multiple standardized recordings of blood pressure at the 3 year examination.

Within person variability of blood pressure is particularly high in childhood, (361) and the importance of measuring blood pressure multiple times in epidemiological studies of children has previously been highlighted. (354) In Project Viva, to reduce biases resulting from equipment, subject, environment, and technique, blood pressure was measured according to a standardized protocol by trained research assistants using calibrated Dinamap Pro-100 oscillometric automated monitors, which recorded blood pressure up to five times at 1-minute intervals. Measurement conditions were recorded and controlled for in all analyses. Previous research has shown that multiple measurements are vital in estimating childhood blood pressure, (354) and multilevel analyses including up to five measures for each child were performed, accounting for within and between person variations, and allowing a more precise estimation of blood pressure and its predictors. (358) However, it has been suggested that obtaining data from several visits, days or weeks apart, may be more important than increasing the number of measurements per visit; (354) however, this is difficult to achieve in the context of a large, long term prospective birth cohort study.

Mothers included in the study were relatively well educated and older, and all resided in eastern Massachusetts, potentially limiting generalizability. Also, only 53% of all originally included mother child pairs were accounted for in the present analysis, potentially introducing selection bias and limiting the generalizability/ external validity of findings. Compared to the whole cohort, mothers who were included were indeed slightly more likely to be white and better educated, but no differences existed for household income, maternal pre-pregnancy BMI or children's birthweight, compared to all 2083 participants who delivered a non-premature child.

Inverse associations between leg length and blood pressure emerged after adjustment for height, and as leg and trunk length are the two only components of height, it is not possible to determine whether relatively shorter legs or longer trunks are underlying the observed associations. It has previously been suggested that rather than height per se, the distance from the heart to the vertex of the head is more important for the positive relationship between height and blood pressure that

exists during the growing years. (362) Total sitting height includes the length of the neck and head and it is therefore possible that longer trunks rather than shorter legs drive the observed associations, lending some support to this hypothesis.

While the availability of a range of prospectively collected potential confounding and mediating factors are a strength of this study, children who grow poorly are likely to differ from those who do not with regard to many unmeasured factors, in addition to those controlled for in the present analysis. In the context of an observational study, it is not possible to account for all unknown factors that may influence both growth and blood pressure simultaneously. However, any such factors need to differentially be associated with components of height in order to account for the observed associations. Of the variables considered, surprisingly few fulfilled this criterion and these did not account for the observed link between short leg length and high blood pressure.

SEVENTH OBJECTIVE

While increased levels of CHD morbidity and mortality in those of shorter height have been demonstrated in many studies, some questions remain unanswered. The first Whitehall Study, with an adequate number of people with and without evidence of CHD at baseline, a large number of deaths due to CHD and stroke, a long duration of follow-up, and sufficient power to investigate effect modification, provides the opportunity to address some of these questions.

Symptomatic participants

Not many studies have explored the role of short height in participants with prevalent CHD, and these yielded conflicting results for the prognosis after myocardial infarction. (201-204) Age adjusted mortality rates from coronary heart disease in the first Whitehall Study were, as expected, more than twice as high in participants with CHD at study entry, compared to those without, representing their worse prognosis. The strong, inverse associations between height and CHD mortality observed in this high risk group indicate that short height is not only an important

influence on the development of CHD in an asymptomatic healthy population, but also affects the prognosis in men with evident CHD.

Interaction of early and later life effects

Previous investigations of the association between height and mortality have commonly performed adjustments to account for socioeconomic confounding. Findings from the first Whitehall Study now provide evidence that influences on growth may interact with adult socioeconomic position in their effects on cardiovascular mortality, rather than representing a joint underlying mechanism, and this may explain some of the discrepant findings of earlier studies. A study of Finnish men has previously suggested that those with poor prenatal growth are more vulnerable to the effects of low socioeconomic status on CHD. (124) In contrast, the present study shows that the positive effect of growth in height (or adverse effect of short height) on cardiovascular mortality is particularly apparent in those of higher employment grades. Several circumstances may contribute to these discrepant findings. First, in the Finnish study almost half of the 285 fatal and non-fatal CHD events occurred in labourers. Differences in the effect of birthweight on CHD between social classes were of borderline significance and restricted to labourers. This group is not represented in our analysis, which is based on nearly 4000 deaths in an occupational cohort of British civil servants, all office workers. The comparability of the two populations is therefore questionable. Second, while Barker et al. suggested that the effect of prenatal growth on CHD is more evident in those of low adult social class, this study showed that the association between short height and CHD is strongest in high employment grades. Size at birth and height, although weakly correlated, are markers of growth phases with different determinants and duration, and these may represent separate influences on cardiovascular risk. (172;264)

Research from the 1958 British birth cohort has shown that the shorter height of low birthweight infants was overcome in children from the highest, but not other social classes. (363) This differential 'catch up' growth in height has been attributed to their better social conditions,

including nutrition, education and health care. These inequalities in the realization of growth potential suggest that variation in height within social classes of origin, and particularly for those from most privileged backgrounds, has a larger genetic component than variations in height overall. When investigating differences between employment grades in adulthood, the opposite may be the case. The civil service has provided an opportunity for upward social mobility for children of manual workers, mainly with regard to the clerical grades, and to a lesser degree for the higher grades. (364) Downward social mobility of those from privileged backgrounds to lower employment grades has been much less common. This means that people in higher grades represent the widest spectrum of childhood backgrounds, ranging from those who maintained a privileged position throughout their life, to those who moved up to the greatest extent from the lowest childhood conditions. People moving to a higher class are on average taller than the class they leave and shorter than the class they join, and this has also been observed for the civil service. (365) Upward social mobility therefore results in a decrease in mean height in the higher grades, narrowing height inequalities between grades in adulthood. (345) Within high grades, shorter participants thus represent the upwardly mobile, and their childhood environment and cardiovascular risk differs from the taller participants of continuously high social position. Absolute mortality rates reflect this social mobility, being lowest in the tallest group in the highest employment grade and similar when comparing the shortest group in the highest grade to the tallest group in the grade below (results not shown).

In addition, the relative contribution of early disadvantage for adult cardiovascular risk may be smaller in men in lower employment grades with increased risk factors and higher absolute mortality. Thus the strongest relationship between short height and CVD may be expected in lower risk participants in the higher grades.

Length of follow up

The inverse association between height and mortality was not confined to the first period of follow-up, contrary to a suggestion based on earlier follow-up of this study, (272) and providing

no evidence that associations may be restricted to participants whose short height was a result of existing disease in childhood or shrinkage in adulthood. The issue of reverse causality has been examined in long term follow-ups of young adults in Scotland and the US. (165;183) In these studies, participants' height was assessed at University entry, minimizing any potential influence of shrinkage owing to concomitant disease. In both studies greater stature offered protection against CHD.

Strength and limitations

Strengths of the present study include its almost complete follow-up for mortality, minimising potential selection bias; the availability of information on a range of potential covariates, including socioeconomic position, smoking and obesity; and extended follow-up with a large number of deaths, so facilitating examination of reverse causality. Despite these advantages, the study invariably has some weaknesses. In having only a single baseline assessment of the cohort, there will have been some measurement misclassification, albeit non-differential with respect to the exposure of interest. The generalizability of findings from an occupational cohort of male civil-servants is limited. The study of participants of socioeconomic status higher than the general population average, and thus of taller stature and with lower mortality rates, may result in an underestimation of the association between height and CHD. Contrary to this notion, our results suggest that this association may be particularly marked in socially homogenous cohorts. (151;165;173;183) Given their related aetiologies, the association between height and CHD would be expected to be similar to that with ischemic, but not hemorrhagic stroke. (200) However, information on stroke sub-types was not sufficiently well characterized to allow separate investigation.

CONCLUSIONS AND IMPLICATIONS

Many studies have demonstrated an inverse association between height and cardiovascular risk in adult life. This, together with recent evidence of long term influences of childhood conditions on adult cardiovascular risk, has led to speculations about early life influences as origins of atherosclerosis and symptomatic cardiovascular disease. Leg length, one component of height, was proposed to be useful as a sensitive marker of early environmental factors that are socially distributed and may link poor growth, atherosclerosis and cardiovascular risk, and this has provided the background of this thesis.

In line with this, findings of pulse pressure, a marker of arterial stiffness, and systolic blood pressure being significantly greater in men and women of shorter height and leg length, but not trunk length, have supported a role of factors limiting early linear growth for the development of high blood pressure in later life. Importantly, these associations were shown to be significantly amplified with age, and this may be regarded as evidence for the hypothesis that people with poor growth are more susceptible to the effects of ageing on the arterial tree. Findings from the NSHD were validated in participants of the Whitehall II cohort, who also provided evidence of inverse associations between poor growth and specific measures of vascular function, arterial distensibility and stiffness, in adult men.

The prevalence of isolated systolic hypertension, arteriosclerosis and other diseases associated with aging continue to rise as the elderly population grows and future studies may show whether associations are even more marked in older populations. Nutritional factors influence the age related rise of blood pressure, largely responsible for the high prevalence of hypertension in industrialized countries, and populations with low salt intake, for example, have been shown to be relatively free from hypertension. (366) If nutritional factors limiting growth contribute to the tracking of cardiovascular risk throughout life, preventive measures aimed at reducing the rise of

blood pressure and arterial stiffness during midlife will need to be implemented early in life. Findings of associations between relatively shorter leg length and higher blood pressure observed in 3 year old children of Project Viva are in support of this.

As outlined above, leg length is generally regarded a marker of early influences during the childhood phase of growth and potentially underlying causal factors were discussed. Stature is to some degree genetically determined, (367) but there is little evidence that genetic factors underlie the link between poor growth and cardiovascular risk. (189;225;278) Importantly, poor growth and shorter height are more common in men and women growing up and living in adverse socioeconomic circumstances, and stature thus reflects socioeconomic disadvantage over the life-course. Accordingly, socioeconomic differences in height and its components were observed or have previously been reported for all studies of adults included in this report. (115;138;151;152) Large differences in height and its components according to socioeconomic position were also found in a sample of Filipino-American women, a comparatively short population. While the high risk of diabetes in these women differed significantly by childhood and adult socioeconomic factors, leg length, but not trunk length, was shown to be the factor most strongly associated with the risk of CHD.

Because of the social distribution of growth and stature, and the well documented influence of social disadvantage on cardiovascular risk, it is likely that factors linking poor growth and cardiovascular risk are socially distributed. In all studies, adjustments were performed to investigate the role of prenatal growth, socioeconomic factors or other potentially confounding and mediating factors. While the role of prenatal growth was shown to be limited for the associations that were investigated, the influence of socioeconomic factors appeared more complex. While adjustments for indicators of social position in childhood and adulthood did not account for the observed associations, issues of residual confounding and effect modification arose.

Differences in results of randomized trials and observational studies investigating socially distributed exposures, such as vitamin intake or hormone replacement therapy, have highlighted that even careful adjustments do not preclude residual influences, due to the measurement error, biases and the complexity of associations and confounding structure. (271) Indicators of social position that are available in long term prospective studies are unlikely to adequately capture the different pathways through which early disadvantage or deprivation may limit growth and affect atherosclerosis and cardiovascular disease. Importantly, adjustment for socioeconomic factors that are hypothesized to contribute to or underlie the relationships between growth and cardiovascular risk will represent overadjustment if not interpreted in the context of the underlying causal model.

Further, adjustments for socioeconomic factors may be inappropriate if effect modification is present. The differential associations between short height and cardiovascular mortality between employment grades that were observed in men with and without prevalent CHD in the first Whitehall study have provided some evidence for the complex interactions between poor growth and socioeconomic position that are present.

Taking together evidence of a) early life exposures specifically affecting leg, rather than trunk length, b) the notion that up until puberty, and particularly during the childhood phase of growth, a much greater proportion of increases in height is due to leg growth, making it more vulnerable to environmental exposures, c) secular increases in height, attributed to improved childhood conditions, largely affecting leg length, and d) inverse associations with markers of cardiovascular risk being observed for leg length, rather than trunk length, it may not be surprising that factors limiting the growth of the long bones of the legs have been suggested to contribute to the origins of atherosclerosis and cardiovascular risk.

While findings of this thesis lend some support to this hypothesis and have shown that shorter leg length is associated with increased arterial stiffness, subclinical atherosclerosis and cardiovascular

risk, potentially from an early age on and with effects being amplified with age, they also highlight that some of these claims should be treated with caution.

In particular, they question the specificity of leg length as a marker of early influences operating during the childhood phase of growth that are responsible for the increased cardiovascular risk associated with shorter height. Factors simultaneously influencing growth and arterial development, stiffness and atherosclerosis are likely to act over prolonged periods of time and be influenced by a complex set of socioeconomic factors at different ages.

Future and ongoing longitudinal studies may shed light on the role of tempo of growth and timing of puberty for associations between growth and cardiovascular risk and this may help to identify children with growth patterns that would benefit from early monitoring and management of cardiovascular risk.

TABLES

TABLE 1 CHARACTERISTICS OF MEN AND WOMEN OF THE NSHD AT AGE 53 YEARS

	N	MEN	WOMEN	
	MEN/ WOMEN			
		MEANS (SE)		P-VALUE*
BIRTHWEIGHT (G)	1724/ 1695	3461.8 (12.5)	3320.8 (11.7)	≤ 0.001
WEIGHT (KG)	1451/ 1501	83.7 (0.36)	71.6 (0.37)	≤ 0.001
BMI (KG/M^2)	1452/ 1496	27.4 (0.11)	27.4 (0.14)	0.82
WAIST-HIP RATIO (%)	1452/ 1504	93.6 (0.16)	80.7 (0.17)	≤ 0.001
HEIGHT (M)	1729/ 1700	174.7 (0.16)	161.6 (0.15)	≤ 0.001
LEG LENGTH (M)	1724/ 1698	82.7 (0.12)	74.8 (0.12)	≤ 0.001
TRUNK LENGTH (M)	1724/ 1698	92.0 (0.10)	86.8 (0.10)	≤ 0.001
SYSTOLIC BLOOD PRESSURE	1441/ 1464	140.0 (0.52)	132.2 (0.51)	≤ 0.001
DIASTOLIC BLOOD PRESSURE	1441/ 1464	87.3 (0.32)	81.6 (0.30)	≤ 0.001
PULSE PRESSURE	1441/ 1464	52.7 (0.35)	50.6 (0.36)	≤ 0.001
		PROPORTIONS		P-VALUE*
FATHER IN A NON-MANUAL CLASS	1644/ 1604	41.2	41.7	0.79
EDUCATION AT A-LEVEL OR MORE	1626/ 1599	41.5	27.5	≤ 0.001
NON-MANUAL SOCIAL CLASS	1690/ 1608	60.4	71.7	≤ 0.001
ANTIHYPERTENSIVE DRUG USE	1461/ 1517	13.8	15.5	0.20
CURRENT CIGARETTE SMOKER	1461/ 1517	23.9	22.7	0.46
REGULAR EXERCISE	1460/ 1517	52.1	49.2	0.13

* t-test for differences in means and chi-squared test for differences in proportions

TABLE 2 MEAN (95% CI) PULSE PRESSURE IN EACH OF THE FOUR HEIGHT AND LEG LENGTH GROUPS AND DIFFERENCES IN Z-SCORES COMPARING EACH WITH THE SHORTEST GROUP

PULSE PRESSURE	MEANS	DIFFERENCES IN Z-SCORES		
		MODEL A*	MODEL B**	MODEL C***
MEN [1363]				
HEIGHT				
1 (≤ 170.2 CM)	54.6 (53.2; 56.0)	0	0	0
2 (> 170.2 CM – 174.8 CM)	52.9 (51.5; 54.3)	-0.14 (-0.28; 0.01)	-0.13 (-0.28; 0.01)	-0.13 (-0.28; 0.02)
3 (> 174.8 CM – 178.9 CM)	52.8 (51.3; 54.2)	-0.11 (-0.26; 0.04)	-0.10 (-0.25; 0.05)	-0.09 (-0.24; 0.05)
4 (> 179.9 CM)	51.0 (49.6; 52.4)	-0.24 (-0.39;-0.10)	-0.23 (-0.37;-0.08)	-0.22 (-0.36;-0.07)
P-TREND	≤ 0.001	0.003	0.007	0.01
LEG LENGTH				
1 (≤ 79.3 CM)	55.8 (54.4; 57.2)	0	0	0
2 (> 79.3 CM – 82.6 CM)	53.9 (52.5; 55.3)	-0.14 (-0.28; 0.01)	-0.13 (-0.27; 0.02)	-0.13 (-0.27; 0.02)
3 (> 82.6 CM – 85.8 CM)	50.8 (49.4; 52.2)	-0.35 (-0.49;-0.12)	-0.34 (-0.49;-0.19)	-0.34 (-0.48;-0.19)
4 (> 85.8 CM)	50.7 (49.3; 52.1)	-0.34 (-0.49;-0.19)	-0.33 (-0.47;-0.18)	-0.32 (-0.47;-0.17)
P-TREND	≤ 0.001	≤ 0.001	≤ 0.001	≤ 0.001
WOMEN [1355]				
HEIGHT				
1 (≤ 158.0 CM)	52.9 (51.5; 54.3)	0	0	0
2 (> 158.0 CM – 161.6 CM)	51.6 (50.1; 53.0)	-0.09 (-0.24; 0.06)	-0.07 (-0.22; 0.08)	-0.08 (-0.23; 0.07)
3 (> 161.6 CM – 165.5 CM)	49.2 (47.7; 50.6)	-0.25 (-0.40;-0.11)	-0.24 (-0.39;-0.09)	-0.24 (-0.39;-0.09)
4 (> 165.5 CM)	48.4 (46.9; 49.8)	-0.28 (-0.43;-0.14)	-0.27 (-0.42;-0.12)	-0.27 (-0.41;-0.12)
P-TREND	≤ 0.001	≤ 0.001	≤ 0.001	≤ 0.001
LEG LENGTH				
1 (≤ 71.8 CM)	53.3 (51.9; 54.8)	0	0	0
2 (> 71.8 CM – 74.7 CM)	50.5 (49.1; 52.0)	-0.18 (-0.33;-0.03)	-0.17 (-0.31;-0.02)	-0.17 (-0.32;-0.02)
3 (> 74.7 CM – 77.7 CM)	49.7 (48.3; 51.2)	-0.23 (-0.38;-0.08)	-0.21 (-0.36;-0.06)	-0.22 (-0.37;-0.07)
4 (> 77.7 CM)	48.6 (47.2; 50.1)	-0.30 (-0.45;-0.15)	-0.29 (-0.44;-0.14)	-0.28 (-0.43;-0.13)
P-TREND	≤ 0.001	≤ 0.001	≤ 0.001	≤ 0.001

* Model A: Adjustment for use of antihypertensive medication, body mass index, waist-hip ratio and smoking
** Model B: As model A, with additional adjustment for childhood social class
*** Model C: As model A, with additional adjustment for birthweight

TABLE 3 MEAN (95% CI) SYSTOLIC BLOOD PRESSURE IN EACH OF THE FOUR HEIGHT AND LEG LENGTH GROUPS AND DIFFERENCES IN Z-SCORES COMPARING EACH WITH THE SHORTEST GROUP

SYSTOLIC PRESSURE	MEANS	DIFFERENCES IN Z-SCORES		
		MODEL A*	MODEL B**	MODEL C***
MEN [1363]				
HEIGHT				
1	141.7 (139.7; 143.8)	0	0	0
2	140.8 (138.7; 142.8)	-0.06 (-0.20; 0.08)	-0.05 (-0.19; 0.09)	-0.05 (-0.19; 0.09)
3	140.0 (137.9; 142.2)	-0.06 (-0.20; 0.09)	-0.04 (-0.18; 0.11)	-0.03 (-0.18; 0.11)
4	137.6 (135.5; 139.7)	-0.17 (-0.32;-0.03)	-0.14 (-0.28; 0.00)	-0.14 (-0.28; 0.01)
P-TREND	0.006	0.03	0.08	0.09
LEG LENGTH				
1	143.1 (141.0; 145.2)	0	0	0
2	142.3 (140.2; 144.3)	-0.03 (-0.17; 0.11)	-0.01 (-0.16; 0.13)	-0.02 (-0.16; 0.12)
3	138.1 (136.0; 140.2)	-0.21 (-0.36;-0.07)	-0.20 (-0.34;-0.05)	-0.20 (-0.35;-0.06)
4	136.5 (134.5; 138.6)	-0.25 (-0.40;-0.12)	-0.23 (-0.37;-0.08)	-0.23 (-0.37;-0.08)
P-TREND	≤ 0.001	≤ 0.001	≤ 0.001	≤ 0.001
WOMEN [1355]				
HEIGHT				
1	135.2 (133.2; 137.2)	0	0	0
2	133.6 (131.5; 135.7)	-0.06 (-0.20; 0.08)	-0.05 (-0.19; 0.10)	-0.05 (-0.20; 0.09)
3	131.6 (129.5; 133.7)	-0.15 (-0.29;-0.01)	-0.15 (-0.29;-0.00)	-0.14 (-0.28; 0.00)
4	128.1 (125.9; 130.2)	-0.28 (-0.42;-0.13)	-0.27 (-0.42;-0.12)	-0.27 (-0.41;-0.12)
P-TREND	≤ 0.001	≤ 0.001	≤ 0.001	≤ 0.001
LEG LENGTH				
1	135.6 (133.5; 137.7)	0	0	0
2	132.6 (130.6; 134.7)	-0.10 (-0.25; 0.05)	-0.09 (-0.23; 0.06)	-0.09 (-0.24; 0.05)
3	131.2 (129.1; 133.3)	-0.16 (-0.30;-0.01)	-0.14 (-0.29; 0.01)	-0.15 (-0.29; 0.00)
4	129.5 (127.4; 131.5)	-0.23 (-0.38;-0.08)	-0.22 (-0.37;-0.08)	-0.22 (-0.37;-0.07)
P-TREND	≤ 0.001	0.002	0.003	0.003

* Model A: Adjustment for use of antihypertensive medication, body mass index, waist-hip ratio and smoking
** Model B: As model A, with additional adjustment for childhood social class
*** Model C: As model A, with additional adjustment for birthweight

TABLE 4 MEAN (95% CI) DIASTOLIC BLOOD PRESSURE IN EACH OF THE FOUR HEIGHT AND LEG LENGTH GROUPS AND DIFFERENCES IN Z-SCORES COMPARING EACH WITH THE SHORTEST GROUP

DIASTOLIC PRESSURE	MEAN	DIFFERENCES IN Z-SCORES		
		MODEL A*	MODEL B**	MODEL C***
MEN [1363]				
HEIGHT				
1	87.1 (85.8; 88.4)	0	0	0
2	87.9 (86.6; 89.2)	0.05 (-0.09; 0.20)	0.06 (-0.08; 0.21)	0.06 (-0.08; 0.20)
3	87.2 (85.9; 88.6)	0.03 (-0.11; 0.18)	0.05 (-0.09; 0.20)	0.05 (-0.09; 0.20)
4	86.7 (85.4; 88.0)	-0.01 (-0.16; 0.13)	0.02 (-0.13; 0.16)	0.01 (-0.13; 0.16)
P-TREND	0.5	0.8	0.8	0.9
LEG LENGTH				
1	87.3 (86.0; 88.6)	0	0	0
2	88.4 (87.1; 89.7)	0.10 (-0.04; 0.25)	0.12 (-0.03; 0.26)	0.11 (-0.03; 0.25)
3	87.3 (86.0; 88.6)	0.04 (-0.11; 0.18)	0.05 (-0.09; 0.20)	0.04 (-0.10; 0.19)
4	85.9 (84.6; 87.2)	-0.04 (-0.19; 0.11)	-0.01 (-0.16; 0.14)	-0.02 (-0.17; 0.13)
P-TREND	0.07	0.4	0.7	0.6
WOMEN [1355]				
HEIGHT				
1	82.3 (81.1; 83.5)	0	0	0
2	82.1 (80.8; 83.3)	0.01 (-0.14; 0.15)	0.01 (-0.14; 0.15)	0.01 (-0.14; 0.15)
3	82.4 (81.2; 83.7)	0.05 (-0.10; 0.19)	0.04 (-0.11; 0.19)	0.05 (-0.10; 0.19)
4	79.7 (78.4; 81.0)	-0.13 (-0.28; 0.01)	-0.14 (-0.29; 0.01)	-0.14 (-0.29; 0.01)
P-TREND	0.009	0.2	0.1	0.2
LEG LENGTH				
1	82.2 (81.0; 83.5)	0	0	0
2	82.1 (80.9; 83.3)	0.04 (-0.11; 0.19)	0.05 (-0.10; 0.20)	0.04 (-0.11; 0.19)
3	81.5 (80.2; 82.7)	0.01 (-0.14; 0.16)	0.01 (-0.14; 0.16)	0.01 (-0.14; 0.16)
4	80.8 (79.6; 82.1)	-0.04 (-0.19; 0.11)	-0.04 (-0.19; 0.12)	-0.04 (-0.19; 0.12)
P-TREND	0.08	0.5	0.5	0.6

* Model A: Adjustment for use of antihypertensive medication, body mass index, waist-hip ratio and smoking
** Model B: As model A, with additional adjustment for childhood social class
*** Model C: As model A, with additional adjustment for birthweight

TABLE 5 CHARACTERISTICS OF THE SAMPLE IN RELATION TO HEIGHT, LEG AND TRUNK LENGTH

RISK FACTORS	N**	HEIGHT			
		1 SHORTEST GROUP	2	3 TALLEST GROUP	
			MEANS		P-VALUE*
BIRTHWEIGHT (G)	3419	3271	3375	3535	≤ 0.001
BMI AT 36 YEARS (KG/M^2)	3048	24.2	23.9	23.7	≤ 0.001
BMI AT 43 YEARS (KG/M^2)	3228	25.6	25.2	24.8	≤ 0.001
BMI AT 53 YEARS (KG/M^2)	2948	27.9	27.3	27.1	≤ 0.001
WAIST-HIP RATIO AT 53 YEARS (%)	2956	87.4	86.8	86.9	0.20
			PROPORTIONS		P-VALUE*
MALE SEX	3429	50.7	50.4	50.2	0.79
FATHER IN A NON-MANUAL CLASS	3248	31.3	42.5	51.1	≤ 0.001
EDUCATION AT A-LEVEL OR MORE	3225	26.7	36.6	40.6	≤ 0.001
NON-MANUAL SOCIAL CLASS	3298	57.4	68.9	71.5	≤ 0.001
ANTIHYPERTENSIVE DRUGS AGE 36	3079	2.6	0.9	0.9	≤ 0.001
ANTIHYPERTENSIVE DRUGS AGE 43	3251	4.6	3.3	1.9	≤ 0.001
ANTIHYPERTENSIVE DRUGS AGE 53	2978	16.4	16.1	11.5	0.002
CURRENT CIGARETTE SMOKER	2978	25.5	23.9	20.4	0.007
REGULAR EXERCISE	2977	43.8	53.0	55.3	≤ 0.001

* Chi-squared test for linear trend across categories
** Numbers are based on the model including height and may vary slightly in analysis of leg or trunk length

TABLE 5 CONTINUED

RISK FACTORS	LEG LENGTH			
	1 SHORTEST GROUP	2	3 TALLEST GROUP	
		MEANS		P-VALUE*
BIRTHWEIGHT (G)	3296	3375	3505	≤ 0.001
BMI AT 36 YEARS (KG/M^2)	24.3	23.8	23.6	≤ 0.001
BMI AT 43 YEARS (KG/M^2)	25.8	25.0	24.8	≤ 0.001
BMI AT 53 YEARS (KG/M^2)	28.1	27.4	26.7	≤ 0.001
WAIST-HIP RATIO AT 53 YEARS (%)	87.0	86.9	87.2	0.56
		PROPORTIONS		P-VALUE*
MALE SEX	50.7	50.0	50.5	0.91
FATHER IN A NON-MANUAL CLASS	33.0	42.5	48.8	≤ 0.001
EDUCATION AT A-LEVEL OR MORE	29.3	35.5	38.8	≤ 0.001
NON-MANUAL SOCIAL CLASS	61.0	68.1	68.8	≤ 0.001
ANTIHYPERTENSIVE DRUGS AGE 36	1.8	1.1	1.5	0.50
ANTIHYPERTENSIVE DRUGS AGE 43	4.8	2.4	2.8	0.009
ANTIHYPERTENSIVE DRUGS AGE 53	16.7	14.3	12.9	0.02
CURRENT CIGARETTE SMOKER	24.0	23.4	22.5	0.44
REGULAR EXERCISE	47.7	51.6	52.8	0.02

* Chi-squared test for linear trend across categories

TABLE 5 CONTINUED

RISK FACTORS	TRUNK LENGTH			
	1 SHORTEST GROUP	2	3 TALLEST GROUP	
		MEANS		P-VALUE*
BIRTHWEIGHT (G)	3313	3380	3487	≤ 0.001
BMI AT 36 YEARS (KG/M^2)	23.8	24.0	23.9	0.41
BMI AT 43 YEARS (KG/M^2)	25.1	25.4	25.2	0.57
BMI AT 53 YEARS (KG/M^2)	27.2	27.6	27.4	0.28
WAIST-HIP RATIO AT 53 YEARS (%)	87.9	86.7	86.5	≤ 0.001
		PROPORTIONS		P-VALUE*
MALE SEX	50.3	49.7	51.1	0.70
FATHER IN A NON-MANUAL CLASS	33.7	41.9	49.4	≤ 0.001
EDUCATION AT A-LEVEL OR MORE	28.1	34.9	41.0	≤ 0.001
NON-MANUAL SOCIAL CLASS	58.5	66.8	72.8	≤ 0.001
ANTIHYPERTENSIVE DRUGS AGE 36	2.2	1.2	1.0	0.02
ANTIHYPERTENSIVE DRUGS AGE 43	3.9	3.1	2.9	0.21
ANTIHYPERTENSIVE DRUGS AGE 53	15.5	14.5	14.1	0.38
CURRENT CIGARETTE SMOKER	26.4	22.4	21.1	0.005
REGULAR EXERCISE	45.2	50.8	56.1	≤ 0.001

* Chi-squared test for linear trend across categories

TABLE 6 CROSS-SECTIONAL ASSOCIATIONS BETWEEN COMPONENTS OF HEIGHT AND BLOOD PRESSURE MEASURES AT EACH AGE (REGRESSION COEFFICIENTS AND 95 PERCENT CONFIDENCE INTERVALS)

			PULSE PRESSURE		SYSTOLIC PRESSURE		DIASTOLIC PRESSURE	
36 YEARS								
		N†	COEFFICIENT	95% CI	COEFFICIENT	95% CI	COEFFICIENT	95% CI
HEIGHT	OVERALL*	3034	-0.029	-0.093, 0.035	-0.12	-0.20, -0.034	-0.089	-0.16, -0.020
	MEN	1516	0.013	-0.077, 0.10	-0.038	-0.15, 0.076	-0.051	-0.15, 0.046
	WOMEN	1518	-0.078	-0.17, 0.012	-0.21	-0.34, -0.088	-0.13	-0.23, -0.034
	INTERACTION‡		P=0.16		P=0.044		P=0.24	
LEG LENGTH	OVERALL*	3030	-0.0085	-0.088, 0.072	-0.10	-0.21, 0.0041	-0.93	-0.18, -0.0056
	MEN	1514	-0.014	-0.13, 0.10	-0.067	-0.21, 0.080	-0.052	-0.18, 0.071
	WOMEN	1516	-0.0021	-0.11, 0.11	-0.14	-0.29, 0.013	-0.14	-0.26, -0.014
	INTERACTION‡		P=0.88		P=0.50		P=0.34	
TRUNK LENGTH	OVERALL*	3032	-0.048	-0.14, 0.047	-0.11	-0.24, 0.013	-0.065	-0.17, 0.039
	MEN	1514	0.058	-0.080, 0.20	0.014	-0.16, 0.19	-0.044	-0.19, 0.10
	WOMEN	1518	-0.16	-0.29, -0.030	-0.25	-0.43, -0.067	-0.087	-0.23, 0.059
	INTERACTION‡		P=0.024		P=0.042		P=0.69	

* Adjusted for sex
† Numbers are based on the model including pulse pressure and may vary slightly in analysis of systolic or diastolic blood pressure
‡ Test for interaction is for sex by component of height in a model including both men and women

TABLE 6 CONTINUED

			PULSE PRESSURE		SYSTOLIC PRESSURE		DIASTOLIC PRESSURE	
43 YEARS								
		N†	COEFFICIENT	95% CI	COEFFICIENT	95% CI	COEFFICIENT	95% CI
HEIGHT	OVERALL*	3154	-0.065	-0.13, -0.00048	-0.15	-0.23, -0.057	-0.080	-0.15, -0.013
	MEN	1586	-0.071	-0.16, 0.015	-0.092	-0.21, 0.025	-0.021	-0.11, 0.070
	WOMEN	1568	-0.057	-0.15, 0.039	-0.21	-0.34, -0.076	-0.15	-0.25, -0.05
	INTERACTION‡		P=0.83		P=0.20		P=0.059	
LEG LENGTH	OVERALL*	3153	-0.095	-0.18, -0.013	-0.19	-0.30, -0.078	-0.096	-0.18, -0.0098
	MEN	1585	-0.10	-0.22, 0.0087	-0.15	-0.30, 0.0051	-0.044	-0.16, 0.075
	WOMEN	1568	-0.085	-0.21, 0.035	-0.24	-0.40, -0.072	-0.15	-0.28, -0.028
	INTERACTION‡		P=0.82		P=0.43		P=0.21	
TRUNK LENGTH	OVERALL*	3155	-0.016	-0.11, 0.082	-0.069	-0.20, 0.065	-0.054	-0.16, 0.049
	MEN	1585	-0.027	-0.16, 0.11	-0.017	-0.20, 0.17	0.0097	-0.13, 0.15
	WOMEN	1570	-0.0043	-0.15, 0.14	-0.12	-0.32, 0.072	-0.12	-0.27, 0.029
	INTERACTION‡		P=0.82		P=0.44		P=0.22	

* Adjusted for sex

† Numbers are based on the model including pulse pressure and may vary slightly in analysis of systolic or diastolic blood pressure.

‡ Test for interaction is for sex by component of height in a model including both men and women.

TABLE 6 CONTINUED

			PULSE PRESSURE		SYSTOLIC PRESSURE		DIASTOLIC PRESSURE	
53 YEARS								
		N†	COEFFICIENT	95% CI	COEFFICIENT	95% CI	COEFFICIENT	95% CI
HEIGHT	OVERALL*	2905	-0.25	-0.33, -0.17	-0.36	-0.47, -0.25	-0.11	-0.18, -0.04
	MEN	1441	-0.23	-0.33, -0.12	-0.31	-0.46, -0.15	-0.08	-0.18, 0.017
	WOMEN	1464	-0.28	-0.40, -0.16	-0.42	-0.59, -0.26	-0.14	-0.24, -0.045
	INTERACTION‡		P=0.51		P=0.32		P=0.37	
LEG LENGTH	OVERALL*	2903	-0.36	-0.46, -0.26	-0.48	-0.62, -0.34	-0.12	-0.21, -0.03
	MEN	1440	-0.38	-0.51, -0.25	-0.50	-0.70, -0.31	-0.12	-0.24, 0.0017
	WOMEN	1463	-0.34	-0.48, -0.19	-0.45	-0.66, -0.25	-0.12	-0.24, 0.0043
	INTERACTION‡		P=0.65		P=0.74		P=0.96	
TRUNK LENGTH	OVERALL*	2904	-0.057	-0.17, 0.059	-0.13	-0.30, 0.041	-0.071	-0.17, 0.032
	MEN	1440	-0.01	-0.17, 0.15	-0.016	-0.25, 0.22	-0.0039	-0.15, 0.14
	WOMEN	1464	-0.11	-0.28, 0.06	-0.25	-0.49, -0.0071	-0.14	-0.29, -0.0003
	INTERACTION‡		P=0.43		P=0.18		P=0.18	

* Adjusted for sex
† Numbers are based on the model including pulse pressure and may vary slightly in analysis of systolic or diastolic blood pressure
‡ Test for interaction is for sex by component of height in a model including both men and women

TABLE 7 THE EFFECTS OF HEIGHT, LEG AND TRUNK LENGTH ON PULSE PRESSURE, SYSTOLIC AND DIASTOLIC BLOOD PRESSURE BETWEEN 36 AND 53 YEARS. REGRESSION COEFFICIENTS AND 95 PERCENT CONFIDENCE INTERVALS FOR THE EFFECT ON BLOOD PRESSURE AT 36 YEARS (INTERCEPT) AND ON THE LINEAR CHANGE (SLOPE) BETWEEN 36 AND 53 YEARS FROM A MULTILEVEL MODEL INCLUDING 9086 OBSERVATIONS

	INTERCEPT (MMHG)			SLOPE (MMHG/YEAR)		
PULSE PRESSURE	COEFFICIENT	95% CI	P-VALUE*	COEFFICIENT	95% CI	P-VALUE*
HEIGHT	-0.005	-0.064, 0.054	0.87	-0.014	-0.020, -0.0081	≤0.001
LEG LENGTH	0.010	-0.063, 0.083	0.79	-0.020	-0.026, -0.014	≤0.001
TRUNK LENGTH	-0.040	-0.13, 0.046	0.36	-0.001	-0.0088, 0.067	0.80
SYSTOLIC BLOOD PRESSURE	COEFFICIENT	95% CI	P-VALUE*	COEFFICIENT	95% CI	P-VALUE*
HEIGHT	-0.091	-0.17, -0.013	0.023	-0.013	-0.021, -0.0052	≤0.001
LEG LENGTH	-0.086	-0.18, 0.012	0.085	-0.021	-0.029, -0.013	≤0.001
TRUNK LENGTH	-0.095	-0.21, 0.021	0.11	-0.0001	-0.0098, 0.0098	0.99
DIASTOLIC BLOOD PRESSURE†	COEFFICIENT	95% CI	P-VALUE*	COEFFICIENT	95% CI	P-VALUE*
HEIGHT	-0.083	-0.15, -0.020	0.010	-0.001	-0.0049, 0.0029	0.62
LEG LENGTH	-0.088	-0.17, -0.0076	0.032	-0.002	-0.0079, 0.0039	0.51
TRUNK LENGTH	-0.053	-0.15, 0.041	0.27	-0.001	-0.0088, 0.0068	0.80

* Chi-squared test for linear trend

† Model for diastolic blood pressure differs slightly from others, as it does not include a quadratic term for age

TABLE 8 THE EFFECT OF HEIGHT, LEG AND TRUNK LENGTH ON PULSE PRESSURE, SYSTOLIC AND DIASTOLIC BLOOD PRESSURE BETWEEN 36 AND 53 YEARS. REGRESSION COEFFICIENTS AND 95 PERCENT CONFIDENCE INTERVALS FOR THE EFFECT ON THE LINEAR CHANGE OF BLOOD PRESSURE (SLOPE) BETWEEN 36 AND 53 YEARS FROM MULTILEVEL MODELS INCLUDING 7110 OBSERVATIONS BEFORE AND AFTER ADJUSTMENTS

	PULSE PRESSURE					
	HEIGHT			LEG LENGTH		
	COEFFICIENT	95% CI	P-VALUE*	COEFFICIENT	95% CI	P-VALUE*
UNADJUSTED	-0.013	-0.019, -0.0071	≤0.001	-0.021	-0.029, -0.013	≤0.001
ADJUSTMENT FOR ANTIHYPERTENSIVE DRUGS	-0.012	-0.018, -0.0061	≤0.001	-0.020	-0.028, -0.012	≤0.001
ADJUSTMENT FOR BODY MASS INDEX†	-0.012	-0.018, -0.0061	≤0.001	-0.019	-0.027, -0.011	≤0.001
ADJUSTMENT FOR ADULT FACTORS‡	-0.013	-0.019, -0.0071	≤0.001	-0.021	-0.029, -0.013	≤0.001
ADJUSTMENT FOR EARLY LIFE FACTORS§	-0.014	-0.020, -0.0081	≤0.001	-0.021	-0.029, -0.013	≤0.001
ADJUSTMENT FOR ALL VARIABLES ABOVE	-0.011	-0.017, -0.0051	≤0.001	-0.018	-0.026, -0.010	≤0.001
	SYSTOLIC BLOOD PRESSURE					
	HEIGHT			LEG LENGTH		
	COEFFICIENT	95% CI	P-VALUE*	COEFFICIENT	95% CI	P-VALUE*
UNADJUSTED	-0.015	-0.023, -0.0072	≤0.001	-0.022	-0.032, -0.012	≤0.001
ADJUSTMENT FOR ANTIHYPERTENSIVE DRUGS	-0.013	-0.021, -0.0052	≤0.001	-0.021	-0.031, -0.011	≤0.001
ADJUSTMENT FOR BODY MASS INDEX†	-0.012	-0.020, -0.0042	0.003	-0.015	-0.025, -0.0052	0.003
ADJUSTMENT FOR ADULT FACTORS‡	-0.014	-0.022, -0.0062	≤0.001	-0.022	-0.032, -0.012	≤0.001
ADJUSTMENT FOR EARLY LIFE FACTORS§	-0.014	-0.022, -0.0062	≤0.001	-0.022	-0.032, -0.012	≤0.001
ADJUSTMENT FOR ALL VARIABLES ABOVE	-0.010	-0.018, -0.0022	0.012	-0.015	-0.025, -0.0052	0.003

* Chi-squared test for linear trend.
† Adjustment includes body mass index as a time varying covariate and an interaction term for BMI and age
‡ Adjustment for adult life factors: educational attainment, smoking, exercise and adult social class
§ Adjustment for early life factors: birthweight and childhood social class

TABLE 9 AGE ADJUSTED CHARACTERISTICS OF MEN AND WOMEN PARTICIPATING IN THE WHITEHALL II STUDY VISIT 1997-99

VARIABLES	N	MEANS (SD)/ PROPORTIONS		
	MEN/ WOMEN	MEN	WOMEN	P-VALUE
AGE (YEARS)	3457/ 1534	55.5 (6.0)	56.1 (6.0)	0.0007
HEIGHT AT PHASE 1 (M)	3457/ 1534	176.5 (6.7)	162.9 (6.4)	< 0.0001
HEIGHT AT PHASE 5 (M)	3457/ 1534	176.2 (6.7)	162.3 (6.4)	< 0.0001
LEG LENGTH (M)	3457/ 1534	83.8 (4.4)	76.4 (4.3)	< 0.0001
TRUNK LENGTH (M)	3457/ 1534	92.4 (3.7)	85.9 (3.8)	< 0.0001
BIRTHWEIGHT (LBS)	2287/ 1084	7.6 (1.3)	7.2 (1.4)	< 0.0001
PULSE PRESSURE (MMHG)	3449/ 1531	44.5 (11.0)	46.5 (12.8)	< 0.0001
SBP (MMHG)	3449/ 1531	122.6 (15.9)	121.4 (17.6)	< 0.0001
DBP (MMHG)	3449/ 1531	78.2 (10.5)	75.0 (10.0)	< 0.0001
CHOLESTEROL (MMOL/L)	3425/ 1509	5.9 (1.04)	6.0 (1.08)	< 0.0001
HDL CHOLESTEROL (MMOL/L)	3020/ 1337	1.38 (0.35)	1.66 (0.43)	< 0.0001
TRIGLYCERIDE (MMOL/L)*	3425/ 1509	1.23 (0.92)	1.01 (0.64)	< 0.0001
WAIST-HIP RATIO (%)	3354/ 1498	92.5 (6.3)	79.8 (6.9)	< 0.0001
BODY MASS INDEX (KG/M^2)	3423/ 1527	26.0 (3.4)	26.5 (5.0)	0.0002
FASTING GLUCOSE (G/L)†	3245/ 1426	5.1 (0.50)	4.9 (0.52)	< 0.0001
2HR GLUCOSE (G/L)†	2952/ 1277	5.9 (1.6)	6.1 (1.5)	0.0003
ANTIHYPERTENSIVE TREATMENT	3441/ 1526	12.4	15.9	0.0006
DIABETES (%)	3457/ 1534	5.1	5.3	0.75
CHILDHOOD SOCIAL CLASS I/II	3253/ 1368	45.2	43.3	0.19
LOW ADULT GRADE (%)	3457/ 1534	6.8	41.5	< 0.0001
CURRENT SMOKER (%)	3450/ 1525	9.4	12.7	0.0005
HIGH ALCOHOL INTAKE (%)	3441/ 1526	12.4	15.9	0.0006

* Geometric mean
† Excludes participants with diabetes

TABLE 10 AGE ADJUSTED CORRELATION COEFFICIENTS FOR HEIGHT, LEG LENGTH, TRUNK LENGTH AND BIRTHWEIGHT IN THE NSHD AND WHITEHALL II STUDY

MEASURE	HEIGHT	TRUNK LENGTH	LEG LENGTH	BIRTHWEIGHT
NSHD: 1495 WOMEN (COEFFICIENTS SHOWN IN THE UPPER RIGHT CORNER OF THE TABLE) AND 1444 MEN				
HEIGHT	-	0.60 (P < 0.001)	0.73 (P < 0.001)	0.22 (P < 0.001)
TRUNK LENGTH	0.62 (P < 0.001)	-	-0.11 (P < 0.001)	0.13 (P < 0.001)
LEG LENGTH	0.76 (P < 0.001)	-0.05 (P=0.08)	-	0.16 (P < 0.001)
BIRTHWEIGHT	0.27 (P < 0.001)	0.17 (P < 0.001)	0.20 (P < 0.001)	-
WHITEHALL STUDY: 1084 WOMEN (COEFFICIENTS SHOWN IN THE UPPER RIGHT CORNER) AND 2287 MEN				
HEIGHT	-	0.76 (P < 0.001)	0.83 (P < 0.001)	0.19 (P < 0.001)
TRUNK LENGTH	0.78 (P < 0.001)	-	0.27 (P < 0.001)	0.17 (P < 0.001)
LEG LENGTH	0.87 (P < 0.001)	0.38 (P < 0.001)	-	0.15 (P < 0.001)
BIRTHWEIGHT	0.22 (P < 0.001)	0.17 (P < 0.001)	0.19 (P < 0.001)	-

TABLE 11 AGE ADJUSTED DIFFERENCES IN LEVELS OF CARDIOVASCULAR RISK FACTORS PER STANDARD DEVIATION INCREASE IN HEIGHT

	COEFFICIENT (95% CONFIDENCE INTERVAL)				
	FULL SAMPLE		RESTRICTED SAMPLE		
ADJUSTMENT	N	AGE ADJUSTED	N	AGE ADJUSTED	FULLY ADJUSTED§
WOMEN					
AGE (PHASE 5)	1534	-1.06 (-1.36; -0.75)‡	994	-0.90 (-1.28; -0.52)‡	-0.59 (-0.98; -0.21)†
PULSE PRESSURE (MMHG)	1531	-1.26 (-1.88; -0.64)‡	985	-1.13 (-1.89; -0.37)†	-1.01 (-1.79; -0.23)†
SYSTOLIC PRESSURE (MMHG)	1531	-2.22 (-3.09; -1.36)‡	985	-2.10 (-3.16; -1.03)‡	-1.76 (-2.83; -0.68)‡
DIASTOLIC PRESSURE (MMHG)	1531	-0.96 (-1.48; -0.45)‡	985	-0.96 (-1.60; -0.33)†	-0.75 (-1.39; -0.11)#
CHOLESTEROL (MMOL/L)	1509	-0.03 (-0.08; 0.03)	886	-0.06 (-0.12; 0.01)	-0.05 (-0.12; 0.02)
HDL CHOLESTEROL (MMOL/L)	1337	0.02 (-0.0009; 0.05)	867	0.02 (-0.008; 0.05)	0.008 (-0.02; 0.04)
TOTAL/HDL CHOLESTEROL*	1337	-0.01 (-0.03; 0.001)	867	-0.02 (-0.04; -0.001)#	-0.01 (-0.03; 0.006)
TRIGLYCERIDES (MMOL/L)*	1509	-0.05 (-0.08; -0.03)‡	986	-0.04 (-0.06; -0.006)#	-0.03 (-0.06; 0.004)
FASTING GLUCOSE (G/L)	1426	-0.007 (-0.04; 0.02)	944	0.01 (-0.02; 0.05)	0.02 (-0.01; 0.05)
2 HR GLUCOSE (G/L)	1277	-0.18 (-0.26; -0.09)‡	852	-0.12 (-0.22; -0.01)#	-0.10 (-0.21; 0.007)
WAIST-HIP RATIO (%)	1498	-0.80 (-1.15; -0.45)‡	976	-0.90 (-1.32; -0.48)‡	-0.77 (-1.21; -0.34)‡
MEN					
AGE (PHASE 5)	3457	-0.74 (-0.94; -0.54)‡	2165	-0.41 (-0.66; -0.17)‡	-0.54 (-0.79; -0.29)‡
PULSE PRESSURE (MMHG)	3449	-0.40 (-0.75; -0.03)#	2151	-0.49 (-0.94; -0.03)#	-0.42 (-0.90; 0.05)
SYSTOLIC PRESSURE (MMHG)	3449	-0.41 (-0.93; 0.11)	2151	-0.41 (-1.07; 0.25)	-0.20 (-0.87; 0.47)
DIASTOLIC PRESSURE (MMHG)	3449	-0.02 (-0.37; 0.34)	2151	0.08 (-0.38; 0.54)	0.22 (-0.24; 0.68)
CHOLESTEROL (MMOL/L)	3425	-0.07 (-0.10; -0.03)‡	2150	-0.11 (-0.15; -0.06)‡	-0.11 (-0.16; -0.06)‡
HDL CHOLESTEROL (MMOL/L)	3020	0.00006 (-0.01; 0.01)	1889	-0.002 (-0.02; 0.01)	-0.005 (-0.02; 0.01)
TOTAL/HDL CHOLESTEROL*	3020	-0.01 (-0.02; -0.002)#	1889	-0.02 (-0.03; -0.003)#	-0.02 (-0.03; -0.002)#
TRIGLYCERIDES (MMOL/L)*	3425	-0.03 (-0.05; -0.01)‡	2150	-0.03 (-0.05; -0.007)†	-0.03 (-0.05; -0.0006)#
FASTING GLUCOSE (G/L)	3245	0.02 (-0.002; 0.004)	2055	0.02 (-0.005; 0.04)	0.02 (-0.006; 0.04)
2 HR GLUCOSE (G/L)	2952	-0.17 (-0.22; -0.11)‡	1880	-0.15 (-0.21; -0.08)‡	-0.14 (-0.21; -0.06)‡
WAIST-HIP RATIO (%)	3354	-0.77 (-0.98; -0.56)‡	2115	-0.62 (-0.89; -0.35)‡	-0.61 (-0.90; -0.33)‡

* Based on log transformed values; # p-value ≤ 0.05; † $p \leq 0.01$; ‡ $p \leq 0.001$

§ Includes adjustment for birthweight, childhood social class, adult grade, and antihypertensive treatment (blood pressure outcomes)

TABLE 12 AGE ADJUSTED DIFFERENCES IN LEVELS OF CARDIOVASCULAR RISK FACTORS PER STANDARD DEVIATION INCREASE IN LEG LENGTH

	COEFFICIENT (95% CONFIDENCE INTERVAL)				
	FULL SAMPLE		RESTRICTED SAMPLE		
ADJUSTMENT	N	AGE ADJUSTED	N	AGE ADJUSTED	FULLY ADJUSTED§
WOMEN					
AGE (PHASE 5)	1534	-0.23 (-0.54; 0.07)	994	-0.19 (-0.57; 0.19)	-0.10 (-0.47; 0.27)
PULSE PRESSURE (MMHG)	1531	-0.87 (-1.48; -0.27)†	985	-0.90 (-1.65; -0.16)#	-0.80 (-1.55; -0.05)#
SYSTOLIC PRESSURE (MMHG)	1531	-1.72 (-2.56; -0.87)‡	985	-1.88 (-2.92; -0.83)‡	-1.72 (-2.75; -0.70)‡
DIASTOLIC PRESSURE (MMHG)	1531	-0.84 (-1.34; -0.35)‡	985	-0.98 (-1.60; -0.35)†	-0.92 (-1.53; -0.31)†
CHOLESTEROL (MMOL/L)	1509	-0.05 (-0.10; 0.008)	886	-0.06 (-0.13; 0.002)	-0.06 (-0.12; 0.01)
HDL CHOLESTEROL (MMOL/L)	1337	0.02 (-0.008; 0.04)	867	0.02 (-0.007; 0.05)	0.02 (-0.01; 0.05)
TOTAL/HDL CHOLESTEROL*	1337	-0.01 (-0.03; 0.0003)	867	-0.02 (-0.04; -0.005)†	-0.02 (-0.04; -0.002)#
TRIGLYCERIDES (MMOL/L)*	1509	-0.05 (-0.08; -0.03)‡	986	-0.05 (-0.08; -0.02)‡	-0.04 (-0.07; -0.01)†
FASTING GLUCOSE (G/L)	1426	-0.02 (-0.04; 0.01)	944	0.007 (-0.03; 0.04)	0.01 (-0.02; 0.05)
2 HR GLUCOSE (G/L)	1277	-0.14 (-0.23; -0.06)‡	852	-0.11 (-0.21; -0.0004)#	-0.09 (-0.20; 0.02)
WAIST-HIP RATIO (%)	1498	-0.09 (-0.44; 0.26)	976	-0.40 (-0.82; 0.03)	-0.32 (-0.75; 0.12)
MEN					
AGE (PHASE 5)	3457	-0.21 (-0.41; -0.01)#	2165	-0.03 (-0.28; 0.21)	-0.08 (-0.32; 0.16)
PULSE PRESSURE (MMHG)	3449	-0.37 (-0.72; -0.01)#	2151	-0.66 (-1.11; -0.22)†	-0.61 (-1.07; -0.15)†
SYSTOLIC PRESSURE (MMHG)	3449	-0.58 (-1.10; -0.06)#	2151	-0.93 (-1.58; -0.28)†	-0.79 (-1.44; -0.15)#
DIASTOLIC PRESSURE (MMHG)	3449	-0.21 (-0.57; 0.14)	2151	-0.27 (-0.72; 0.18)	-0.18 (-0.62; 0.27)
CHOLESTEROL (MMOL/L)	3425	-0.08 (-0.11; -0.04)‡	2150	-0.11 (-0.16; -0.07)‡	-0.12 (-0.16; -0.07)‡
HDL CHOLESTEROL (MMOL/L)	3020	0.006 (-0.007; 0.02)	1889	0.002 (-0.01; 0.02)	0.0005 (-0.02; 0.02)
TOTAL/HDL CHOLESTEROL*	3020	-0.02 (-0.03; -0.009)‡	1889	-0.02 (-0.04; -0.01)‡	-0.02 (-0.04; -0.009)‡
TRIGLYCERIDES (MMOL/L)*	3425	-0.04 (-0.06; -0.02)‡	2150	-0.04 (-0.07; -0.02)‡	-0.04 (-0.06; -0.02)‡
FASTING GLUCOSE (G/L)	3245	0.009 (-0.008; 0.03)	2055	0.006 (-0.02; 0.03)	0.006 (-0.02; 0.03)
2 HR GLUCOSE (G/L)	2952	-0.14 (-0.19; -0.08)‡	1880	-0.11 (-0.18; -0.05)‡	-0.10 (-0.17; -0.03)†
WAIST-HIP RATIO (%)	3354	-0.42 (-0.63; -0.21)‡	2115	-0.29 (-0.56; -0.02)#	-0.29 (-0.56; -0.01)#

* Based on log transformed values; # p-value ≤ 0.05; † $p \leq 0.01$; ‡ $p \leq 0.001$

§ Includes adjustment for birthweight, childhood social class, adult grade, and antihypertensive treatment (blood pressure outcomes)

TABLE 13 AGE ADJUSTED DIFFERENCES IN LEVELS OF CARDIOVASCULAR RISK FACTORS PER STANDARD DEVIATION INCREASE IN TRUNK LENGTH

	COEFFICIENT (95% CONFIDENCE INTERVAL)				
	FULL SAMPLE		RESTRICTED SAMPLE		
ADJUSTMENT	N	AGE ADJUSTED	N	AGE ADJUSTED	FULLY ADJUSTED§
WOMEN					
AGE (PHASE 5)	1534	-1.50 (-1.80; -1.21)‡	994	-1.30 (-1.67; -0.93)‡	-0.91 (-1.29; -0.53)‡
PULSE PRESSURE (MMHG)	1531	-1.13 (-1.76; -0.51)‡	985	-0.89 (-1.65; -0.12)#	-0.77 (-1.56; 0.03)
SYSTOLIC PRESSURE (MMHG)	1531	-1.79 (-2.66; -0.92)‡	985	-1.40 (-2.46; -0.33)†	-0.92 (-2.02; 0.17)
DIASTOLIC PRESSURE (MMHG)	1531	-0.65 (-1.17; -0.14)†	985	-0.51 (-1.15; 0.13)	-0.16 (-0.81; 0.49)
CHOLESTEROL (MMOL/L)	1509	0.01 (-0.04; 0.07)	886	-0.02 (-0.09; 0.05)	-0.02 (-0.09; 0.05)
HDL CHOLESTEROL (MMOL/L)	1337	0.02 (-0.003; 0.04)	867	0.01 (-0.02; 0.04)	-0.008 (-0.04; 0.02)
TOTAL/HDL CHOLESTEROL*	1337	-0.008 (-0.02; 0.009)	867	-0.007 (-0.03; 0.01)	0.002 (-0.02; 0.02)
TRIGLYCERIDES (MMOL/L)*	1509	-0.03 (-0.05; -0.002)#	986	-0.004 (-0.03; 0.03)	0.007 (-0.02; 0.04)
FASTING GLUCOSE (G/L)	1426	0.006 (-0.02; 0.03)	944	0.02 (-0.02; 0.05)	0.02 (-0.01; 0.06)
2 HR GLUCOSE (G/L)	1277	-0.15 (-0.24; -0.07)‡	852	-0.09 (-0.20; 0.02)	-0.08 (-0.19; 0.03)
WAIST-HIP RATIO (%)	1498	-1.35 (-1.70; -0.99)‡	976	-1.21 (-1.65; -0.78)‡	-1.07 (-1.53; -0.62)‡
MEN					
AGE (PHASE 5)	3457	-1.10 (-1.29; -0.90)‡	2165	-0.76 (-1.01; -0.50)‡	-0.92 (-1.17; -0.67)‡
PULSE PRESSURE (MMHG)	3449	-0.27 (-0.63; 0.10)	2151	-0.06 (-0.54; 0.41)	0.02 (-0.47; 0.50)
SYSTOLIC PRESSURE (MMHG)	3449	-0.03 (-0.56; 0.50)	2151	0.44 (-0.24; 1.12)	0.68 (-0.006; 1.36)
DIASTOLIC PRESSURE (MMHG)	3449	0.24 (-0.12; 0.60)	2151	0.50 (0.03; 0.98)	0.66 (0.19; 1.13)
CHOLESTEROL (MMOL/L)	3425	-0.03 (-0.06; 0.01)	2150	-0.05 (-0.10; -0.007)#	-0.06 (-0.11; -0.008)#
HDL CHOLESTEROL (MMOL/L)	3020	-0.007 (-0.02; 0.006)	1889	-0.008 (-0.02; 0.009)	-0.01 (-0.03; 0.007)
TOTAL/HDL CHOLESTEROL*	3020	0.002 (-0.009; 0.01)	1889	-0.001 (-0.02; 0.01)	0.0006 (-0.01; 0.02)
TRIGLYCERIDES (MMOL/L)*	3425	-0.005 (-0.02; 0.01)	2150	-0.002 (-0.03; 0.02)	0.006 (-0.02; 0.03)
FASTING GLUCOSE (G/L)	3245	0.02 (0.005; 0.04)	2055	0.03 (0.003; 0.05)	0.03 (0.002; 0.05)
2 HR GLUCOSE (G/L)	2952	-0.14 (-0.20; -0.08)‡	1880	-0.13 (-0.20; -0.06)‡	-0.12 (-0.20; -0.05)‡
WAIST-HIP RATIO (%)	3354	-0.90 (-1.12; -0.69)‡	2115	-0.81 (-1.09; -0.53)‡	-0.79 (-1.08; -0.51)‡

* Based on log transformed values; # p-value ≤ 0.05; † $p \leq 0.01$; ‡ $p \leq 0.001$

§ Includes adjustment for birthweight, childhood social class, adult grade, and antihypertensive treatment (blood pressure outcomes)

TABLE 14 AGE ADJUSTED CHARACTERISTICS OF MEN AND WOMEN PARTICIPATING IN THE WHITEHALL II STUDY VISIT 2003-04

VARIABLE	N	MEANS/ PROPORTIONS		
	MEN/ WOMEN	MEN	WOMEN	P-VALUE
AGE (YEARS)	2953/ 1159	62.3	61.9	0.08
WHITE EUROPEAN (%)	2950/ 1158	93.5	85.3	0.0001
YEARS OF FOLLOW-UP (PHASE 3-7)	2823/ 1103	11.3	11.1	0.0001
INTIMA MEDIA THICKNESS (MM)#	2952/ 1158	0.780	0.766	0.0001
BETA STIFFNESS INDEX #	2929/ 1140	10.90	10.31	0.0001
DISTENSIBILITY (10^{-3}/KPA)#	2929/ 1140	13.92	15.08	0.0001
SBP (MMHG)	2950/ 1158	127.4	125.6	0.001
DBP (MMHG)	2950/ 1158	74.2	72.6	0.0001
PP (MMHG)	2950/ 1158	53.2	53.0	0.56
MAP (MMHG)	2950/ 1158	91.9	90.3	0.0001
PREVALENT CHD (%)	2953/ 1159	16.4	20.5	0.002
PREVALENT CHD EXCL. ANGINA (%)	2953/ 1159	10.8	9.9	0.40
DIABETES (%)	2953/ 1159	6.8	6.6	0.88
HYPERTENSION (%)	2953/ 1159	35.8	38.7	0.07
DYSLIPIDAEMIA (%)	2953/ 1159	53.0	34.1	0.0001
NEVER SMOKER (%)	2944/ 1155	52.2	62.7	0.0001
CURRENT SMOKER (%)	2944/ 1155	6.4	8.3	0.04
HIGH ALCOHOL INTAKE (%)	2922/ 1138	21.9	12.8	0.0001
HEALTHY DIET (%)	2920/ 1127	79.0	81.7	0.05
SUFFICIENT PHYSICAL ACTIVITY (%)	2919/ 1138	59.6	45.1	0.0001
HIGHER EDUCATION (%)	2721/ 1023	61.7	44.8	0.0001
PERSONAL INCOME ≥ 25K (%)	2897/ 1110	61.1	30.3	0.0001
PERSONAL INCOME < 15 K (%)	2897/ 1110	11.2	41.1	0.0001
HOUSEHOLD INCOME ≥ 50K (%)	2868/ 1074	32.5	18.9	0.0001
HOUSEHOLD INCOME < 20K (%)	2868/ 1074	15.2	38.6	0.0001
HOUSEHOLD WEALTH < 100K (%)	2880/ 1067	4.6	14.4	0.0001
ADMINISTRATIVE GRADE (%)	2939/ 1149	55.3	23.2	0.0001
MANUAL FATHER'S SOCIAL CLASS (%)	2789/ 1046	37.4	44.0	0.0002
MARRIED/ COHABITING	2940/ 1150	83.2	57.7	0.0001
HEIGHT (M)	2415/ 946	176.4	162.5	0.0001
LEG LENGTH (CM)	2172/ 883	83.9	76.7	0.0001
TRUNK LENGTH (CM)	2174/ 891	92.5	85.8	0.0001
BIRTHWEIGHT (KG)	1944/ 831	3.44	3.26	0.0001
WEIGHT (KG) PHASE 5	2399/ 960	80.6	69.5	0.0001
WEIGHT (KG) PHASE 7	2945/ 1158	81.1	69.4	0.0001
BMI (KG/M^2) PHASE 5	2392/ 942	25.9	26.3	0.006
BMI (KG/M^2) PHASE 5	2945/ 1157	26.4	26.7	0.02
WAIST PHASE 5	2127/ 884	93.4	84.0	0.0001
WAIST PHASE 7	2948/ 1157	95.4	87.4	0.0001

Geometric mean

TABLE 15 AGE ADJUSTED CARDIOVASCULAR RISK FACTORS AND SOCIOECONOMIC CHARACTERISTICS ACROSS GROUPS OF INTIMA MEDIA THICKNESS

MEN	N	QUARTILES OF INTIMA MEDIA THICKNESS				P-VALUE†
(N)		(750)	(739)	(770)	(693)	
INTIMA MEDIA THICKNESS	2952	≤ 0.683	0.700-0.767	0.780-0.883	≥ 0.900	
WHITE EUROPEAN (%)	2949	94.4	95.1	92.8	90.8	0.008
PREVALENT CHD (%)	2952	18.0	17.3	16.1	15.6	0.32
PREV. CHD EXCL. ROSE ANGINA (%)	2952	11.1	12.3	10.6	9.9	0.39
DIABETES (%)	2952	5.9	6.6	5.8	9.9	0.02
HYPERTENSION (%)	2952	29.4	33.9	36.8	44.5	0.0001
DYSLIPIDAEMIA (%)	2952	50.1	52.7	52.9	60.1	0.0003
NEVER SMOKER (%)	2943	53.9	55.5	54.1	43.9	0.0001
CURRENT SMOKER (%)	2943	5.6	5.6	8.0	7.3	0.05
HIGH ALCOHOL INTAKE (%)	2921	22.1	21.6	21.1	24.5	0.32
HEALTHY DIET (%)	2919	79.1	78.2	79.4	78.5	0.71
SUFFICIENT PHYSICAL ACTIVITY (%)	2918	56.9	58.5	61.8	61.5	0.09
HIGHER EDUCATION (%)	2720	57.8	62.5	62.4	64.7	0.02
PERSONAL INCOME ≥ 25K (%)	2896	59.6	62.5	62.7	59.0	0.86
PERSONAL INCOME < 15 K (%)	2896	12.5	9.5	10.3	12.5	0.98
HOUSEHOLD INCOME ≥ 50K (%)	2867	31.3	33.5	33.4	32.1	0.59
HOUSEHOLD INCOME < 20K (%)	2867	14.6	12.9	14.9	17.9	0.07
HOUSEHOLD WEALTH < 100K (%)	2879	3.5	4.7	4.3	6.6	0.02
ADMINISTRATIVE GRADE (%)	2938	55.2	55.8	54.2	54.6	0.47
MANUAL FATHER'S SOCIAL CLASS (%)	2788	34.7	36.0	39.8	40.6	0.03
MARRIED/ COHABITING (%)	2939	82.4	83.2	83.9	83.3	0.47

† Chi-squared test for trend

TABLE 15 CONTINUED

WOMEN	N	QUARTILES OF INTIMA MEDIA THICKNESS				P-VALUE†
(N)		(307)	(254)	(301)	(296)	
INTIMA MEDIA THICKNESS	1158	≤ 0.683	0.685-0.750	0.767-0.845	≥ 0.850	
WHITE EUROPEAN (%)	1157	89.4	88.6	85.1	78.4	0.0001
PREVALENT CHD (%)	1158	17.1	19.0	20.9	23.1	0.04
PREV. CHD EXCL. ROSE ANGINA (%)	1158	8.4	7.5	10.8	11.7	0.06
DIABETES (%)	1158	7.9	6.0	6.8	6.5	0.62
HYPERTENSION (%)	1158	25.2	37.1	40.3	51.2	0.0001
DYSLIPIDAEMIA (%)	1158	28.4	32.2	38.6	37.0	0.02
NEVER SMOKER (%)	1154	59.6	66.1	61.0	62.1	0.92
CURRENT SMOKER (%)	1154	8.5	9.5	8.7	9.0	0.68
HIGH ALCOHOL INTAKE (%)	1137	15.8	11.3	11.6	12.7	0.34
HEALTHY DIET (%)	1126	81.5	84.6	78.1	81.5	0.54
SUFFICIENT PHYSICAL ACTIVITY (%)	1137	54.2	42.1	42.8	40.1	0.002
HIGHER EDUCATION (%)	1022	43.9	45.5	43.8	46.1	0.77
PERSONAL INCOME ≥ 25K (%)	1109	30.9	29.2	33.1	25.8	0.35
PERSONAL INCOME < 15 K (%)	1109	40.2	42.9	39.7	42.4	0.59
HOUSEHOLD INCOME ≥ 50K (%)	1073	20.7	21.2	16.2	17.7	0.25
HOUSEHOLD INCOME < 20K (%)	1073	34.5	43.0	37.8	41.9	0.25
HOUSEHOLD WEALTH < 100K (%)	1066	16.4	15.6	14.1	14.2	0.54
ADMINISTRATIVE GRADE (%)	1148	26.2	22.0	25.8	17.2	0.05
FATHER'S SOCIAL CLASS I/II (%)	1045	44.0	42.7	46.8	42.6	0.99
MARRIED/ COHABITING (%)	1149	53.6	59.8	53.6	61.9	0.09

† Chi-squared test for trend

TABLE 16 AGE ADJUSTED CARDIOVASCULAR RISK FACTORS AND SOCIOECONOMIC CHARACTERISTICS ACROSS GROUPS OF THE BETA STIFFNESS INDEX

MEN	N	QUARTILES OF BETA STIFFNESS INDEX				P-VALUE†
(N)		(732)	(732)	(733)	(732)	
BETA STIFFNESS INDEX	2929	< 8.93	8.93-10.67	10.68-12.96	≥ 12.93	
WHITE EUROPEAN (%)	2926	97.2	94.4	94.5	88.0	0.0001
PREVALENT CHD (%)	2929	16.1	16.1	17.0	16.3	0.64
PREV. CHD EXCL. ROSE ANGINA (%)	2929	11.8	10.2	10.9	10.4	0.59
DIABETES (%)	2929	5.5	6.0	7.1	8.4	0.01
HYPERTENSION (%)	2929	32.1	33.6	38.7	37.7	0.003
DYSLIPIDAEMIA (%)	2929	48.3	50.4	54.3	57.9	0.0001
NEVER SMOKER (%)	2920	54.8	52.9	51.0	50.1	0.18
CURRENT SMOKER (%)	2920	6.1	6.0	4.8	9.3	0.32
HIGH ALCOHOL INTAKE (%)	2898	22.1	24.0	21.3	18.1	0.02
HEALTHY DIET (%)	2896	79.7	79.0	82.3	76.1	0.37
SUFFICIENT PHYSICAL ACTIVITY (%)	2895	60.0	61.7	61.0	55.8	0.11
HIGHER EDUCATION (%)	2698	61.2	62.3	62.3	60.3	0.73
PERSONAL INCOME ≥ 25K (%)	2874	64.7	63.4	61.5	55.7	0.001
PERSONAL INCOME < 15 K (%)	2874	10.3	9.8	9.8	14.3	0.04
HOUSEHOLD INCOME ≥ 50K (%)	2845	33.4	33.5	33.2	29.5	0.27
HOUSEHOLD INCOME < 20K (%)	2845	12.7	13.6	14.3	18.9	0.007
HOUSEHOLD WEALTH < 100K (%)	2857	3.6	3.9	4.5	5.8	0.04
ADMINISTRATIVE GRADE (%)	2915	60.7	55.2	57.0	49.9	0.002
MANUAL FATHER'S SOCIAL CLASS (%)	2766	36.8	39.6	38.1	35.1	0.50
MARRIED/ COHABITING (%)	2916	83.3	84.7	85.4	79.7	0.48

† Chi-squared test for trend

TABLE 16 CONTINUED

WOMEN	N	QUARTILES OF BETA STIFFNESS INDEX				P-VALUE†
(N)		(285)	(285)	(285)	(285)	
BETA STIFFNESS INDEX	1140	< 8.31	8.31-10.07	10.08-12.58	≥ 12.58	
WHITE EUROPEAN (%)	1139	86.3	87.1	87.7	79.8	0.03
PREVALENT CHD (%)	1140	22.2	22.2	20.2	19.4	0.49
PREV. CHD EXCL. ROSE ANGINA (%)	1140	9.0	10.1	10.9	9.5	0.68
DIABETES (%)	1140	6.4	4.9	7.4	7.9	0.24
HYPERTENSION (%)	1140	28.5	38.0	42.5	43.2	0.0002
DYSLIPIDAEMIA (%)	1140	35.7	36.0	36.4	29.1	0.22
NEVER SMOKER (%)	1136	59.4	64.4	62.7	64.6	0.10
CURRENT SMOKER (%)	1136	11.6	8.7	6.3	7.7	0.04
HIGH ALCOHOL INTAKE (%)	1119	11.0	11.7	14.0	10.9	0.68
HEALTHY DIET (%)	1108	82.4	81.0	85.4	74.0	0.14
SUFFICIENT PHYSICAL ACTIVITY (%)	1120	39.3	49.1	47.2	44.2	0.65
HIGHER EDUCATION (%)	1008	43.2	45.7	41.6	45.8	0.96
PERSONAL INCOME ≥ 25K (%)	1092	30.5	28.9	32.2	26.4	0.74
PERSONAL INCOME < 15 K (%)	1092	40.8	42.0	39.9	43.8	0.75
HOUSEHOLD INCOME ≥ 50K (%)	1056	21.2	18.9	17.6	15.5	0.10
HOUSEHOLD INCOME < 20K (%)	1056	41.4	36.9	37.0	41.6	0.76
HOUSEHOLD WEALTH < 100K (%)	1048	10.3	17.9	12.3	17.6	0.71
ADMINISTRATIVE GRADE (%)	1130	22.6	24.3	24.9	19.0	0.62
FATHER'S SOCIAL CLASS I/II (%)	1027	40.7	41.0	49.0	42.8	0.60
MARRIED/ COHABITING (%)	1131	58.9	63.0	57.9	53.7	0.40

† Chi-squared test for trend

TABLE 17 AGE ADJUSTED CARDIOVASCULAR RISK FACTORS AND SOCIOECONOMIC CHARACTERISTICS ACROSS GROUPS OF DISTENSIBILITY

MEN	N	QUARTILES OF DISTENSIBILITY COEFFICIENT				P-VALUE†
(N)		(732)	(732)	(733)	(732)	
DISTENSIBILITY COEFFICIENT	2929	< 11.45	11.45-14.08	14.08-17.20	≥ 17.21	
WHITE EUROPEAN (%)	2926	89.8	93.9	93.7	96.7	0.0001
PREVALENT CHD (%)	2929	16.5	16.7	17.1	15.8	0.76
PREV. CHD EXCL. ROSE ANGINA (%)	2929	11.1	10.3	10.7	11.9	0.69
DIABETES (%)	2929	9.3	7.8	5.9	4.2	0.0001
HYPERTENSION (%)	2929	45.7	41.6	30.9	25.3	0.0001
DYSLIPIDAEMIA (%)	2929	58.8	58.3	48.8	47.4	0.0001
NEVER SMOKER (%)	2920	50.8	50.1	53.5	55.5	0.05
CURRENT SMOKER (%)	2920	8.6	6.0	5.7	5.8	0.25
HIGH ALCOHOL INTAKE (%)	2898	19.6	21.9	23.7	20.3	0.60
HEALTHY DIET (%)	2896	74.9	79.8	82.2	79.5	0.14
SUFFICIENT PHYSICAL ACTIVITY (%)	2895	56.8	60.2	60.9	60.4	0.18
HIGHER EDUCATION (%)	2698	61.1	59.8	64.3	61.4	0.27
PERSONAL INCOME ≥ 25K (%)	2874	54.6	61.6	63.7	64.2	0.0005
PERSONAL INCOME < 15 K (%)	2874	14.8	8.6	11.1	9.9	0.06
HOUSEHOLD INCOME ≥ 50K (%)	2845	27.4	32.6	34.7	33.9	0.02
HOUSEHOLD INCOME < 20K (%)	2845	19.5	13.0	15.1	12.1	0.008
HOUSEHOLD WEALTH < 100K (%)	2857	6.0	5.6	3.0	3.4	0.004
ADMINISTRATIVE GRADE (%)	2915	50.2	55.9	56.3	60.8	0.0008
MANUAL FATHER'S SOCIAL CLASS (%)	2766	35.5	38.7	37.7	37.2	0.65
MARRIED/ COHABITING (%)	2916	80.6	84.3	85.6	83.6	0.38

† Chi-squared test for trend

TABLE 17 CONTINUED

WOMEN	N	QUARTILES OF DISTENSIBILITY COEFFICIENT				P-VALUE†
(N)		(285)	(285)	(285)	(285)	
DISTENSIBILITY COEFFICIENT	1140	< 12.14	12.15-15.51	15.53-19.23	≥ 19.24	
WHITE EUROPEAN (%)	1139	80.8	84.7	89.0	86.9	0.008
PREVALENT CHD (%)	1140	20.7	21.9	19.0	22.1	0.62
PREV. CHD EXCL. ROSE ANGINA (%)	1140	10.3	11.2	8.9	8.3	0.17
DIABETES (%)	1140	8.1	7.2	4.6	7.0	018
HYPERTENSION (%)	1140	53.3	46.6	31.1	19.2	0.0001
DYSLIPIDAEMIA (%)	1140	30.2	38.4	31.1	35.1	0.73
NEVER SMOKER (%)	1136	61.7	68.9	61.7	58.5	0.22
CURRENT SMOKER (%)	1136	9.1	4.8	8.9	11.2	0.12
HIGH ALCOHOL INTAKE (%)	1119	13.9	11.6	14.4	10.2	0.35
HEALTHY DIET (%)	1108	77.5	83.9	82.7	81.5	0.50
SUFFICIENT PHYSICAL ACTIVITY (%)	1120	45.6	41.8	49.8	44.6	0.56
HIGHER EDUCATION (%)	1008	43.7	43.9	45.7	43.7	0.52
PERSONAL INCOME ≥ 25K (%)	1092	28.3	28.4	32.7	30.2	0.37
PERSONAL INCOME < 15 K (%)	1092	41.7	46.0	37.7	39.6	0.19
HOUSEHOLD INCOME ≥ 50K (%)	1056	16.1	17.0	18.3	22.0	0.13
HOUSEHOLD INCOME < 20K (%)	1056	43.5	38.9	33.2	40.4	0.09
HOUSEHOLD WEALTH < 100K (%)	1048	15.7	14.3	15.8	12.4	0.88
ADMINISTRATIVE GRADE (%)	1130	17.6	22.9	25.7	24.1	0.07
FATHER'S SOCIAL CLASS I/II (%)	1027	44.9	47.6	42.7	37.2	0.22
MARRIED/ COHABITING (%)	1131	54.3	56.8	59.5	62.3	0.38

†Chi-squared test for trend

TABLE 18 PERCENT DIFFERENCES IN ARTERIAL MEASURES ACCORDING TO STANDARDIZED ANTHROPOMETRIC MEASURES IN THE WHITEHALL II STUDY

	N	% DIFFERENCE (P-VALUE)	% DIFFERENCE (P-VALUE)	% DIFFERENCE (P-VALUE)
		MODEL 1†	MODEL 2‡	MODEL 3§
MEN				
INTIMA MEDIA THICKNESS				
BIRTHWEIGHT	1932	0.13 (P=0.77)	-0.32 (P=0.46)	-0.11 (P=0.80)
HEIGHT	2401	0.03 (P=0.94)	-1.03 (P=0.01)	-0.23 (P=0.60)
LEG LENGTH	2161	-0.35 (P=0.40)	-1.09 (P=0.01)	-0.69 (P=0.11)
TRUNK LENGTH	2163	0.51 (P=0.22)	-0.53 (P=0.24)	0.39 (P=0.42)
BETA STIFFNESS INDEX				
BIRTHWEIGHT	1920	0.48 (P=0.48)	-0.02 (P=0.97)	0.19 (P=0.78)
HEIGHT	2381	-1.44 (P=0.02)	-3.20 (P=0.0001)	-2.47 (P=0.0002)
LEG LENGTH	2141	-0.76 (P=0.22)	-1.77 (P=0.006)	-1.57 (P=0.02)
TRUNK LENGTH	2143	-1.78 (P=0.005)	-3.54 (P=0.0001)	-2.43 (P=0.0008)
DISTENSIBILITY				
BIRTHWEIGHT	1920	0.10 (P=0.88)	1.03 (0.12)	0.52 (P=0.43)
HEIGHT	2381	1.81 (P=0.004)	4.90 (P=0.0001)	3.67 (P=0.0001)
LEG LENGTH	2141	1.18 (P=0.07)	2.99 (P=0.0001)	2.39 (P=0.0004)
TRUNK LENGTH	2143	1.84 (P=0.006)	4.84 (P=0.0001)	3.37 (P=0.0001)
WOMEN				
INTIMA MEDIA THICKNESS				
BIRTHWEIGHT	824	-0.10 (P=0.86)	-0.38 (P=0.51)	-0.06 (P=0.92)
HEIGHT	941	0.36 (P=0.51)	-0.03 (P=0.96)	0.86 (P=0.14)
LEG LENGTH	878	0.27 (P=0.64)	-0.05 (P=0.93)	0.20 (P=0.73)
TRUNK LENGTH	886	0.37 (P=0.51)	0.01 (P=0.99)	1.61 (P=0.01)
BETA STIFFNESS INDEX				
BIRTHWEIGHT	811	2.74 (P=0.007)	2.74 (P=0.008)	3.35 (P=0.001)
HEIGHT	926	-0.27 (P=0.78)	-0.34 (P=0.73)	0.42 (P=0.69)
LEG LENGTH	864	0.94 (P=0.35)	1.03 (P=0.32)	0.89 (P=0.39)
TRUNK LENGTH	872	-0.99 (P=0.32)	-1.06 (P=0.30)	0.64 (P=0.58)
DISTENSIBILITY				
BIRTHWEIGHT	811	-2.41 (P=0.03)	-2.00 (P=0.08)	-3.19 (P=0.004)
HEIGHT	926	1.29 (P=0.23)	2.15 (P=0.06)	0.71 (P=0.53)
LEG LENGTH	864	-0.39 (P=0.73)	0.06 (P=0.96	1.14 (P=0.87)
TRUNK LENGTH	872	2.36 (P=0.04)	3.09 (P=0.008)	0.60 (P=0.64)

† Model 1: Adjusted for age
‡ Model 2: Adjusted for age and concurrent weight
§ Model 3: Adjusted for age, weight, ethnic group, prevalent CHD, diabetes, hypertension, dyslipidaemia and smoking

TABLE 19 PERCENT DIFFERENCES IN STIFFNESS AND DISTENSIBILITY IN MEN ACCORDING TO STANDARDIZED ANTHROPOMETRIC MEASURES ADJUSTING FOR SOCIOECONOMIC MEASURES

ANTHROPOMETRY	% DIFFERENCE (P-VALUE)	
	STIFFNESS	DISTENSIBILITY
HEIGHT		
MODEL 1† (AS MODEL 3 IN TABLE 18)	-2.47 (P=0.0002)	3.67 (P=0.0001)
MODEL 1 (RESTRICTED SAMPLE‡)	-2.52 (P=0.0004)	3.54 (P=0.0001)
MODEL 1 + HOUSEHOLD INCOME	-2.47 (P=0.0006)	3.46 (P=0.0001)
MODEL 1 + PERSONAL INCOME	-2.51 (P=0.0005)	3.51 (P=0.0001)
MODEL 1 + OCCUPATIONAL GRADE	-2.56 (P=0.0004)	3.57 (P=0.0001)
MODEL 1 + EDUCATION	-2.52 (P=0.0004)	3.54 (P=0.0001)
MODEL 1 + FATHER'S SOCIAL CLASS	-2.59 (P=0.0003)	3.59 (P=0.0001)
MODEL 1 + ALL VARIABLES MENTIONED ABOVE	-2.57 (P=0.0004)	3.57 (P=0.0001)
LEG LENGTH		
MODEL 1† (AS MODEL 3 IN TABLE 18)	-1.57 (P=0.02)	2.39 (P=0.0004)
MODEL 1 (RESTRICTED SAMPLE‡)	-1.73 (P=0.01)	2.45 (P=0.0008)
MODEL 1 + HOUSEHOLD INCOME	-1.70 (P=0.02)	2.41 (P=0.0009)
MODEL 1 + PERSONAL INCOME	-1.73 (P=0.01)	2.44 (P=0.0008)
MODEL 1 + OCCUPATIONAL GRADE	-1.74 (P=0.01)	2.44 (P=0.0008)
MODEL 1 + EDUCATION	-1.73 (P=0.01)	2.44 (P=0.0008)
MODEL 1 + FATHER'S SOCIAL CLASS	-1.78 (P=0.01)	2.48 (P=0.0007)
MODEL 1 + ALL VARIABLES MENTIONED ABOVE	-1.78 (P=0.01)	2.47 (P=0.0008)
TRUNK LENGTH		
MODEL 1† (AS MODEL 3 IN TABLE 17)	-2.43 (P=0.0008)	3.37 (P=0.0001)
MODEL 1 (RESTRICTED SAMPLE‡)	-2.39 (P=0.002)	3.04 (P=0.0002)
MODEL 1 + HOUSEHOLD INCOME	-2.30 (P=0.003)	2.94 (P=0.0003)
MODEL 1 + PERSONAL INCOME	-2.36 (P=0.002)	3.00 (P=0.0002)
MODEL 1 + OCCUPATIONAL GRADE	-2.41 (P=0.002)	3.04 (P=0.0002)
MODEL 1 + EDUCATION	-2.36 (P=0.002)	3.03 (P=0.0002)
MODEL 1 + FATHER'S SOCIAL CLASS	-2.44 (P=0.002)	3.08 (P=0.0001)
MODEL 1 + ALL VARIABLES MENTIONED ABOVE	-2.38 (P=0.002)	3.00 (P=0.0002)

‡ Includes 2099 men with complete information on all covariates
† Model 1: Adjusted for age, weight, ethnic group, prevalent CHD, diabetes, hypertension, dyslipidaemia and smoking

TABLE 20 CHARACTERISTICS OF WOMEN IN THE FILIPINA STUDY

	N	MEANS/ PROPORTIONS (95 % CONFIDENCE INTERVALS)
AGE (YEARS)	389	58.7 (57.8; 59.7)
AGE AT IMMIGRATION >45 YEARS (%)	382	48.4 (43.4; 53.5)
YEARS SINCE IMMIGRATION (YEARS)	382	16.6 (15.5; 17.7)
HEIGHT (CM)	389	153.2 (152.6; 153.8)
LEG LENGTH (CM)	389	70.7 (70.4; 71.1)
SITTING HEIGHT (CM)	389	82.4 (82.1; 82.8)
WEIGHT (KG)	389	59.5 (58.5; 60.5)
BODY MASS INDEX (KG/M^2)	389	25.3 (24.9; 25.6)
OBESITY (%)	389	9.8 (6.8; 12.7)
WAIST CIRCUMFERENCE (CM)	389	80.8 (79.8; 81.7)
WAIST HIP RATIO	389	0.83 (0.83; 0.84)
DIABETES (%)	389	31.4 (26.7; 36.0)
CORONARY HEART DISEASE (%)	389	22.4 (18.2; 26.5)
ALCOHOL CONSUMPTION ≥3 TIMES/WEEK (%)	389	1.0 (0.0; 2.0)
PHYSICAL ACTIVITY ≥ 3 TIMES/WEEK (%)	387	65.9 (61.2; 70.6)
CURRENT SMOKER (%)	387	11.4 (8.2; 14.5)
DYSLIPIDAEMIA (%)	389	53.2 (48.3; 58.2)
FAMILY HISTORY OF DIABETES (%)	389	36.0 (31.2; 40.8)
FAMILY HISTORY OF HEART DISEASE (%)	370	23.5 (19.2; 27.8)
CHILDHOOD FAMILY INCOME	380	
POOR		20.7 (16.7; 24.9)
AVERAGE		70.3 (65.7; 74.9)
WELL-OFF		9.0 (6.1; 11.8)
EDUCATION	386	
≤ 12 YEARS		31.1 (26.5; 35.7)
13-15 YEARS		17.4 (13.6; 21.1)
≥ 16 YEARS		51.6 (46.6; 56.5)
ADULT HOUSEHOLD INCOME	330	
≤ 15K		34.2 (28.5; 38.7)
15-44.9K		32.1 (27.1; 37.2)
≥ 45K		33.6 (29.1; 39.4)
ECONOMIC SCORE	323	
0		7.1 (4.3; 9.9)
1		32.8 (27.7; 37.9)
2		29.1 (24.2; 34.1)
3		25.1 (20.4; 29.8)
4		5.9 (3.3; 8.5)
BIRTH YEAR	383	
BEFORE 1938		50.1 (45.1; 55.1)
1938-1940		12.3 (9.0; 15.6)
1941-1947		18.8 (14.9; 22.7)
AFTER 1947		18.8 (14.9; 22.7)

TABLE 21 AGE ADJUSTED MEANS OF ANTHROPOMETRIC MEASURES ACCORDING TO SOCIOECONOMIC POSITION IN CHILD AND ADULTHOOD IN FILIPINO WOMEN

	MEANS (95% CONFIDENCE INTERVALS)		
	HEIGHT (M)	LEG LENGTH (CM)	TRUNK LENGTH (CM)
BIRTH YEAR (N=382)			
BEFORE 1938	1.54 (1.53; 1.55)	70.84 (70.01; 71.68)	83.08 (82.39; 83.77)
1938-1940	1.55 (1.54; 1.57)	72.12 (71.09; 73.15)	83.05 (82.19; 83.90)
1941-1947	1.52 (1.51; 1.54)	70.16 (69.17; 71.16)	82.26 (81.44; 83.08)
AFTER 1947	1.51 (1.48; 1.53)	70.05 (68.63; 71.48)	80.46 (79.28; 81.64)
P_{TREND}	0.02	0.24	0.005
CHILDHOOD INCOME (N=373)			
POOR	1.52 (1.51; 1.53)	70.25 (69.45; 71.05)	81.60 (80.94; 82.27)
AVERAGE	1.53 (1.53; 1.54)	70.73 (70.30; 71.16)	82.65 (82.29; 83.01)
WELL-OFF	1.55 (1.53; 1.57)	71.77 (70.55; 72.99)	82.87 (81.86; 83.88)
P_{TREND}	0.008	0.05	0.001
EDUCATION (N=380)			
≤ 12 YEARS	1.52 (1.51; 1.53)	70.31 (69.63; 70.98)	81.90 (81.34; 82.46)
13-15 YEARS	1.53 (1.52; 1.54)	70.67 (79.80; 71.54)	82.30 (81.58; 83.02)
≥ 16 YEARS	1.54 (1.53; 1.55)	71.00 (70.47; 71.50)	82.84 (82.42; 83.27)
P_{TREND}	0.02	0.12	0.009
ADULT INCOME (N=324)			
≤ 15K	1.52 (1.51; 1.53)	70.17 (69.47; 70.87)	82.04 (81.46; 82.63)
15-44.9K	1.54 (1.53; 1.56)	71.29 (70.60; 71.98)	83.17 (82.60; 83.74)
≥ 45K	1.54 (1.53; 1.55)	71.28 (70.57; 71.99)	82.91 (82.31; 83.50)
P_{TREND}	0.02	0.04	0.05
ECONOMIC SCORE (N=317)			
0	1.52 (1.49; 1.54)	69.76 (68.26; 71.26)	82.00 (80.76; 83.23)
1	1.52 (1.51; 1.53)	70.26 (69.54; 70.98)	81.97 (81.38; 82.56)
2	1.55 (1.54; 1.56)	71.37 (70.64; 72.11)	83.49 (82.88; 84.09)
3	1.54 (1.53; 1.56)	71.38 (70.55; 72.21)	82.87 (82.19; 83.55)
4	1.55 (1.53; 1.58)	71.73 (70.09; 73.38)	83.37 (82.01; 84.73)
P_{TREND}	0.003	0.009	0.02

TABLE 21 CONTINUED

	MEANS (95% CONFIDENCE INTERVALS)	
	BMI (KG/M^2)	WAIST (CM)
BIRTH YEAR (N=382)		
BEFORE 1938	25.7 (24.9; 26.6)	81.9 (79.6; 84.1)
1938-1940	25.7 (24.7; 26.7)	83.0 (80.2; 85.7)
1941-1947	24.9 (23.9; 25.9)	79.6 (76.9; 82.2)
AFTER 1947	24.2 (22.8; 25.7)	77.7 (73.9; 81.5)
P_{TREND}	0.13	0.10
CHILDHOOD INCOME (N=373)		
POOR	25.5 (24.7; 26.3)	81.5 (79.3; 83.6)
AVERAGE	25.3 (24.8; 25.7)	80.5 (79.3; 81.6)
WELL-OFF	25.0 (23.8; 26.2)	81.2 (77.9; 84.4)
P_{TREND}	0.48	0.68
EDUCATION (N=380)		
≤ 12 YEARS	26.0 (25.3; 26.6)	83.6 (81.8; 85.4)
13-15 YEARS	25.4 (24.6; 26.3)	79.8 (77.6; 82.1)
≥ 16 YEARS	24.8 (24.3; 25.3)	79.3 (78.0; 80.7)
P_{TREND}	0.008	0.0004
ADULT INCOME (N=324)		
≤ 15K	24.9 (24.2; 25.5)	80.1 (78.3; 81.9)
15-44.9K	25.9 (25.3; 26.6)	82.3 (80.5; 84.0)
≥ 45K	25.0 (24.3; 25.7)	78.9 (77.0; 80.7)
P_{TREND}	0.75	0.39
ECONOMIC SCORE (N=317)		
0	24.95 (23.5; 26.4)	81.6 (76.7; 84.5)
1	25.00 (24.3; 25.7)	80.0 (78.2; 81.9)
2	25.69 (25.0; 26.4)	81.6 (79.7; 83.5)
3	25.22 (24.4; 26.0)	79.4 (77.3; 81.6)
4	24.86 (23.3; 26.4)	80.0 (75.7; 84.3)
P_{TREND}	0.76	0.73

TABLE 22 ODDS RATIOS FOR DIABETES IN FILIPINO WOMEN (MINIMUM N=304)

	ODDS RATIO (95% CONFIDENCE INTERVALS)	
RISK FACTOR	AGE ADJUSTED†	FULLY ADJUSTED#
HEIGHT		
1 SHORTEST (<148.6 CM)	1	1
2 (148.6-152.4 CM)	1.21 (0.64; 2.27)	1.04 (0.51; 2.12)
3 (152.4-157.5 CM)	1.13 (0.58; 2.20)	0.59 (0.26; 1.30)
4 TALLEST (>157.5 CM)	1.90 (0.99; 3.66)	1.16 (0.54; 2.48)
P_{TREND}	0.07	0.96
LEG LENGTH		
1 SHORTEST (<68.6 CM)	1	1
2 (68.6-70.5 CM)	0.94 (0.49; 1.80)	0.76 (0.37; 1.58)
3 (70.5-73.0 CM)	1.12 (0.59; 2.11)	0.77 (0.36; 1.63)
4 TALLEST (>73.0 CM)	1.32 (0.70; 2.49)	0.73 (0.35; 1.55)
P_{TREND}	0.32	0.45
TRUNK LENGTH		
1 SHORTEST (<80.0 CM)	1	1
2 (80.0-82.6 CM)	0.80 (0.41; 1.54)	0.67 (0.31; 1.45)
3 (82.6-84.5 CM)	1.08 (0.58; 2.00)	0.64 (0.31; 1.33)
4 TALLEST (>84.5 CM)	1.67 (0.86; 3.27)	1.09 (0.50; 2.35)
P_{TREND}	0.13	0.94
CHILDHOOD FAMILY INCOME		
POOR	1	1
AVERAGE	0.48 (0.28; 0.83)	0.48 (0.25; 0.90)
WELL-OFF	0.34 (0.13; 0.90)	0.26 (0.08; 0.82)
P_{TREND}	0.005	0.007
EDUCATION		
≤ 12 YEARS	1	1
13-15 YEARS	0.78 (0.40; 1.51)	0.72 (0.32; 1.63)
≥ 16 YEARS	0.41 (0.24; 0.72)	0.44 (0.23; 0.84)
P_{TREND}	0.001	0.01
ADULT HOUSEHOLD INCOME		
≤ 15K	1	1
15-44.9K	0.58 (0.31; 1.08)	0.34 (0.16; 0.70)
≥ 45K	0.24 (0.11; 0.55)	0.16 (0.06; 0.42)
P_{TREND}	0.0008	0.0002
ECONOMIC SCORE		
0	1	1
1	0.73 (0.29; 1.85)	0.55 (0.18; 1.68)
2	0.40 (0.15; 1.09)	0.19 (0.06; 0.62)
3	0.22 (0.07; 0.68)	0.11 (0.03; 0.42)
4	0.14 (0.02; 0.79)	0.07 (0.01; 0.51)
P_{TREND}	0.0006	<0.0001

† Adjusted for current age and age at immigration
# Additionally includes BMI, waist, family history of diabetes, smoking, exercise, employment status, household size

TABLE 23 ODDS RATIOS FOR CORONARY HEART DISEASE IN FILIPINO WOMEN (MINIMUM N=304)

	ODDS RATIO (95% CONFIDENCE INTERVALS)	
RISK FACTOR	AGE ADJUSTED†	FULLY ADJUSTED##
HEIGHT		
1 SHORTEST (<148.6 CM)	1	1
2 (148.6-152.4 CM)	0.89 (0.45; 1.76)	0.77 (0.36; 1.64)
3 (152.4-157.5 CM)	0.91 (0.45; 1.84)	0.82 (0.38; 1.76)
4 TALLEST (>157.5 CM)	0.67 (0.32; 1.40)	0.45 (0.19; 1.07)
P_{TREND}	0.33	0.10
LEG LENGTH		
1 SHORTEST (<68.6 CM)	1	1
2 (68.6-70.5 CM)	0.60 (0.31; 1.19)	0.52 (0.24; 1.12)
3 (70.5-73.0 CM)	0.53 (0.26; 1.05)	0.52 (0.24; 1.11)
4 TALLEST (>73.0 CM)	0.44 (0.22; 0.91)	0.32 (0.14; 0.74)
P_{TREND}	0.02	0.01
TRUNK LENGTH		
1 SHORTEST (<80.0 CM)	1	1
2 (80.0-82.6 CM)	0.60 (0.28; 1.29)	0.56 (0.25; 1.27)
3 (82.6-84.5 CM)	1.17 (0.61; 2.24)	0.76 (0.36; 1.62)
4 TALLEST (>84.5 CM)	0.80 (0.38; 1.69)	0.48 (0.20; 1.13)
P_{TREND}	0.95	0.16
CHILDHOOD FAMILY INCOME		
POOR	1	1
AVERAGE	0.72 (0.40; 1.32)	0.71 (0.37; 1.37)
WELL-OFF	0.47 (0.16; 1.40)	0.45 (0.15; 1.40)
P_{TREND}	0.14	0.15
EDUCATION		
≤ 12 YEARS	1	1
13-15 YEARS	1.21 (0.55; 2.66)	1.40 (0.58; 3.35)
≥ 16 YEARS	1.30 (0.69; 2.46)	1.47 (0.71; 3.06)
P_{TREND}	0.43	0.32
ADULT HOUSEHOLD INCOME		
≤ 15K	1	1
15-44.9K	0.69 (0.33; 1.43)	0.61 (0.27; 1.38)
≥ 45K	0.64 (0.27; 1.52)	0.78 (0.30; 2.01)
P_{TREND}	0.32	0.61
ECONOMIC SCORE		
0	1	1
1	0.55 (0.20; 1.53)	0.43 (0.14; 1.38)
2	0.46 (0.15; 1.37)	0.38 (0.11; 1.27)
3	0.39 (0.12; 1.30)	0.41 (0.11; 1.54)
4	0.19 (0.03; 1.15)	0.14 (0.02; 0.96)
P_{TREND}	0.07	0.13

† Adjusted for current age and age at immigration
Additionally includes BMI, waist, family history, menopausal status, HRT, hypertension, dyslipidaemia, smoking,exercise

TABLE 24 ODDS RATIOS FOR DIABETES AND CORONARY HEART DISEASE FROM MODELS INCLUDING ALL RISK FACTORS SIMULTANEOUSLY

	ODDS RATIO (95% CONFIDENCE INTERVALS)	P-VALUE
DIABETES (N=305)		
AGE (YEARS)	1.04 (0.99; 1.09)	0.07
AGE AT IMMIGRATION (YEARS)	0.99 (0.96; 1.03)	0.74
WAIST CIRCUMFERENCE (CM)	1.07 (1.03; 1.10)	<0.0001
CHILDHOOD FAMILY INCOME (PER CATEGORY↑)	0.66 (0.36; 1.20)	0.17
EDUCATION (PER CATEGORY↑)	0.72 (0.50; 1.04)	0.08
ADULT HOUSEHOLD INCOME (PER CATEGORY↑)	0.40 (0.24; 0.66)	0.0003
FAMILY HISTORY OF DIABETES (Y/N)	5.14 (2.72; 9.70)	<0.0001
CURRENT EMPLOYMENT STATUS (Y/N)	1.34 (0.72; 2.51)	0.36
NUMBER OF HOUSEHOLD MEMBERS	0.99 (0.82; 1.19)	0.91
CORONARY HEART DISEASE (N=380)		
AGE (YEARS)	1.02 (0.99; 1.07)	0.22
AGE AT IMMIGRATION (YEARS)	0.98 (0.96; 1.01)	0.17
WAIST CIRCUMFERENCE (CM)	1.03 (1.01; 1.06)	0.01
HYPERTENSION (Y/N)	1.74 (0.98; 3.08)	0.06
DYSLIPIDAEMIA (Y/N)	1.62 (0.51; 5.18)	0.42
REGULAR EXERCISE (Y/N)	1.67 (0.94; 2.97)	0.08
LEG LENGTH (PER CATEGORY↑)	0.72 (0.56; 0.91)	0.006

TABLE 25 CHARACTERISTICS OF 564 GIRLS AND 569 BOYS PARTICIPATING IN PROJECT VIVA 03-06

VARIABLE	N	MEANS (SD)/ PROPORTIONS		P-VALUE
	GIRLS/ BOYS	GIRLS	BOYS	
MATERNAL AND FAMILY CHARACTERISTICS				
MATERNAL AGE AT ENROLMENT (YEARS)	564/ 569	32.8 (4.8)	32.3 (5.2)	0.05
MATERNAL HEIGHT (CM)	564/ 569	164.7 (6.9)	165.4 (7.0)	0.13
PATERNAL HEIGHT (CM)	553/ 558	179.6 (7.6)	179.1 (7.8)	0.29
MATERNAL PRE-PREGNANCY BMI (KG/M^2)	562/ 567	24.5 (5.1)	24.6 (5.1)	0.68
GESTATIONAL WEIGHT GAIN (KG)	556/ 561	15.2 (5.4)	16.2 (5.3)	0.001
SMOKING DURING PREGNANCY (%)	564/ 569	8.5	12.1	0.05
MULTIPARITY (%)	564/569	53.9	52.7	0.69
MATERNAL RACE/ ETHNICITY (% WHITE)	564/ 569	73.8	71.9	0.48
MOTHER MARRIED/ COHABITATING (%)	563/ 569	93.1	92.6	0.77
MOTHER'S EDUCATION ≥ COLLEGE GRADUATE (%)	564/ 566	73.9	70.1	0.16
HOUSEHOLD INCOME ≥ 70,000 DOLLARS (%)	528/ 517	68.9	65.8	0.27
MATERNAL HYPERTENSION (%)	552/ 554	1.6	1.4	0.80
PREGNANCY INDUCED HYPERTENSION (%)	552/ 554	8.7	9.9	0.48
CHILDHOOD CHARACTERISTICS DURING INFANCY				
GESTATIONAL AGE (WEEKS)	564/ 569	39.7 (1.4)	39.6 (1.5)	0.41
BIRTHWEIGHT (KG)	564/ 568	3.46 (0.47)	3.58 (0.54)	< 0.0001
BIRTHLENGTH (CM)	342/ 328	49.6 (2.0)	50.2 (2.1)	< 0.0001
BIRTHWEIGHT FOR GESTATIONAL AGE (Z-VALUE)	564/ 568	0.23 (0.92)	0.21 (0.98)	0.06
BREASTFEEDING DURATION AT 1 YEAR (MONTHS)	540/ 536	6.55 (4.5)	6.41 (4.6)	0.62
CHILDHOOD CHARACTERISTICS AGE 3 YEARS				
AGE (MONTHS)	564/ 569	39.0 (3.5)	39.4 (4.3)	0.09
SYSTOLIC BLOOD PRESSURE (MMHG)	564/ 569	92.1 (11.6)	92.41 (9.6)	0.64
DIASTOLIC BLOOD PRESSURE (MMHG)	564/ 569	58.1 (8.4)	58.33 (7.8)	0.64
MEAN ARTERIAL PRESSURE (MMHG)	564/ 569	69.4 (8.9)	69.69 (7.7)	0.61
PULSE PRESSURE (MMHG)	564/ 569	34.0 (7.8)	34.09 (7.3)	0.87
WEIGHT (KG)	564/ 569	15.4 (2.2)	16.12 (2.2)	< 0.0001
BMI (KG/M^2)	564/ 569	16.3 (1.5)	16.69 (1.5)	< 0.0001
BMI Z-SCORE	564/ 569	0.41 (0.99)	0.53 (1.1)	0.06
HEIGHT (CM)	564/ 569	96.86 (4.31)	98.13 (4.6)	< 0.0001
LEG LENGTH (CM)	564/ 569	41.57 (2.53)	42.04 (2.8)	0.003
LEG LENGTH (% OF HEIGHT)	564/ 569	42.95 (1.44)	42.82 (1.5)	0.16
TRUNK LENGTH (CM)	564/ 569	55.19 (2.57)	56.09 (2.6)	< 0.0001
DIFFERENCE IN Z-SCORES (LEG AND TRUNK)	564/ 569	0 (1.1)	0 (1.1)	1.00

TABLE 26 MEAN DIFFERENCE IN ANTHROPOMETRY AT AGE 3 YEARS ACCORDING TO EARLY LIFE FACTORS, ADJUSTED FOR AGE, SEX AND ETHNIC GROUP (REGRESSION COEFFICIENTS AND 95% CONFIDENCE INTERVALS)

VARIABLE	LEG LENGTH (CM)	TRUNK LENGTH (CM)	% LEG LENGTH	DIFFERENCE IN Z-SCORES
MATERNAL AND FAMILY CHARACTERISTICS				
MATERNAL AGE AT ENROLMENT (PER YEARS)	-0.03 (-0.05; 0.001)	0.01 (-0.02; 0.04)	-0.02 (-0.04; -0.003)*	-0.01 (-0.03; -0.002)*
SMOKING DURING PREGNANCY	0.27 (-0.15; 0.69)	0.08 (-0.38; 0.55)	0.13 (-0.13; 0.40)	0.08 (-0.12; 0.27)
MATERNAL HEIGHT (PER CM)	0.10 (0.08, 0.12)‡	0.09 (0.07; 0.11)‡	0.02 (0.006; 0.03)†	0.002 (-0.007; 0.01)
PATERNAL HEIGHT (PER CM)	0.08 (0.06, 0.09)‡	0.08 (0.06; 0.10)‡	0.009 (-0.002; 0.02)	-0.003 (-0.01; 0.005)
PRE-PREGNANCY BMI (PER KG/M^2)	0.02 (-0.01; 0.05)	0.03 (0.003; 0.06)*	-0.03 (-0.02; 0.01)	-0.005 (-0.02; 0.007)
GESTATIONAL WEIGHT GAIN (PER KG)	0.01 (-0.01; 0.03)	0.02 (-0.003; 0.05)	-0.003 (-0.02; 0.01)	-0.005 (-0.02, 0.006)
PRIMIGRAVIDA	0.06 (-0.20; 0.31)	0.21 (-0.07; 0.49)	-0.07 (-0.23; 0.10)	-0.06 (-0.18; 0.06)
MOTHER NOT MARRIED AND/ OR COHABITATING	0.03 (-0.49; 0.56)	-0.25 (-0.83; 0.32)	0.15 (-0.18; 0.48)	0.11 (-0.14; 0.35)
MOTHER'S EDUCATION < COLLEGE GRADUATE	0.02 (-0.28; 0.32)	0.03 (-0.30; 0.36)	0.006 (-0.18; 0.19)	-0.005 (-0.14; 0.13)
HOUSEHOLD INCOME < 70K (%)	-0.09 (-0.39; 0.21)	-0.12 (-0.45; 0.22)	0.003 (-0.19; 0.19)	0.008 (-0.13; 0.15)
NO MATERNAL HYPERTENSION	-0.61 (-1.67; 0.44)	-0.36 (-1.51; 0.80)	-0.25 (-0.91; 0.41)	-0.10 (-0.59; 0.39)
NO PREGNANCY INDUCED HYPERTENSION	-0.14 (-0.58; 0.31)	0.19 (-0.30; 0.67)	-0.17 (-0.45; 0.11)	-0.12 (-0.33; 0.09)
CHILDHOOD CHARACTERISTICS DURING INFANCY				
GESTATIONAL AGE (PER WEEK)	0.08 (-0.01; 0.17)	-0.004 (-0.10; 0.10)	0.05 (-0.004; 0.11)	0.031 (-0.01; 0.07)
BIRTHWEIGHT (PER KG)	0.96 (0.71; 1.21)‡	0.98 (0.70; 1.25)‡	0.13 (-0.03; 0.29)	-0.017 (-0.14; 0.10)
BIRTHLENGTH (PER CM)	0.35 (0.28; 0.43)‡	0.35 (0.27; 0.44)‡	0.06 (0.005; 0.11)*	-0.004 (-0.04; 0.03)
BIRTHWEIGHT FOR GEST. AGE (Z-VALUE)	0.53 (0.40; 0.66)‡	0.62 (0.48; 0.76)‡	0.04 (-0.05; 0.12)	-0.040 (-0.10; 0.02)
BREASTFEEDING DURATION (PER MONTH)	-0.03 (-0.06; 0.001)	-0.04 (-0.07; -0.01)*	-0.0003 (-0.02; 0.02)	0.004 (-0.01; 0.02)
CHILDHOOD CHARACTERISTICS AGE 3 YEARS				
WEIGHT (KG)	0.51 (0.45; 0.56)‡	0.79 (0.74; 0.84)‡	-0.05 (-0.09; -0.01)†	-0.11 (-0.14; -0.09)‡
BMI (KG/M^2)	0.02 (-0.07; 0.10)	0.43 (0.34; 0.52)‡	-0.18 (-0.23; -0.13)‡	-0.16 (-0.20; -0.12) ‡
HEIGHT (CM)	0.47 (0.45; 0.49)‡	0.53 (0.51; 0.55)‡	0.04 (0.02; 0.06)‡	-0.03 (-0.05; -0.02)‡

* p-value ≤ 0.5; † p-value ≤ 0.01; ‡ p-value ≤ 0.001

TABLE 27 REGRESSION COEFFICIENTS (95% CONFIDENCE INTERVALS) FOR ASSOCIATIONS BETWEEN ANTHROPOMETRY AND BLOOD PRESSURE AT AGE 3 YEARS FROM SEPARATE MULTIVARIATE RANDOM EFFECTS REGRESSION MODELS (N=1133)

ANTHROPOMETRY	MODEL	SBP	DBP	MAP	PP
HEIGHT	SIMPLE ADJUSTED MODEL#	0.42 (0.28; 0.56)‡	0.16 (0.05; 0.26)†	0.25 (0.14, 0.35) ‡	0.27 (0.16; 0.37)‡
	+ADJUSTMENT FOR WEIGHT	-0.06 (-0.26; 0.13)	0.01 (-0.14; 0.16)	-0.02 (-0.17, 0.14)	-0.06 (-0.21; 0.09)
	FULLY ADJUSTED§	-0.03 (-0.22; 0.17)	0.03 (-0.12; 0.18)	0.01 (-0.15, 0.16)	-0.05 (-0.20; 0.10)
WEIGHT	SIMPLE ADJUSTED MODEL#	1.18 (0.92; 1.44)‡	0.40 (0.20; 0.60)‡	0.67 (0.47, 0.87) ‡	0.79 (0.59; 0.99)‡
	+ADJUSTMENT FOR HEIGHT	1.26 (0.90; 1.63)‡	0.39 (0.11; 0.68)†	0.69 (0.40, 0.98) ‡	0.87 (0.60; 1.15) ‡
	FULLY ADJUSTED§	1.32 (0.95; 1.69)‡	0.43 (0.15; 0.72)†	0.74 (0.45, 1.03) ‡	0.89 (0.60; 1.17) ‡
LEG LENGTH	SIMPLE ADJUSTED MODEL#	0.32 (0.09; 0.55)†	0.13 (-0.05; 0.30)	0.19 (0.01, 0.37)*	0.18 (0.01; 0.35)*
	+ADJUSTMENT FOR HEIGHT	-0.61 (-0.98; -0.24)‡	-0.21 (-0.50; 0.07)	-0.35 (-0.64, 0.06)*	-0.45 (-0.73; -0.17)†
	+ADJUSTMENT FOR WEIGHT	-0.39 (-0.77; -0.02)*	-0.15 (-0.43; 0.14)	-0.23 (-0.52, 0.06)	-0.30 (-0.59; -0.02)*
	FULLY ADJUSTED§	-0.35 (-0.74; 0.04)	-0.21 (-0.51; 0.09)	-0.26 (-0.56, 0.05)	-0.19 (-0.49; -0.10)
TRUNK LENGTH	SIMPLE ADJUSTED MODEL#	0.74 (0.52; 0.96)‡	0.27 (0.11; 0.44)‡	0.43 (0.26, 0.60) ‡	0.50 (0.33; 0.66)‡
	+ADJUSTMENT FOR HEIGHT	0.61 (0.24; 0.98)‡	0.21 (-0.07; 0.50)	0.35 (0.06, 0.64)*	0.45 (0.17; 0.73)†
	+ADJUSTMENT FOR WEIGHT	0.39 (0.02; 0.77)*	0.15 (-0.14; 0.43)	0.23 (-0.06, 0.52)	0.30 (0.02; 0.59)*
	FULLY ADJUSTED§	0.35 (-0.04; 0.74)	0.21 (-0.09; 0.51)	0.26 (-0.05, 0.56)	0.19 (-0.10; 0.49)
LEG LENGTH (%)	SIMPLE ADJUSTED MODEL#	-0.44 (–0.80, -0.07)*	-0.16 (–0.43, 0.12)	-0.25 (–0.53, 0.03)	-0.33 (-0.60, -0.05)*
	+ADJUSTMENT FOR WEIGHT	-0.40 (–0.75, -0.05)*	-0.14 (–0.42, 0.13)	-0.23 (–0.51, 0.05)	-0.31 (–0.57, -0.04)*
	FULLY ADJUSTED§	-0.35 (–0.73, 0.03)	-0.22 (–0.51, 0.07)	-0.26 (–0.56, 0.03)	-0.19 (–0.48, 0.10)
DIFFERENCE IN Z-SCORES	SIMPLE ADJUSTED MODEL#	-0.90 (-1.40; -0.41)‡	-0.32 (-0.69; 0.060)	-0.52 (-0.90; -0.13)†	-0.66 (-1.03; -0.28)‡
	+ADJUSTMENT FOR WEIGHT	-0.53 (-1.02; -0.047)*	-0.19 (-0.57; 0.19)	-0.31 (-0.69; 0.07)	-0.42 (-0.78; -0.05)*
	FULLY ADJUSTED§	-0.46 (-0.98; 0.05)	-0.28 (-0.68; 0.12)	-0.34 (-0.74; 0.06)	-0.26 (-0.65; 0.13)

Adjusted for sex, age, state, arm, cuff size, body position, indicator for the sequence number (1st through 5th)
§ Additionally adjusted for ethnic group and birthweight; * p-value for trend ≤ 0.05; † p-value ≤ 0.01; ‡ p-value ≤ 0.001

TABLE 28 AGE ADJUSTED MEANS AND PREVALENCES OF BASELINE PHYSICAL CHARACTERISTICS IN RELATION TO ADULT HEIGHT

	HEIGHT			P_{TREND}
VARIABLE	TERTILE 1 (≤ 173.0 CM	TERTILE 2 (173.1 – 178.0 CM	TERTILE 3 (>178.0 CM	
(N)	4939	6490	5742	
MEANS (SE)				
AGE AT ENTRY (YEARS)	53.6 (0.1)	52.0 (0.1)	50.9 (0.1)	< 0.001
SYSTOLIC BLOOD PRESSURE (MMHG)	136.4 (0.3)	136.6 (0.3)	136.8 (0.3)	0.18
DIASTOLIC BLOOD PRESSURE (MMHG)	84.2 (0.2)	84.6 (0.2)	84.8 (0.2)	0.01
BODY MASS INDEX (KG/M^2)	25.0 (0.04)	24.8 (0.04)	24.5 (0.04)	< 0.001
CHOLESTEROL (MMOL/L)	5.16 (0.02)	5.10 (0.02)	5.05 (0.02)	0.001
FEV_1 (L/SEC)	2.81 (0.01)	3.14 (0.01)	3.41 (0.01)	< 0.001
PROPORTIONS (SE)				
LOW WORK GRADE	34.1 (0.7)	23.6 (0.5)	18.6 (0.5)	< 0.001
NO PARTNER	15.1 (0.5)	11.3 (0.4)	9.7 (0.4)	< 0.001
CHD AT BASELINE	20.1 (0.5)	18.1 (0.5)	17.2 (0.5)	< 0.001
CURRENT CIGARETTE SMOKER	44.3 (0.7)	41.9 (0.6)	38.6 (0.7)	< 0.001
GLUCOSE INTOLERANCE	6.2 (0.4)	5.9 (0.3)	4.2 (0.3)	< 0.001
DIABETES	1.8 (0.2)	1.1 (0.1)	1.1 (0.2)	0.001

TABLE 29 HAZARD RATIOS (95 PERCENT CONFIDENCE INTERVALS) FOR CARDIOVASCULAR MORTALITY ASSOCIATED WITH AN INCREASE OF 15 CM IN HEIGHT BY EMPLOYMENT GRADE IN MEN WITHOUT CHD AT BASELINE

OUTCOME	EMPLOYMENT GRADE	HEIGHT MEAN (SE)	N	DEATHS	AGE ADJUSTED+ HAZARD RATIO (95%CI)	AGE ADJUSTED+ P-VALUE	FULLY ADJUSTED# HAZARD RATIO (95%CI)	FULLY ADJUSTED# P-VALUE
CVD	ALL	175.9 (0.1)	13885	3975	0.89 (0.83-0.95)	0.001	0.91 (0.85-0.98)	0.009
	HIGH	176.6 (0.1)	10408	2784	0.84 (0.77-0.91)	< 0.001	0.87 (0.80-0.95)	0.002
	MIDDLE	174.0 (0.1)	2234	763	0.96 (0.82-1.13)	0.79	0.97 (0.83-1.15)	0.73
	LOW	173.2 (0.2)	1243	428	1.05 (0.87-1.26)	0.52	1.03 (0.85-1.25)	0.75
	TEST FOR INTERACTION				P=0.02		P=0.05	
CHD	ALL	175.9 (0.1)	13885	2530	0.81 (0.74-0.88)	< 0.001	0.84 (0.77-0.92)	< 0.001
	HIGH	176.6 (0.1)	10408	1781	0.77 (0.69-0.85)	< 0.001	0.81 (0.73-0.90)	< 0.001
	MIDDLE	174.0 (0.1)	2234	478	0.84 (0.69-1.03)	0.10	0.87 (0.71-1.07)	0.19
	LOW	173.2 (0.2)	1243	271	0.95 (0.75-1.20)	0.65	0.94 (0.74-1.19)	0.59
	TEST FOR INTERACTION				P=0.09		P=0.21	
STROKE	ALL	175.9 (0.1)	13885	738	0.91 (0.78-1.08)	0.28	0.90 (0.76-1.06)	0.21
	HIGH	176.6 (0.1)	10408	517	0.82 (0.67-1.01)	0.06	0.82 (0.67-1.00)	0.05
	MIDDLE	174.0 (0.1)	2234	146	1.18 (0.82-1.72)	0.37	1.17 (0.80-1.70)	0.42
	LOW	173.2 (0.2)	1243	75	1.06 (0.68-1.66)	0.80	1.01 (0.64-1.60)	0.95
	TEST FOR INTERACTION				P=0.13		P=0.16	

+ Analysis of all grades combined is also adjusted for grade

Multiple adjustment is for age, smoking habit, cholesterol, systolic and diastolic blood pressure, body mass index, forced expiratory volume in one second (adjusted for height), glucose intolerance and diabetes

TABLE 30 HAZARD RATIOS (95 PERCENT CONFIDENCE INTERVALS) FOR CARDIOVASCULAR MORTALITY ASSOCIATED WITH AN INCREASE OF 15 CM IN HEIGHT BY EMPLOYMENT GRADE IN MEN WITH PREVALENT CHD AT BASELINE

OUTCOME	EMPLOYMENT GRADE	HEIGHT MEAN (SE)	N	DEATHS	AGE ADJUSTED+		FULLY ADJUSTED#	
					HAZARD RATIO (95%CI)	P-VALUE	HAZARD RATIO (95%CI)	P-VALUE
CVD	ALL	174.9 (0.1)	3254	1466	0.78 (0.70-0.87)	< 0.001	0.80 (0.72-0.90)	< 0.001
	HIGH	175.9 (0.1)	2207	960	0.75 (0.65-0.86)	< 0.001	0.75 (0.65-0.87)	< 0.001
	MIDDLE	173.3 (0.3)	601	280	0.84 (0.65-1.09)	0.19	0.93 (0.72-1.20)	0.58
	LOW	171.8 (0.4)	446	226	0.83 (0.64-1.08)	0.16	0.84 (0.65-1.10)	0.21
	TEST FOR INTERACTION				P=0.41		P=0.27	
CHD	ALL	174.9 (0.1)	3254	1000	0.74 (0.65-0.85)	< 0.001	0.77 (0.67-0.88)	< 0.001
	HIGH	175.9 (0.1)	2207	644	0.66 (0.55-0.79)	< 0.001	0.67 (0.56-0.80)	< 0.001
	MIDDLE	173.3 (0.3)	601	196	0.91 (0.66-1.23)	0.53	1.00 (0.74-1.36)	0.98
	LOW	171.8 (0.4)	446	160	0.88 (0.65-1.20)	0.42	0.90 (0.66-1.24)	0.52
	TEST FOR INTERACTION				P=0.06		P=0.03	
STROKE	ALL	174.9 (0.1)	3254	214	0.76 (0.56-1.02)	0.07	0.76 (0.56-1.03)	0.07
	HIGH	175.9 (0.1)	2207	153	0.76 (0.53-1.09)	0.13	0.74 (0.50-1.07)	0.10
	MIDDLE	173.3 (0.3)	601	37	0.74 (0.37-1.49)	0.40	0.80 (0.41-1.53)	0.49
	LOW	171.8 (0.4)	446	24	0.80 (0.36-1.79)	0.58	0.81 (0.34-1.91)	0.63
	TEST FOR INTERACTION				P=0.93		P=0.81	

+ Analysis of all grades combined is also adjusted for grade

Multiple adjustment is for age, smoking habit, cholesterol, systolic and diastolic blood pressure, body mass index, forced expiratory volume in one second (adjusted for height), glucose intolerance and diabetes

TABLE 31 HAZARD RATIOS (95 PERCENT CONFIDENCE INTERVALS) FOR CARDIOVASCULAR MORTALITY ASSOCIATED WITH AN INCREASE OF 15 CM IN HEIGHT ACCORDING TO LENGTH OF FOLLOW-UP IN ALL MEN

OUTCOME	FOLLOW-UP PERIOD	N	DEATHS	AGE ADJUSTED		FULLY ADJUSTED#	
				HAZARD RATIO (95%CI)	P-VALUE	HAZARD RATIO (95%CI)	P-VALUE
CVD	ALL	17139	5441	0.82 (0.77-0.87)	≤0.001	0.87 (0.82-0.93)	≤0.001
	0-9 YEARS	17139	971	0.71 (0.62-0.81)	≤0.001	0.78 (0.68-0.90)	≤0.001
	10-19 YEARS	15247	1650	0.87 (0.78-0.97)	0.009	0.93 (0.83-1.04)	0.20
	20-29 YEARS	11967	2036	0.80 (0.73-0.89)	≤0.001	0.85 (0.77-0.94)	0.001
	30+ YEARS	7368	784	0.96 (0.81-1.12)	0.58	0.99 (0.84-1.17)	0.88
	TEST FOR INTERACTION			P=0.25		P=0.22	
CHD	ALL	17139	3530	0.75 (0.70-0.81)	≤0.001	0.81 (0.75-0.87)	≤0.001
	0-9 YEARS	17139	757	0.67 (0.58-0.79)	≤0.001	0.75 (0.64-0.88)	≤0.001
	10-19 YEARS	15247	1098	0.83 (0.73-0.95)	0.005	0.89 (0.78-1.02)	0.10
	20-29 YEARS	11967	1251	0.73 (0.64-0.83)	≤0.001	0.79 (0.69-0.89)	≤0.001
	30+ YEARS	7368	424	0.78 (0.62-0.97)	0.03	0.82 (0.66-1.03)	0.09
	TEST FOR INTERACTION			P=0.41		P=0.36	
STROKE	ALL	17139	952	0.86 (0.75-0.99)	0.04	0.86 (0.74-1.00)	0.04
	0-9 YEARS	17139	99	0.78 (0.51-1.20)	0.26	0.85 (0.54-1.32)	0.46
	10-19 YEARS	15247	262	0.74 (0.57-0.97)	0.03	0.75 (0.57-0.99)	0.04
	20-29 YEARS	11967	410	0.79 (0.63-0.98)	0.03	0.79 (0.63-0.98)	0.04
	30+ YEARS	7368	181	1.42 (1.02-1.99)	0.04	1.43 (1.01-2.01)	0.04
	TEST FOR INTERACTION			P=0.39		P=0.43	

Full adjustment is for age, employment grade, smoking habit, cholesterol, systolic and diastolic blood pressure, body mass index, forced expiratory volume in one second (adjusted for height), glucose intolerance and diabetes

APPENDIX

APPENDIX 1 CONTACT AND RESPONSE RATES OF THE NSHD AT AGE 53 YEARS.

ORIGINAL COHORT		5362
DEAD BY 53 YEARS	-469	
LIVING ABROAD AT 53 YEARS	-580	
ALIVE AND RESIDENT IN ENGLAND, SCOTLAND OR WALES		4313
PREVIOUSLY REFUSED	-640	
UNTRACED AT 53 YEARS	-330	
CONTACT ATTEMPTED		3386
NEW TEMPORARY OR PERMANENT REFUSALS	-380	
CONTACTED AND GAVE INFORMATION		3035
HOME VISIT		2989
POSTAL CONTACT ONLY		46
RESPONSE RATES		
OF THE WHOLE COHORT (3035/5362)		56.6%
OF THOSE ALIVE AND RESIDENT IN ENGLAND, SCOTLAND OR WALES (3035/4313)		70.4%
OF THOSE CONTACTED AT 53 YEARS (3035/3386)		89.6%
THOSE ALIVE AND RESIDENT AS A % OF THE ORIGINAL COHORT		80.4%

APPENDIX 2 PARAMETERS AND ESTIMATES OF THE BASIC MULTILEVEL MODELS

In the following equations, y_{ij} denotes the blood pressure (pulse pressure, systolic or diastolic blood pressure) of subject j (j=1, ..., N) on measurement occasion i (i=1,2,3) and x_{ij} the age at which that measurement was taken (36, 43 and 53 years). The fixed parameter β_0 represents the mean intercept or, in this example, the overall mean blood pressure at age 36 years. The fixed parameter β_1 represents the mean slope or equivalently the linear change in blood pressure for each yearly increase in age. β_2 - β_5 denote the fixed effects of the quadratic increase of blood pressure with age, sex, an interaction term for the linear change of blood pressure by sex and an interaction term for the quadratic increase of blood pressure by sex, respectively. The basic multilevel model for repeated measures of blood pressure at age 36, 43 and 53 years is then written as

$$y_{ij} \sim \mathrm{N}(XB, \Omega)$$

$$y_{ij} = \beta_{0ij}x_{0} + \beta_{1ij}x_{1ij} + \beta_{2}x_{2ij} + \beta_{3}x_{3j} + \beta_{4}x_{4ij} + \beta_{5}x_{5ij}$$

$$\beta_{0ij} = \beta_0 + u_{0j} + e_{0ij}$$

$$\beta_{1ij} = \beta_1 + u_{1j}$$

$$\begin{bmatrix} u_{0j} \\ u_{1j} \end{bmatrix} \sim \mathrm{N}(0, \Omega_u) : \Omega_u = \begin{bmatrix} \sigma^2_{u0} & \\ \sigma_{u10} & \sigma^2_{u1} \end{bmatrix}$$

$$\begin{bmatrix} e_{0ij} \\ e_{1ij} \end{bmatrix} \sim \mathrm{N}(0, \Omega_e) : \Omega_e = \begin{bmatrix} \sigma^2_{e0} & \\ \sigma_{e10} & 0 \end{bmatrix}$$

$$-2*log(like) = 24643.690$$

The parameters u_{0j} and u_{1j} are the random (between-individual) effects which allow each individual to have their own intercept and slope respectively and indicate the deviation of each individual's

intercept and slope from the mean intercept and slope. These "level 2" random effects parameters are assumed to be bivariate normal with mean 0 and variance defined by the variance-covariance matrix which has entries given by the variance of u_{0j} ($\text{var}(u_{0j})=\sigma^2_{u0}$), the variance of u_{1j} ($\text{var}(u_{1j})=\sigma^2_{u1}$) and the covariance between u_{0j} and u_{1j} ($\text{cov}(u_{0j},u_{1j})=\sigma_{u10}$). The within-individual ("level 1") variation e_{0ij} at age 36 years is also allowed to vary with age (e_{1ij}) and is assumed to be bivariate normally distributed, with mean 0 and variance defined by the variance-covariance matrix which has entries given by the variance of e_{0ij} ($\text{var}(e_{0ij})=\sigma^2_{e0}$), the variance of e_{1ij} ($\text{var}(e_{1ij})=\sigma^2_{e1}$) and the covariance between e_{0ij} and e_{1ij} ($\text{cov}(e_{0ij},e_{1ij})$. The variance σ^2_{e1} was set to 0, so that the level 1 variance increased linearly with age.

Estimates for the basic models including pulse pressure, systolic and diastolic blood pressure, respectively, are given below.

PULSE PRESSURE

$y_{ij} \sim N(XB, \Omega)$

$y_{ij} = \beta_{0ij}x_0 + \beta_{1ij}x_{1ij} + 0.066(0.005)x_{2ij} + -2.126(0.418)x_{3j} + 0.784(0.116)x_{4ij} + -0.046(0.006)x_{5ij}$

$\beta_{0ij} = 44.245(0.294) + u_{0j} + e_{0ij}$

$\beta_{1ij} = -0.625(0.082) + u_{1j}$

$$\begin{bmatrix} u_{0j} \\ u_{1j} \end{bmatrix} \sim N(0, \Omega_u) : \Omega_u = \begin{bmatrix} 36.593(3.883) & \\ -0.711(0.284) & 0.146(0.033) \end{bmatrix}$$

$$\begin{bmatrix} e_{0ij} \\ e_{1ij} \end{bmatrix} \sim N(0, \Omega_e) : \Omega_e = \begin{bmatrix} 86.036(3.756) & \\ 1.191(0.233) & 0 \end{bmatrix}$$

*-2*log(like)* = 68687.630

SYSTOLIC BLOOD PRESSURE

$y_{ij} \sim N(XB, \Omega)$

$y_{ij} = \beta_{0ij}x_0 + \beta_{1ij}x_{1ij} + 0.067(0.005)x_{2ij} + -5.427(0.548)x_{3j} + 0.474(0.136)x_{4ij} + -0.036(0.008)x_{5ij}$

$\beta_{0ij} = 122.718(0.386) + u_{0j} + e_{0ij}$

$\beta_{1ij} = -0.109(0.096) + u_{1j}$

$$\begin{bmatrix} u_{0j} \\ u_{1j} \end{bmatrix} \sim N(0, \Omega_u) : \Omega_u = \begin{bmatrix} 97.849(6.301) & \\ -0.160(0.430) & 0.468(0.050) \end{bmatrix}$$

$$\begin{bmatrix} e_{0ij} \\ e_{1ij} \end{bmatrix} \sim N(0, \Omega_e) : \Omega_e = \begin{bmatrix} 117.529(5.287) & \\ 1.267(0.330) & 0 \end{bmatrix}$$

*-2*log(like)* = 73504.520

DIASTOLIC BLOOD PRESSURE

$$y_{ij} \sim \mathrm{N}(XB, \Omega)$$

$$y_{ij} = \beta_{0ij}x_{0} + \beta_{1ij}x_{1ij} + \text{-3.616(0.418)}x_{2j} + \text{-0.131(0.032)}x_{3ij}$$

$$\beta_{0ij} = \text{78.454(0.295)} + u_{0j} + e_{0ij}$$

$$\beta_{1ij} = \text{0.524(0.023)} + u_{1j}$$

$$\begin{bmatrix} u_{0j} \\ u_{1j} \end{bmatrix} \sim \mathrm{N}(0, \Omega_u) : \Omega_u = \begin{bmatrix} \text{54.459(4.179)} & \\ \text{-0.477(0.265)} & \text{0.089(0.027)} \end{bmatrix}$$

$$\begin{bmatrix} e_{0ij} \\ e_{1ij} \end{bmatrix} \sim \mathrm{N}(0, \Omega_e) : \Omega_e = \begin{bmatrix} \text{97.384(3.622)} & \\ \text{-0.496(0.197)} & 0 \end{bmatrix}$$

$$-2*log(like) = \text{68251.630}$$

APPENDIX 3 PROJECT VIVA RESPONSE RATES AT THE 3 YEAR FOLLOW-UP

ORIGINAL COHORT (LIVE BIRTHS)		2128
NOT INPERSON ELIGIBLE (NO PREGNANCY FFQ) AND NOT IN IMMUNE SUBSTUDY	-177	
ELIGIBLE FOR 3 YEAR INPERSON VISIT		1951
DISENROLLED BEFORE 3 YEAR FOLLOW-UP	-97	
"REFUSED" TODDLER ENROLLMENT BEFORE 3 YEAR FOLLOW-UP	-275	
"UNENROLLED" AT 3 YEAR FOLLOW-UP	-37	
REFUSED TODDLER ENROLLMENT AT 3 YEAR FOLLOW-UP	-26	
MISSING VISIT FORMS – NO 3 YEAR VISIT	-29	
NO 3 YEAR DATA ("NOT YET")	-118	
CONTACTED AND GAVE INFORMATION		1369
POSTAL/ PHONE CONTACT ONLY		106
HOME VISIT		1263
MISSING BLOOD PRESSURE DATA	-92	
MISSING ATHROPOMETRY	-21	
PREMATURE BIRTHS	-17	
FINAL COHORT FOR ANALYSIS		1133
RESPONSE RATES		
OF THE WHOLE COHORT		53%
OF THOSE ELIGIBLE FOR THE 3 YEAR FOLLOW-UP		58%
OF THOSE ATTENDING THE 3 YEAR FOLLOW-UP		83%

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THESIS RELATED PUBLICATIONS

Chapter 4

Langenberg C, Hardy R, Kuh D, Wadsworth ME. Influence of height, leg and trunk length on pulse pressure, systolic and diastolic blood pressure. *J Hypertens* 2003; 21:537-43.

Chapter 5

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Chapter 10

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