

CARDIOVASCULAR MEDICINE

Associations of components of adult height with coronary heart disease in postmenopausal women: the British women's heart and health study

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Objective: To assess the associations between components of adult height and coronary heart disease (CHD) in postmenopausal women.

Methods: Cross sectional analysis of 4286 women randomly selected from 23 British towns. The association of components of adult height with prevalent CHD ($n = 694$) were assessed.

Results: Shorter stature, shorter leg length, and trunk length were all associated with CHD in age adjusted analyses. The association between trunk length and CHD was attenuated to the null with adjustment for smoking. The leg length–CHD association was independent of smoking, socioeconomic position in childhood and adulthood, birth weight, and other potential confounders. Insulin resistance did not appear to be an important mediating factor in the association between leg length and CHD. After full adjustment for all potential confounding factors the odds ratio (95% confidence interval) of CHD for a 1 SD (4.3 cm) increase in leg length was 0.84 (0.77 to 0.93) and the odds ratio for a 1 SD (0.05) increase in the leg to trunk ratio was 0.85 (0.79 to 0.95).

Conclusions: The specific association between leg length and CHD suggests that early life environmental exposures that influence skeletal growth also influence CHD risk in later life.

All stature is associated with decreased risk of coronary heart disease (CHD) independently of socioeconomic position or smoking behaviour.^{1, 2} Several plausible explanations exist for this association. Firstly, genetic factors that determine growth patterns may be associated with CHD risk. Secondly, coronary artery vessel diameter increases with height, and vessels with smaller diameters may result in clinical disease outcomes with relatively smaller amounts of atherosclerosis.¹ Thirdly, adult height shrinks with age and with general ill health and immobility, and so the height–CHD association may really be one of reverse causation.³ Fourthly, the association between height and CHD may simply be a reflection of the established birth weight–CHD association.⁴ Lastly, factors affecting childhood growth, such as infant feeding, childhood diet, and parental smoking, may also influence CHD risk and hence explain the link.⁵

In some studies the height–CHD association is attenuated to the null with control for lung function.⁶ However, lung function is itself adversely affected by a number of early life exposures.^{7–9} It is therefore possible that the height–CHD association is attenuated with adjustment for lung function because, to some extent, height and lung function are measures of similar adverse early life exposures. This may then be overadjustment.¹⁰

One way of further exploring the height–CHD association is to look at the specific associations of the components of height (leg length and trunk length) with CHD. Leg length, in particular (as opposed to trunk length), may be a useful biomarker of prepubertal environmental influences on childhood growth. This is because up until puberty a much greater proportion of the increase in total height is due to increases in leg length.^{5, 11} Further, the dramatic increases in height in industrialised countries over the past century appear to have arisen more from increases in leg length than in trunk growth.¹² These trends have occurred as result of

improvements in childhood circumstances—in particular improvements in nutrition and reductions in serious infections. If there is a specific association between leg length and CHD, it is unlikely to be explained by shrinkage and reverse causation, since shrinkage occurs mainly (due to osteoporotic collapse) in the trunk.

Few studies have assessed the association between components of adult height and CHD. In one study of middle aged men, leg length was the component of height that was responsible for the height–CHD association.¹³ In a second study, leg length measured in childhood (boys and girls aged 2–14 years) was also found to be inversely associated with CHD mortality over 52 years of follow up.¹⁴ Leg length has also been found to be specifically associated with insulin resistance and non-insulin dependent diabetes, with people with shorter legs being more insulin resistant and having a greater prevalence of diabetes.^{13, 15} It has been suggested that adverse early life exposures may increase CHD risk in later life by an effect on insulin resistance.¹⁶ However, to date few studies have assessed this possibility.

The aims of this study were: (1) to examine the association between components of adult height (leg length and trunk length) and CHD to determine whether the results in one previous study of middle aged men could be replicated in a study of older women; (2) to determine the effect of adjustment for lung function on the associations between components of adult height and CHD; and (3) to examine the role of insulin resistance as a mediating factor between these associations.

Abbreviations: CHD, coronary heart disease; CI, confidence interval; ELISA, enzyme linked immunosorbent assay; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; HOMA, homeostasis model assessment

METHODS

Full details of the selection of participants and measurements have been reported.^{15–17} Women aged 60–79 years were randomly selected from general practitioner lists in 23 British towns. A total of 4286 women (60% of those invited) participated and baseline data (self completed questionnaire, research nurse interview, physical examination, and primary care medical record review) were collected between April 1999 and March 2001. Local ethics committee approvals were obtained.

Prevalent CHD was defined as any participant with a primary care record of myocardial infarction or angina (including those with a history of a coronary artery bypass operation or angioplasty) or any participant who reported ever having a doctor diagnose one of these conditions.¹⁷ Cases of myocardial infarction were verified by the participant's medical practitioner according to World Health Organization criteria.¹⁸

Standing and seated height were measured, without shoes, with a Harpenden Stadiometer recording to the nearest millimetre. Trunk length was calculated as the seated height minus the height of the stool (407 mm). Leg length was taken as the standing height minus the trunk length. Weight was measured in light clothing without shoes to the nearest 0.1 kg with Soehnle portable scales. Waist circumference was taken as the midpoint between the lower rib and the iliac crest. Hip circumference was taken as the largest circumference below the waist.

Lung function was tested with a digital meter vitalograph indicating forced vital capacity (FVC) and forced expiratory volume in one second (FEV₁). The vitalograph was calibrated each day with a 1 litre syringe and automated so that results were adjusted for ambient temperature. For each assessment a research nurse demonstrated the technique to the participant. The participants were then given the opportunity to practice the procedure. They were then required to perform a minimum of three reproducible FVC measures (within 5% of maximum FVC produced). The output that produced the highest sum of FVC and FEV₁ was used in the analyses.

Blood samples were taken after a minimum of six hours' fast (except for diabetics who used insulin). Glucose and insulin were measured on fasting venous plasma samples. Insulin was measured with a specific enzyme linked immunosorbent assay (ELISA), which does not cross react with proinsulin.¹⁹ Insulin resistance was estimated according to the homeostasis model assessment (HOMA) as the product of fasting plasma glucose (mmol/l) and insulin (μ U/ml) divided by the constant 22.5.²⁰ Since HOMA scores are a less accurate reflection of insulin resistance among older diabetic patients,²¹ we did not calculate HOMA scores for women with diabetes. Total cholesterol, high density lipoprotein cholesterol, and triglyceride concentrations were measured on frozen serum samples with a Hitachi 747 analyser and standard reagents supplied by Roche Diagnostics. A Dinamap 1846SX vital sign monitor was used to measure blood pressure, which was taken as the mean of two measures obtained with the patient seated and relaxed.

Statistical analysis

Multiple logistic regression was used to examine associations of components of height with prevalent CHD. A series of models was constructed in which prevalent CHD was the outcome (dependent variable) and components of height (total height, leg length, trunk length, and leg to trunk ratio), entered as continuous standard deviation scaled variables, were the main explanatory variables.

The first three models were concerned with assessing the effect of potential confounding factors on the associations

(age, smoking and lung function, and social class). Age and lung function were entered as continuous variables, since they were linearly associated with prevalent CHD. Smoking (never, past, or current) and social class (I, professional; II, managerial and technical; III_{nm}, skilled manual; III_m, skilled manual; IV, partly skilled; V, unskilled; VI, armed forces; and the long term unemployed) were entered as dummy variables.

In the fourth model components of the insulin resistance syndrome were added. The aim was to assess whether there is evidence that these are important intermediaries on the causal pathway between leg length and CHD. Blood pressure, lipid measures, and waist to hip ratio were entered as continuous variables. Because HOMA scores were not estimated for women with diabetes, to enter full data on the spectrum of insulin resistance diabetes status in the multivariable models, a categorical variable combining both HOMA scores and diabetic status was created, with the first five categories defined by the fifths of HOMA scores (among women without diabetes) and a sixth category containing patients with diabetes. There was a strong linear positive association across these six categories of insulin resistance diabetes with CHD prevalence.

In the final model the possibility that considering FEV₁ as a confounding factor in the leg length–CHD association might result in overadjustment was assessed by modelling the associations adjusted for all potential confounding factors except FEV₁ (age, smoking, and social class). Likelihood ratio tests were used to test for interactions between covariates. No strong statistical evidence of interactions was found (all $p > 0.2$). HOMA scores and triglyceride concentrations were positively skewed. Geometric means are presented and logged triglyceride concentrations, which were normally distributed, were used in the regression models. In all analyses robust standard errors, which take into account possible clustering between participants from the same town, were used to estimate p values and 95% confidence intervals (CI).

RESULTS

As previously reported, compared with non-responders, responders were slightly younger and less likely to have experienced a stroke or to have diabetes.¹⁷ The prevalence of myocardial infarction and angina were the same for responders and non-responders.¹⁷ Of the 4286 women 694 had CHD, giving a prevalence of 16.2% (95% CI 15.1% to 17.3%); 80% of these cases were identified in both the medical record review and by self report of a doctor diagnosis, 13% were in the record review only, and 7% were identified by self report only. Of these 694 patients, 220 (31.7%) had a history of myocardial infarction and 470 (67.7%) had a history of angina but with no history of myocardial infarction.

Table 1 shows the age adjusted distributions of components of adult height, potential confounding factors, and potential explanatory factors for women with CHD and without CHD. Women with CHD were older, had shorter leg and trunk lengths, had lower FEV₁, were more obese, were more insulin resistant, had lower high density lipoprotein cholesterol concentrations and higher triglyceride concentrations, and were more likely to have ever smoked and to be from manual social classes in childhood and adulthood than women without CHD.

Table 2 shows the associations of each component of height with CHD before and after adjustment for possible explanatory or confounding factors. Only data for women with complete data on all variables in the final fully adjusted model ($n = 3496$) were analysed. There was no difference in the prevalence of CHD between those with complete data on

Table 1 Age adjusted means and prevalences (95% CIs) of participant characteristics by coronary heart disease (CHD) status

	Women with CHD (n = 694)	Women without CHD (n = 3592)	OR (95% CI) of CHD per SD increase in continuous variables and per exposure in dichotomous variables	p Value
Age (years) (1 SD = 5.5)	70.4 (70.0 to 70.8)	68.6 (68.4 to 68.8)	1.40 (1.29 to 1.52)	<0.001
Height (mm) (1 SD = 61.1)	1576.5 (1571.8 to 1581.2)	1589.7 (1587.7 to 1591.7)	0.79 (0.73 to 0.87)	<0.001
Leg length (mm) (1 SD = 41.1)	749.4 (746.2 to 752.6)	758.9 (757.5 to 760.3)	0.79 (0.72 to 0.86)	<0.001
Trunk length (mm) (1 SD = 35.7)	827.0 (824.3 to 829.7)	830.7 (829.5 to 831.9)	0.89 (0.82 to 0.98)	<0.001
BMI (kg/m ²) (1 SD = 5.0)	28.7 (28.3 to 29.1)	27.4 (27.3 to 27.6)	1.28 (1.18 to 1.39)	<0.001
Waist to hip ratio (1 SD = 0.07)	0.829 (0.823 to 0.834)	0.817 (0.815 to 0.820)	1.18 (1.08 to 1.28)	<0.001
HOMA score* (1 SD = 0.62)	1.93 (1.83 to 2.04)	1.62 (1.58 to 1.66)	1.33 (1.21 to 1.46)	<0.001
Triglycerides* (mmol/l) (1 SD = 0.46)	1.81 (1.74 to 1.87)	1.64 (1.62 to 1.67)	1.23 (1.13 to 1.34)	<0.001
HDLc (mmol/l) (1 SD = 0.46)	1.56 (1.52 to 1.59)	1.67 (1.66 to 1.69)	0.75 (0.68 to 0.83)	<0.001
Systolic BP (mm Hg) (1 SD = 25.2)	145.2 (143.4 to 147.3)	138.8 (137.9 to 139.7)	1.25 (1.15 to 1.35)	<0.001
FEV ₁ (l) (1 SD = 0.52)	1.85 (1.81 to 1.89)	2.00 (1.98 to 2.01)	0.71 (0.64 to 0.78)	<0.001
Ever smoked (%) (reference = never smoked)	48.9 (45.1 to 52.6)	43.8 (42.2 to 45.5)	1.23 (1.04 to 1.45)	<0.001
Manual social class in adulthood (%) (reference = non-manual)	63.5 (59.6 to 67.2)	50.5 (48.8 to 52.2)	1.73 (1.45 to 2.08)	<0.001
Manual social class in childhood (%) (reference = non-manual)	81.2 (77.8 to 84.2)	76.3 (74.8 to 77.7)	1.38 (1.10 to 1.73)	<0.001

All means and prevalences are age adjusted with the exception of age.

*Geometric means.

BMI, body mass index; BP, blood pressure; CI, confidence interval; FEV₁, forced expiratory volume in one second; HDLc, high density lipoprotein cholesterol; HOMA, homeostasis model assessment (insulin resistance); OR, odds ratio.

all of these variables and those without these complete data: age adjusted prevalence for those with complete data 15.9 (95% CI 14.6 to 16.9) versus 16.9 (95% CI 16.4 to 21.9) for those without complete data (p = 0.4). To further assess possible selection bias arising through missing data the age adjusted odds ratios in table 2 can be compared with those based on complete data in table 1. It can be seen that there is no difference in these values. In age adjusted analyses height, leg length, and trunk length were all inversely associated with CHD. The effects were stronger for leg length than for trunk length.

Adjustment for both smoking and FEV₁ attenuated all of the associations, though some association between leg length and CHD remained. Additional adjustment for childhood and adult social class had very little effect on any of the associations. Further adjustment for components of the insulin resistance syndrome slightly attenuated the leg length-CHD association but this was not pronounced, suggesting that insulin resistance and its associated metabolic risk factors may not be important mediating factors in the association between leg length and CHD. When the effect of each component of the insulin resistance syndrome on the association were examined separately the results did not differ substantially from those presented in table 2 for the effect of all components entered simultaneously in the model.

Both components of height were associated with FEV₁—the association between leg length and FEV₁ was slightly

greater than the association between trunk length and FEV₁. The age adjusted change in leg length for a 1 SD increase in FEV₁ was 12.1 mm (95% CI 10.8 to 13.5 mm) and that of trunk length was 10.3 mm (95% CI 9.2 to 11.4 mm). The final column of table 2 presents confounder adjusted, but without adjustment for FEV₁, odds ratios for the associations of each component of height. Removing FEV₁ from the models has very little effect on the associations between trunk length and CHD. However, the associations between leg length and the ratio of leg to trunk length and CHD are stronger than those in which FEV₁ is a covariate.

Of the 4286 participants, 1394 (33%) provided details of their birth weight. Those providing birth weight data were younger than those not providing these data (67.9 years versus 69.4 years) but there was no substantive difference in age adjusted prevalence of CHD between these two groups (age adjusted odds ratio of participants with data versus those without: 0.90 (95% CI 0.74 to 1.07), p = 0.15). In this subgroup of participants the age adjusted odds ratio for CHD for a 1 SD increase in leg length was 0.76 (95% CI 0.65 to 0.89). With further adjustment for birth weight this associations was essentially unaltered: 0.79 (95% CI 0.67 to 0.93).

When the analyses were repeated separately for myocardial infarction as the outcome and angina (without history of infarction) as the outcome of interest the results were essentially unchanged from those presented.

Table 2 Odds ratios (95% CIs) for CHD for a 1 SD increase of height, leg length, and trunk length with adjustment for possible explanatory and confounding variables (n = 3469)

Per 1 SD increase of:	Adjustment				
	Age	Age, smoking, FEV ₁	Age, smoking, FEV ₁ , social class*	Age, smoking, FEV ₁ , social class*, insulin resistance†	Age, smoking, social class*
Height (1 SD = 6.4 cm)	0.79 (0.72 to 0.87)	0.87 (0.79 to 0.97)	0.89 (0.80 to 0.98)	0.86 (0.77 to 0.95)	0.80 (0.73 to 0.89)
Leg length (1 SD = 4.3 cm)	0.80 (0.73 to 0.87)	0.86 (0.78 to 0.94)	0.87 (0.79 to 0.96)	0.89 (0.81 to 0.98)	0.84 (0.77 to 0.93)
Trunk length (1 SD = 3.6 cm)	0.89 (0.81 to 0.98)	0.97 (0.88 to 1.07)	0.97 (0.88 to 1.07)	0.97 (0.89 to 1.07)	0.99 (0.92 to 1.09)
Leg to trunk ratio, 1 SD = 0.05	0.88 (0.80 to 0.96)	0.90 (0.82 to 0.98)	0.91 (0.83 to 0.99)	0.93 (0.85 to 1.02)	0.85 (0.79 to 0.95)

*Adult and childhood social class; †components of the insulin resistance syndrome: high density lipoprotein cholesterol and triglyceride concentrations, systolic blood pressure, waist to hip ratio, HOMA diabetes status.

DISCUSSION

There is evidence that exposures operating from before birth and through childhood are important in the aetiology of CHD.²² However, there are few prospective studies with good measures of exposures across different stages of the life course and with follow up to adult disease outcomes, particularly among women and focusing on CHD.^{5–23} As a result there has been growing interest in the use of adult biomarkers of childhood exposures. Adult stature and in particular adult leg length appear to be useful biomarkers of childhood exposures that affect adult CHD risk.⁵ In this study leg length and trunk length were both inversely associated with prevalent CHD in simple age adjusted models. The association between trunk length and CHD was fully explained by the confounding effects of smoking. The leg length–CHD association was not explained by confounding. Adjustment for lung function attenuated the leg length–CHD association, though some inverse association remained. The finding that adjustment for FEV₁ attenuates the leg length–CHD association supports the hypothesis that these two may, in part, be markers of similar adverse early life environmental exposures, since lung function would not directly affect adult leg length. In this context adjustment for FEV₁ probably causes overadjustment. The best unconfounded estimate of the association between leg length and CHD in this study is 0.82 (95% CI 0.74 to 0.90) and for the association between the ratio of leg length to trunk length and CHD is 0.84 (95% CI 0.78 to 0.93), as presented in the final column of table 2.

Study strengths and limitations

An important strength of this study is the availability of detailed anthropometric data and lung function tests. Our response rate (60%) is moderate but consistent with other contemporary large epidemiological surveys.²⁴ As reported previously respondents to our study were slightly younger than non-respondents and less likely to have a primary care medical record of a stroke (though the prevalence of CHD among responders and non-responders was the same).¹⁷ Our findings would only be biased if the associations were in the opposite direction to those presented here, or were non-existent, among non-responders, both of which seem unlikely. Our study was cross sectional and a potential limitation is survivor bias. This would be important if large numbers of participants had died of CHD before the age of 70 years (the mean age of study participants). Death from CHD among women before the age of 70 years is relatively uncommon—of 49 363 deaths among women aged 30–69 years in England and Wales in 1999, 3826 (7.8%) were caused by CHD.²⁵ Further, studies assessing the association between height and survival have reported inconsistent results, but two large studies found no effect of height on survival.^{26–27} Survivor bias is therefore unlikely to explain our results. In cross sectional analyses we are unable to assess the change in the association between leg length and CHD over time and the results from this study of older, largely (99%) white women may not be generalisable to other groups. One previous study has, however, shown that leg length is the specific component of height that is associated with CHD in middle aged men.¹³

How our results help in explaining the height–CHD associations

The specific association of leg length with CHD does not support the height–CHD association being caused by increased vessel diameter in taller people or to differential shrinkage, since both of these explanations would have similar effects, or even stronger effects, in the trunk–CHD association. The effect is unlikely to be a reflection of the birth weight–CHD association, since adjustment for birth

weight did not importantly alter the association between leg length and CHD. Our study did not determine whether genetic effects that influence childhood growth are also associated with CHD risk. However, the findings of a recent study with adult anthropometric data on two generations suggest that genetic factors are not important in the associations between components of height and CHD risk factors (blood pressure and cholesterol), since adjustment for parental height had very little effect on these associations.¹⁰

Implications

A specific association between leg length and CHD probably reflects an association between adverse prepubertal environmental factors that affect growth and result in increased CHD risk in later life. Our results suggest that childhood exposures, as well as intrauterine exposures, influence adult CHD. Adjustment for components of the insulin resistance syndrome only slightly attenuated the leg length–CHD association. It is possible that the effect of components of the insulin resistance syndrome on these associations is weakened by regression dilution.²⁸ Further, we do not have measures on procoagulation, fibrinolysis, and inflammatory markers, which may be part of the insulin resistance syndrome.^{29–30} In one study leg length has been shown to be specifically associated with fibrinogen concentrations.¹³ Had we been able to include these in our final multivariable model it is possible that further attenuation would have resulted. However, our findings do not provide strong support for the hypothesis that insulin resistance and its associated metabolic risk factors explain the association between early life risk factors and CHD in adulthood.

Leg length appears to be a biomarker for factors acting specifically in the prepubertal period. Breast feeding, high energy diets at age 2, and affluent social circumstances are all specifically associated with longer leg length.^{31–33} Furthermore, growth is stunted among children whose parents smoke.^{34–36} Thus, these factors—infant and childhood nutrition and parental smoking—may be important early life risk factors for CHD. Our results emphasise the importance of early life exposures in the aetiology of CHD and the need for programmes aimed at improving child health for the prevention of CHD. Further research should attempt to identify specific modifiable childhood exposures that increase CHD risk.

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Persistent nicorandil induced oral ulceration

C M Healy, Y Smyth, S R Flint

Four patients with nicorandil induced ulceration are described. Nicorandil induced ulcers are very painful and distressing for patients. Clinically they appear as large, deep, persistent ulcers that have punched out edges. They are poorly responsive to topical steroids and usually require alteration of nicorandil treatment. The ulceration tends to occur at high doses and all four cases reported here were on doses of 40 mg per day or greater. In these situations reduction of nicorandil dose may be sufficient to promote ulcer healing and prevent further recurrence. However, complete cessation of nicorandil may be required.

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Spontaneous coronary artery dissection involving the left main stem: assessment by intravascular ultrasound

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This case report describes the devastating consequences of spontaneous coronary dissection in a 36 year old female patient who otherwise had a normal coronary arteriogram.

Intravascular ultrasound showed coronary artery dissection and intramural haematoma at the left main stem coronary artery. Acute coronary syndrome developed and subsequently surgical revascularisation was performed successfully.

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Long term survival in primary pulmonary hypertension

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The mean survival of patients with severe primary pulmonary hypertension (PPH) is < 3 years without appropriate treatment. There are no long term reports on the spontaneous course of mild PPH over a longer period. Stable long term follow up is described of a 39 year old patient with PPH without treatment over a 30 year period. PPH had been diagnosed 30 years previously after right heart catheterisation (mean pulmonary artery pressure 35 mm Hg) and 30 years later, repeated measurements showed nearly unchanged haemodynamic parameters. Further examinations confirmed the diagnosis of PPH. It is suggested that PPH with modestly limited physical activity does not always seem to coincide with progression of the disease and, therefore, it may be feasible to withhold treatment while closely monitoring these patients.

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