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# Short Stature and Heart Disease: Nature or Nurture?

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Kee F (Department of Epidemiology, the Queen's University of Belfast, Mulhouse, Royal Victoria Hospital, Belfast BT12 6BJ, Northern Ireland), Nicaud V, Tiret L, Evans A, O'Reilly D and de Backer G for The EARS Group. Short stature and heart disease: nature or nurture? *International Journal of Epidemiology* 1997; **26**: 748–756.

**Background.** Previous studies have demonstrated that short men are at increased risk of coronary heart disease (CHD). It has been suggested that the inverse relationship between adult height and CHD risk could be attributable to the fetal origins of CHD.

**Method.** The hypothesis that transmissible factors could partly explain the association has been tested in the European Atherosclerosis Research Studies (I and II), in which a sample of healthy university students (cases), drawn from 18 European countries (male:  $n = 721$ ; female:  $n = 330$ ), whose fathers had had a documented myocardial infarction before the age of 55 years were compared to age- and sex-matched controls (male:  $n = 1056$ ; female:  $n = 638$ ). Information about lifestyle and birthweight was collected and a fasting blood sample was obtained from each subject.

**Results.** In females there was no difference in height between cases and controls but male cases were shorter than controls, on average by one cm, both in the EARS I ( $P = 0.02$ ) and the EARS II studies ( $P = 0.01$ ) and this difference was independent of reported birthweight and the fathers' educational attainment. In logistic regression the relationship was independent of the subjects' apolipoprotein B level, the other major biological discriminator of case-control status.

**Conclusion.** In men at least, height appears to be an independent transmissible risk factor for CHD.

**Keywords:** coronary heart disease, risk, short stature transmissibility

A number of case-control and cohort studies, from Britain,<sup>1–4</sup> Europe,<sup>5–8</sup> and more recently from north America<sup>9–11</sup> have demonstrated that adult height is a risk factor for coronary heart disease (CHD). The association persists even after adjusting for other risk factors such as smoking, blood pressure, serum cholesterol, body mass index and lung function.<sup>3,10,12</sup> While it is clear that early environment influences attained height,<sup>13</sup> the relationship between height and CHD risk survives adjustment for childhood socioeconomic circumstances.<sup>6,14</sup> Birthweight is also related to adult height and body mass index,<sup>3,13,15</sup> but few of the studies relating CHD risk and adult height have adjusted directly for birthweight.<sup>3</sup> It has been suggested that the inverse

relationship between adult height and CHD risk could be attributable to the fetal origins of CHD.<sup>16</sup> However, the fetal origins hypothesis, as proposed by Barker, refers to fetal undernutrition as the main cause of impaired fetal growth. While it has been demonstrated, particularly in animal studies, that undernutrition *in utero* leads to persisting changes in a range of metabolic and physiological parameters, it is very likely that genetic factors influence fetal growth and participate in the 'early programming' of CHD. Their possible role has not yet been properly examined, even in two recent twin studies.<sup>17,18</sup>

The height-risk relationship could, on the other hand, be somewhat artefactual if disease processes in adult life were responsible for loss of height. For example, the height-CHD risk association in the Whitehall Civil Servants' Study was eliminated after exclusion of subjects with cardiovascular disease at baseline, offering, it was claimed, indirect support for a 'shrinkage' hypothesis.<sup>4</sup>

The European Atherosclerosis Research Study (EARS I & II) offers a design to investigate whether the relationship between height and CHD risk has a transmissible component. As part of a large case-control study of transmissible risk factors for CHD, healthy

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This paper was prepared on behalf of the group by: Frank Kee, Laurence Tiret, Viviane Nicaud, A Evans, Denis O'Reilly, Guy de Backer.

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students were recruited from 18 European universities.<sup>19,20</sup> Cases were university students with a paternal history of myocardial infarction below the age of 55 years, who were compared to age- and sex-matched controls. The design of the study, therefore, allows us to assess the potential contribution of heritable factors to the risk of CHD, assessed in a group of healthy subjects of relatively homogeneous socioeconomic background from countries at very different baseline risks.

## METHODS

A detailed description of the design of the EARS I study is presented elsewhere.<sup>21</sup> Briefly, cases were students, aged 18–26 years, whose fathers had had a proven myocardial infarction (MI) before the age of 55 years, recruited from 14 university student populations in Europe. The participants were from the following universities: Innsbruck, Austria; Ghent, Belgium; Aarhus, Denmark; Helsinki and Oulu, Finland; Bordeaux, France; Hamburg, Germany; Naples, Italy; Barcelona and Reus, Spain; Goteberg, Sweden; Zurich, Switzerland; Bristol and Glasgow, UK. Two age- and sex-matched controls were recruited for each case from the corresponding student register. Details of lifestyle, dietary intake, personal medical history, family history and physiological measurements such as blood pressure, height and weight were obtained using standardized questionnaires and protocols. A second sample of students was recruited in the EARS II study, which differed from the earlier study in seeking additionally to assess case-control differences in post-prandial lipid metabolism. The sampling strategy adopted the same case-control definitions but only male subjects were recruited in EARS II and there was only one control per case. In all, 71 subjects participated in both studies but they have been excluded from the EARS I data set. The recruitment centres in Goteberg, Bordeaux, Barcelona and Innsbruck did not participate in EARS II but they were replaced by centres in: Belfast, Northern Ireland; Tallinn, Estonia; Lisbon, Portugal; Athens, Greece. Birthweight data were collected in EARS II questionnaires but not in EARS I. Height was measured twice and the mean of the two measurements was used in the analysis.

This report, therefore, relates to 314 male and 330 female cases and 641 male and 638 controls from EARS I and 407 male cases and 415 controls from EARS II.

The analyses were performed using the statistical software SAS (SAS Inst Inc, Cary, NC). All analyses were adjusted for age and centre. The homogeneity of the case-control differences in height or birthweight

across different categories was tested by introducing an interaction term in the analysis of variance.

## RESULTS

In both studies, the mean age of cases and controls was similar (22.7 years versus 22.7 years, and 22.8 versus 22.9 years respectively). In both studies male students with a paternal history of premature myocardial infarction were significantly shorter than control students by approximately 1 cm, ( $P = 0.02$  and  $P = 0.01$  respectively). Table 1a gives the mean heights in cases and controls in each centre while Table 1b provides the  $\beta$  coefficients from the logistic regression. In EARS I, this difference was homogeneous across populations but in EARS II there was a significant interaction between population and status, mainly due to the differences in Glasgow and Athens being in the opposite direction. Female cases and controls were not significantly different in height. The remaining analyses relate only to male subjects.

In the EARS II study, there was no significant difference in the birthweights of cases and controls (Table 1). Birthweight was not available for 64 cases and 65 controls. There was no significant difference between cases and controls in the ascertainment sources for birthweight (Table 2), which was based on mother's recall for 66% and 65% of subjects respectively, and there was no difference in the mean birthweight according to ascertainment source. Dividing the sample into quartiles based on birthweight, there was an obvious relationship between birthweight and attained height, smaller babies tending to become shorter adults (Figure 1), but the case-control difference in height was of similar magnitude across the quartiles. Because social class is a possible confounding factor, case-control differences in birthweight and height were examined in different groups according to the fathers' educational attainment (Tables 3a and 3b). In EARS I and in EARS II, the case-control differences in height were of similar magnitude in all categories.

The case-control differences in height were retested in a multiple logistic regression after first adjusting for age, centre, father's education and birthweight but this did not modify the results, ( $P = 0.01$ ). Additional adjustment for the mothers' educational attainment had no significant effect on the result (data not shown).

Other biological risk factors for heart disease have been studied in EARS. Their associations with height and birthweight are shown in Table 4. Height was negatively correlated with a number of risk factors, including apolipoprotein B (apo B), low density lipoprotein (LDL) cholesterol, triglycerides, and insulin levels.

TABLE 1a Mean height (SEM) in EARS I and EARS II and mean birthweight (SEM) in EARS II according to centre and case/control status

Centres	EARS I Height (cm)				EARS II Height (cm)		EARS II Birthweight (g)	
	Cases M = 314; F = 330 Mean (SEM)		Controls M = 641; F = 638 Mean (SEM)		Cases n = 407 Mean (SEM)	Controls n = 415 Mean (SEM)	Cases n = 343 Mean (SEM)	Controls n = 350 Mean (SEM)
	Males	Females	Males	Females				
Oulu	180.8 (1.6)	166.4 (1.1)	183.3 (1.1)	167.7 (0.8)	180.9 (1.3)	181.7 (1.3)	3687 (114)	3633 (114)
Helsinki	178.1 (1.2)	169.2 (1.6)	180.3 (0.8)	165.7 (1.1)	179.7 (1.1)	180.1 (1.1)	3495 (97)	3687 (94)
Talinn	–	–	–	–	180.7 (1.1)	181.5 (1.0)	3663 (96)	3483 (90)
Goteburg	183.6 (1.7)	168.7 (1.1)	184.3 (1.2)	169.3 (0.8)	–	–	–	–
Aarhus	179.0 (1.3)	169.1 (1.2)	183.5 (0.8)	170.4 (0.8)	182.8 (1.1)	184.5 (1.1)	3504 (98)	3550 (98)
Hamburg	184.6 (1.1)	171.6 (1.1)	184.7 (0.8)	170.3 (0.9)	180.9 (1.1)	184.0 (1.1)	<i>(missing data)</i>	
Glasgow	176.4 (1.4)	159.5 (1.5)	176.9 (1.0)	163.2 (1.0)	179.7 (1.1)	176.8 (1.1)	3538 (97)	3344 (100)
Belfast	–	–	–	–	175.8 (1.1)	180.6 (1.1)	3368 (96)	3318 (96)
Bristol	178.8 (1.5)	163.7 (2.4)	181.0 (1.2)	165.7 (1.8)	177.9 (1.3)	182.2 (1.3)	3165 (115)	3129 (112)
Ghent	180.6 (1.1)	166.0 (1.1)	179.8 (0.7)	167.4 (0.8)	178.4 (1.1)	178.4 (1.1)	3526 (100)	3464 (100)
Innsbruck	179.9 (1.2)	168.1 (1.4)	182.2 (0.8)	167.5 (1.0)	–	–	–	–
Zurich	180.0 (1.4)	166.1 (1.1)	180.4 (1.1)	167.0 (0.9)	180.5 (1.0)	181.1 (1.0)	3365 (91)	3512 (91)
Reus	174.2 (1.6)	159.7 (1.0)	174.2 (1.1)	160.0 (0.7)	175.6 (1.1)	176.6 (1.1)	3462 (98)	3449 (96)
Naples	178.4 (1.6)	160.8 (1.4)	175.1 (1.2)	160.8 (1.1)	174.9 (1.1)	178.2 (1.1)	3578 (100)	3731 (98)
Bordeaux	177.3 (1.6)	164.1 (1.0)	177.9 (1.0)	163.0 (0.7)	–	–	–	–
Barcelona	175.3 (1.5)	160.8 (1.2)	176.8 (1.2)	162.2 (0.9)	–	–	–	–
Lisbon	–	–	–	–	173.6 (1.5)	173.8 (1.5)	3409 (126)	3436 (126)
Athens	–	–	–	–	180.0 (1.2)	176.5 (1.2)	<i>(missing data)</i>	
All	179.0 (0.4)	165.3 (0.4)	180.1 (0.3)	165.7 (0.3)	178.7 (0.3)	179.7 (0.3)	3480 (29)	3478 (29)

Significance of tests:

\*Case/control: height:  $P = 0.02$  (EARS I/males; NS/females),  $P = 0.01$  (EARS II); birthweight, not significant.

Heterogeneity of case/control difference across centres: height: (EARS I) not significant; (EARS II)  $P = 0.01$ ; birthweight, not significant.

TABLE 1b \*Parameter estimates in final model

	Beta coefficient	Standard error	Standardized $\beta$ coefficient	$P$ -value
EARS I (height)	-0.0295	0.0112	-0.1148	0.0086
EARS II (height)	-0.0296	0.0116	-0.1086	0.0106

There was a weak negative correlation with systolic blood pressure only in cases. The correlations of these factors with birthweight was generally weaker and non-significant. Previous analyses have demonstrated that from among those correlated with height, the serum apo B and triglyceride levels, in these EARS recruits at least, appear to be the most important transmissible risk factors for heart disease.<sup>20,21</sup> As these variables were significantly correlated with height, we have re-assessed the strength of the relationship between case-control status and height after adjusting for apo B and

triglyceride levels in a logistic regression. This makes little difference to the comparison, the  $\beta$  coefficients for height, before and after adjustment respectively, being  $-0.030$  and  $-0.026$  in EARS I and  $-0.030$  and  $-0.024$  in EARS II.

## DISCUSSION

The mechanism linking short stature to increased CHD risk is unknown and the balance between genetic and environmental determinants is unclear. It is beyond dispute that environmental factors, probably related to early nutrition, account for a substantial proportion of variation in height in the population. Such an explanation accords well with the observed trends in the height of schoolchildren over the last few decades.<sup>22</sup> While height is normally regarded as a reflection of early life experience, its association with CHD, independent of other known risk factors, is often assumed to arise from the same period. That socioeconomic confounding is not the only explanation for such findings is

TABLE 2 Origin of the estimation of birthweight in EARS II and mean birthweight (SEM) according to the origin of the information

	Cases n = 343		Controls n = 350	
	%	Mean birthweight (SEM)	%	Mean birthweight (SEM)
By document recording	32.1	3465 (54)	32.6	3554 (53)
By mother memory recall	66.4	3477 (37)	65.4	3455 (36)
Other and unspecified	1.5	3872 (239)	2.0	3030 (202)

Case/control difference in the origin of the information: NS.

Birthweight according to the origin of the information: NS.

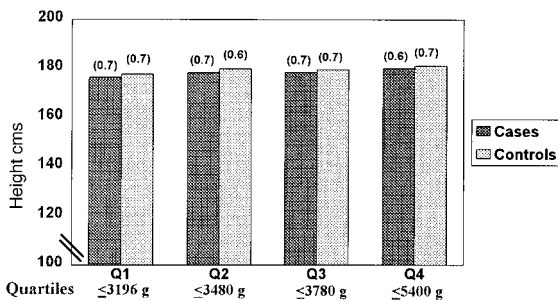


FIGURE 1 Mean height (SEM) in cases and controls according to quartiles of birthweight in EARS II (adjusted for age and centre)

Association between height and birthweight (cases and controls pooled):  $P = 0.001$ .

Heterogeneity of the case/control difference across quartiles of birthweight: NS.

suggested by the fact that very similar associations were observed between height and cardiovascular disease in the socioeconomically homogeneous US population of male physicians.<sup>10</sup>

The hypothesis that early life experience may influence the risk of CHD was supported by Barker's studies showing, in selected cohorts, that low birthweight and weight at one year were associated with an adverse profile for a number of known risk factors such as impaired glucose intolerance, blood pressure and fibrinogen levels.<sup>23,24</sup> However, the early origin of CHD remains controversial and the biological mechanisms behind the associations are still unclear.<sup>25</sup> A recent twin study from Sweden showed no excess of CHD mortality in twins compared to the general Swedish population

despite lower than average birthweight of twins.<sup>17</sup> This finding was considered by the authors to refute the fetal-origins hypothesis although, paradoxically, the same study showed that the shorter twin was more likely to die of heart disease than the taller.<sup>17</sup> As this effect was observed within monozygotic (MZ) and dizygotic (DZ) twins, a genetic effect was not suggested. A better test of a genetic effect, however, would have been a comparison of within-pair discordance in CHD mortality between MZ and DZ twins for the same within-pair difference in height. On the other hand Allison *et al.*<sup>18</sup> demonstrated a strong correlation between intra-pair differences in birthweight and the intra-pair differences in adult height for 699 MZ twin pairs from Minnesota and concluded that the tracking of birthweight and height was more environmentally than genetically determined. Again, this conclusion might have been better sustained had there been a comparison of within-pair differences in adult height between MZ and DZ twins for the same within-pair difference in birthweight. Moreover, whether the birthweight of a twin reflects intra-uterine growth and nutrition in the same way as for a non-twin is open to question and studies of disparate design should be compared with caution.<sup>26</sup>

The results of the present study provide new insight into the relationship between height and CHD risk by showing that this relationship is, at least in part, transmissible. Although our offspring sample is probably not representative of the entire population, the consistency of the findings across a wide spectrum of cultural backgrounds in these European populations, and the replication of the case-control differences in two independent samples (EARS I and II) tends to reinforce this finding. Likewise, though we acknowledged in an earlier publication<sup>27</sup> that the centres had varying participation rates we doubt whether, in the light of the broad consistency of the findings across centres, selection bias could explain our results. If this were so one would presumably have to posit that participation rates were differentially related to height (i.e. that non-recruited cases were taller than non-recruited controls) and we doubt whether this is credible. The question of whether the transmissible character of this relationship has a genetic or an environmental basis cannot be directly answered, although several arguments are rather against an environmental origin. Firstly, after adjusting for the father's or the mother's educational attainment, we found little reduction in the difference in height between students with and without a paternal history of premature myocardial infarction. Moreover, the case-control differences were very homogeneous across the different categories of parent's educational attainment. We were unable to control directly for social class at

TABLE 3a Mean height and birthweight (SEM) in cases and controls according to father's educational level (adjusted for age and centre)

	EARS I (Males) Height (cm)		EARS II Height (cm)		EARS II Birthweight (g)	
	Cases n = 314 Mean (SEM)	Controls n = 641 Mean (SEM)	Cases n = 348 Mean (SEM)	Controls n = 357 Mean (SEM)	Cases n = 343 Mean (SEM)	Controls n = 350 Mean (SEM)
Father's education						
University	179.4 (0.7)	180.6 (0.5)	178.5 (0.6)	179.9 (0.5)	3400 (51)	3450 (47)
Intermediate	179.4 (0.7)	179.9 (0.5)	178.4 (0.7)	179.0 (0.7)	3555 (59)	3426 (58)
Secondary school	179.1 (0.7)	179.9 (0.6)	178.2 (0.7)	180.3 (0.7)	3497 (57)	3559 (61)
Primary school	178.0 (0.9)	179.7 (0.6)	178.6 (0.8)	178.9 (0.9)	3505 (72)	3521 (75)
Significance of height differences across father's education classes* (cases and controls pooled)	NS		NS		NS	
Heterogeneity of case/control difference across categories	NS		NS		NS	

TABLE 3b \*Parameter estimates in final model

	$\beta$ coefficient	Standard error	Standardized $\beta$ coefficient	P-value
Education	0.0823	0.0734	0.0496	0.2624
Birthweight	0.00006	0.0015	0.0198	0.6545
Height	-0.0348	0.0127	-0.1273	0.0061

birth, but our proxy variable, educational attainment, has been shown to be strongly related to social class differences in health.<sup>13</sup> Although we cannot rule out a more subtle difference in social class between cases and controls that would not be accounted for, the relative homogeneity of the university student population, as reflected in particular, by the lack of difference between cases and controls with respect to lifestyle habits such as cigarette consumption, alcohol intake, physical activity or the fatty acid composition of the diet, further argues against a major influence of environment on the observed difference.<sup>28</sup> On the other hand, a genetic difference is quite plausible given the well-known genetic component of height. This does not preclude a possible role of environment in the relationship between height and myocardial infarction, but merely indicates that among all factors influencing this relationship, an inherited contribution is plausible.

The possibility of transmission by the mother, however, cannot be ruled out. If there was assortive mating

for height, spouses of shorter men would themselves be shorter and would transmit, either genetically or during intra-uterine development, this characteristic to their offspring. According to this scenario, the shorter stature of the offspring of men who had suffered a myocardial infarction would be independent of the mechanism linking father's height to disease.

In the studies of Barker *et al.* birthweight was an intermediate link in the relationship between height and disease, the interpretation being that it was a marker of fetal growth. In the EARS II study we did not find any case-control difference in birthweight although there was a clear relationship between birthweight and height. Furthermore the magnitude of the case-control differences in height was comparable across the quartiles of birthweight indicating that birthweight was neither a significant confounder nor an interacting factor. This may indicate that the balance of transmissible and non-transmissible factors acting on myocardial infarction risk is different for height and birthweight. While it is clear that there are common determinants to height and birthweight, it is likely that birthweight is more directly influenced than adult height by fetal nutrition, gestational age and maternal factors. Moreover, birthweight is only a crude summary measure of fetal growth. Interestingly, in a recent study of 20 year olds from Croatia, one of the significant predictors of systolic blood pressure, was father's height, a relationship which was independent of birthweight.<sup>29</sup>

Associations between CHD risk factors such as those shown in Table 4 and birthweight have been demonstrated

TABLE 4 Pearson partial correlation coefficients of height and birthweight with blood pressure, biochemical variables, height, weight and body mass index

	EARS I (Males) Height <sup>a</sup>		EARS II Height <sup>a</sup>		EARS II* Birthweight <sup>b</sup>		EARS II Height <sup>c</sup>	
	Cases n = 314	Controls n = 641	Cases n = 348	Controls n = 357	Cases n = 343	Controls n = 350	Cases n = 348	Controls n = 357
Systolic BP	-0.12*	-0.06	-0.11*	-0.04	-0.10	-0.09	-0.10	-0.02
Diastolic BP	-0.01	0.00	-0.04	-0.00	-0.07	0.07	-0.03	0.00
Pulse pressure	-0.11	-0.06	-0.08	-0.04	-0.04	-0.15	-0.08	-0.03
Total cholesterol	-0.24***	-0.17***	-0.28***	-0.22***	-0.12*	-0.03	-0.26***	-0.22**
LDL cholesterol	-0.22***	-0.18***	-0.30***	-0.21***	-0.14*	0.02	-0.28***	-0.23**
Apolipoprotein B	-0.29***	-0.18***	-0.29***	-0.23***	-0.12*	0.04	-0.27***	-0.24**
Triglycerides (log)	-0.24***	-0.16***	-0.15**	-0.20***	-0.12*	-0.04	-0.15**	-0.20**
Insulin	-0.16**	-0.15***	-0.11	-0.08	-0.13*	-0.12*	-0.10	-0.06
Glucose	-0.07	-0.04	-0.00	-0.06	-0.16**	0.01	-0.00	-0.07
Fibrinogen	0.04	-0.08	-	-	-	-	-	-
Height	-	-	-	-	0.19***	0.18***	-	-
Weight	-	-	-	-	0.11*	0.18***	-	-
Body mass index	-	-	-	-	0.02	0.10	-	-

<sup>a</sup> Correlations were adjusted for age, centre and weight.

<sup>b</sup> Correlations were adjusted for age and centre.

<sup>c</sup> Correlations were adjusted for age, centre, weight and birthweight.

\*  $P \leq 0.05$ , \*\*  $P \leq 0.01$ , \*\*\*  $P \leq 0.001$ .

There was no significant heterogeneity between cases and controls for any correlation.

in several reports by Barker<sup>30-32</sup> and others.<sup>33-35</sup> For some risk factors at least, a significant inverse relationship with birthweight has not been consistently shown.<sup>36,37</sup> In the study by Bergstrom, for example, after controlling for current weight and height, the relationship between high density lipoprotein (HDL) cholesterol and birthweight became non-significant.<sup>32</sup> Alvarsson *et al.*<sup>38</sup> on the other hand, found that the insulin response to glucose was associated with height but not birthweight. We have demonstrated their independent association with attained height. In view of the problem of multi-collinearity, one should caution against over-interpretation of the strength of the associations. Nevertheless, while several of these risk factors have a familial component and have exhibited significant differences between offspring with and without a paternal history of myocardial infarction,<sup>20,21</sup> our results suggest that the relationship between height and CHD risk is independent of these associations. Other mechanisms have thus been posited to explain the height-risk relationship. Some authors have suggested that shorter men are more prone to develop CHD because they have smaller coronary arteries,<sup>39,40</sup> a feature which might influence blood pressure.

A number of caveats to our conclusions must be borne in mind. Firstly, data are not available on gestational age and this may have introduced some 'noise' into our

statistical adjustment for birthweight. However, previous studies linking CHD risk and birthweight have shown that the relationship is observed both before and after adjustment for gestational age.<sup>27,41</sup>

Secondly, documentary evidence of birthweight could only be obtained in a minority of cases. However, this is unlikely to have been a major source of bias, since the methods of ascertainment in both cases and controls (the proportions based on mother's recall or on documentary evidence), were the same. Several other reports have found that mothers' recall is not subject to substantial bias.<sup>37,42,43</sup>

The vast majority of previous studies on this subject have related only to men. However, one study demonstrated that the self-reported height of 910 women with myocardial infarction was significantly less than that of 1140 controls, even after adjusting for other major risk factors.<sup>9</sup> The absence of a similar association in female participants of the EARS study may be a chance finding but given that male and female offspring share many common environmental exposures, including diet, our results may point to heritable factors underlying the height-risk relationship that are more strongly expressed in males than females.

In conclusion, the results of the EARS I and EARS II studies suggest that there is a transmissible component

in the relationship linking height and CHD risk. This transmissible component seems to have little impact on birthweight. Future studies should more formally test a genetic hypothesis linking height and CHD risk, perhaps by examining candidate polymorphisms, particularly those associated with genes responsible for regulating growth factors.

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