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*Short Report*

**Height loss and future coronary heart disease in London: the Whitehall II study**

*Running title: Height loss & coronary heart disease*

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## **Abstract**

*Background.* While several plausible biological mechanisms have been advanced for the association between greater physical stature and lower coronary heart disease (CHD) risk in prospective cohort studies, the importance of one of the principal artifactual explanations – reverse causality due to shrinkage – remains unresolved. To explore this issue, studies with repeat measurements of height are required, however, to date, such data have been lacking.

*Methods.* We analysed data from the Whitehall II prospective cohort study of 3802 men and 1615 women who participated in a physical examination in 1985/88, had their height re-measured in 1997/99, and were then followed for fatal and non-fatal CHD.

*Results.* A mean follow-up of 7.4 years after the second height measurement gave rise to 69 CHD events in men (18 in women). After adjustment for baseline CHD risk factors, greater loss of physical stature between survey and resurvey was associated with an increased risk of CHD in men (hazard ratio; 95% CI for a one SD increase: 1.24; 1.00, 1.53) but not women (0.93; 0.58, 1.50).

*Conclusions.* **It is possible that reverse causality due to shrinkage may contribute to the inverse association between a single measurement of height and later CHD in other studies.**

## **Background**

A series of prospective cohort studies have shown that people who are shorter in middle- and older-age experience an increased risk of future coronary heart disease (CHD).[1] While several biologically plausible mechanisms for this effect have been advanced, the importance of one of the principal artifactual explanations – reverse causality due to shrinkage – remains largely unresolved.[1] That is, the early stages of disease, which are undetectable at study entry, could lead to reductions in height and increase risk of coronary heart disease, thus generating the observed inverse stature-CHD associations.

Three observations provide mixed support for the reverse causality explanation. First, if reverse causality is generating the inverse relation between height with CHD in cohort studies, the magnitude of any height-CHD gradient should diminish over time. This is because individuals with sub-clinical disease at study entry would be expected to die in the earlier stages of follow-up, so contributing a declining proportion of person years to the risk set. In reports from studies with between 20[2] and 36[3] years of follow-up, the absence of a height-CHD effect provides some support for reverse causality. In a second approach, student populations who had their height assessed at University enrolment in early adulthood, when this measurement can largely be regarded as being pre-morbid and therefore pre-shrinkage, were followed for mortality experience. These studies, in contrast, showed greater height was associated with reduced CHD risk[4, 5] so failing to support the reverse causality explanation.

The third observation comes from studies that have examined the relation between components of height – trunk and leg length – and future CHD.[6, 7] With the trunk, but not the leg length, being subject to shrinkage due to osteoporotic vertical collapse, an inverse association of the former but not the latter with CHD would be anticipated if reverse causality was a likely explanation for the inverse overall height-CHD association. The finding that leg length was, in fact, the component of height that

showed the strongest inverse relation with CHD provides evidence against the reverse causality explanation,[6, 7] although this is not a universal finding.[8]

With height measured on only one occasion in these published analyses, none of the three approaches directly explores, nor quantifies, reverse causality due to shrinkage. In the only study of which we are aware to examine the relation of height loss between two time points and subsequent CHD, there was a suggestion of increased risk in **older** men undergoing the greatest degree of shrinkage.[9] We further examine the relation of height loss with later CHD in participants in a prospective cohort study who had their height measured on two occasions. In doing so, we provide the first examination of CHD and height loss in women who typically experience a greater degree of decline in physical stature over time than men.[10]

## **Methods**

Details of the ongoing Whitehall II prospective cohort study have been reported previously.[11] In brief, the baseline survey took place in 1985/88 (Phase 1) when 6895 men and 3413 women aged 35-55 (mean 44.4 years) entered the study. All odd-numbered Phases include a clinical examination in addition to a self-completion questionnaire. In the present analyses, we utilise data from Phases 1 and 5, the latter of which took place in 1997/99 (participants aged 45-69; mean 55.7 years). The University College London ethics committee reviewed and approved the study, and written informed consent was obtained from each participant.

At baseline and Phase 5, height was measured in bare feet to the nearest 1 mm using a stadiometer with the participant standing erect with head in the Frankfort plane. CHD risk factors at baseline were measured using standard protocols and included socioeconomic position (high, intermediate, low - as derived from civil service employment grade), current smoking (yes, no), systolic blood pressure

(mmHg), total cholesterol (mmol/L), diabetes (self-reported) and, in women, menopausal status (self-reported). Body mass index (BMI; kg/m<sup>2</sup>) was computed using the usual formulae (weight[kg]/height [m]<sup>2</sup>).

#### *Ascertainment of CHD*

CHD was based on CHD death or non-fatal myocardial infarction. The records of all study members were traced and flagged using the procedures of the National Health Service Central Registry which led to a notification of death. Potential cases of definite, non-fatal myocardial infarction were ascertained by questionnaire items on chest pain and/or doctor's diagnosis of heart attack, an approach we have used elsewhere.[8] Details of physician diagnosis and investigation results were sought from clinical records for all potential cases of myocardial infarction. Twelve-lead resting electrocardiograms were performed at phases 5 and 7 (Siemens Mingorec) and assigned Minnesota codes. Based on these data, non-fatal myocardial infarction was defined according to MONICA criteria.[12]

#### *Statistical analyses*

Analyses were restricted to study members who provided complete data at Phases 1 and 5, and whose for whom CHD status at follow-up after Phase 5 could be ascertained (3802 men and 1615 women). Using the baseline characteristics, relative to those excluded from the analysis (n=4891), participants included in the analytical sample were younger (44.1 years vs. 44.8 years), more likely to be men (70.2% vs. 63.2%), less likely to be from low SES groups (16.5% vs. 29.5%), and taller (average height 172.6 cm vs. 170.6 cm) (p-value for differences all <0.0001).

In the analyses, the exposures of interest were height at baseline, height at Phase 5, average height loss per decade between these two time points (calculated as: (absolute difference in height[cm] / duration

of follow-up[yr.] \* 10 yr.), and the proportional height loss per decade between these two time points (calculated as: (height loss[cm] / height at baseline[cm]) \* 100% \* (10 yr. / duration of follow-up[yr.]).

## **Results**

As expected, on average, women (163.0 [SD=6.5] cm) were shorter than men (176.6 [SD=6.7] cm) at baseline examination, and the rate of height loss per decade was also greater in women (mean absolute loss 0.52 cm [SD 0.90]) than men (mean height loss 0.35 [SD 0.80] cm; p=value for difference<0.0001). Proportional loss in height per decade was 0.3% (SD=0.6) in women and 0.2% (SD=0.5) in men (p-value for difference<0.0001).

In table 1 we present the associations of absolute height loss between baseline and resurvey with baseline CHD risk factors. As anticipated, age was strongly associated with height loss such that men and women who were older at baseline experienced a greater reduction in stature. Height loss was socially patterned in men – but not women – whereby the more disadvantaged based on their employment grade had a greater height loss. Study members of both sexes who smoked, those with diabetes (men only), and those who were overweight experienced greater height loss. Height loss was not associated with menopausal status in women.

**Table 1. The association of baseline characteristics with rate of height loss between baseline and resurvey: the Whitehall II study<sup>a</sup>**

Baseline characteristic	Overall (mean [SD] or N [%])	Height loss (95% CI) <sup>a</sup> , cm		P-value
<b>Men (N=3802)</b>				
Age, yr	44.0 (6.0)			
35-39	1107 (29.1)	Ref.		
40-44	1069 (28.1)	0.24	(0.18, 0.30)	<0.0001
45-49	721 (19.0)	0.46	(0.39, 0.53)	<0.0001
50-55	905 (23.8)	0.80	(0.73, 0.87)	<0.0001
Systolic blood pressure, mm Hg	124 (14)	-0.00	(-0.03, 0.02)	0.79
BMI, kg/m <sup>2</sup> <sup>b</sup>	24.5 (2.9)	0.02	(0.00, 0.05)	0.04
Total cholesterol, mmol/l	5.9 (1.1)	0.01	(-0.02, 0.03)	0.50
SES, %				
High	1560 (41.0)	Ref.		
Medium	2004 (52.7)	0.08	(0.03, 0.13)	
Low	238 (6.3)	0.18	(0.08, 0.28)	<0.0001
Diabetes				
No	3780 (99.4)	Ref.		
Yes	22 (0.6)	0.34	(0.03, 0.66)	0.03
Current smoking, %				
No	3301 (86.8)	Ref.		
Yes	501 (13.2)	0.09	(0.02, 0.16)	0.01
<b>Women (N=1615)</b>				
Age, yr	44.6 (6.0)			<0.0001
35-39	432 (26.7)	Ref.		
40-44	410 (25.4)	0.24	(0.13, 0.35)	<0.0001
45-49	342 (21.2)	0.54	(0.42, 0.65)	<0.0001
50-55	431 (26.7)	0.88	(0.76, 0.99)	<0.0001
Systolic blood pressure, mm Hg	119 (15)	0.02	(-0.02, 0.06)	0.29
BMI, kg/m <sup>2</sup>	24.3 (4.0)	0.06	(0.02, 0.10)	0.004
Total cholesterol, mmol/l	5.8 (1.1)	0.01	(-0.03, 0.06)	0.54
SES, % <sup>b</sup>				
High	246 (15.2)	Ref.		
Medium	712 (44.1)	-0.05	(-0.17, 0.07)	
Low	657 (40.7)	-0.06	(-0.18, 0.07)	0.43
Diabetes, %				
No	1605 (99.4)	Ref.		
Yes	10 (0.6)	-0.19	(-0.71, 0.32)	0.46
Current smoking, %				
No	1329 (82.3)	Ref.		
Yes	286 (17.7)	0.02	(-0.09, 0.13)	0.70
Post menopause, %				
No	1409 (69.7)	Ref.		
Yes	456 (30.3)	0.06	(-0.11, 0.13)	0.87

<sup>a</sup> Age-adjusted rate of absolute height loss in cm per decade for 1 SD increase in continuous risk factors (systolic blood pressure, BMI and total cholesterol), and age-adjusted difference in height loss per decade from reference group for categorical risk factors (age group [not age-adjusted], socio-economic status, diabetes, smoking, and menopausal status [women only]). Analyses are based on linear regression models.



A mean follow-up of 7.4 years in 3802 Whitehall II men gave rise to 69 CHD events, while in the 1615 women there were 18 such cases (table 2). In women, but not men, there was a negative association between height at both baseline and resurvey with later CHD in age-adjusted analyses (p for sex interaction=0.05 for the height-CHD association for height at both baseline and at resurvey), although this association was attenuated when other covariates were added to the multivariable model. Conversely, height loss between these two time points was associated with CHD in men but not women (p for sex interaction 0.85). The height loss-CHD gradient was essentially unchanged after multiple adjustment, and when height loss was modeled for proportional rather than absolute change.

**Table 2. Hazard ratios<sup>c</sup> (95% CI) for the relationship of a 1 SD increase in height and height loss with future CHD: the Whitehall II study**

	Age-adjusted <sup>a</sup>	Age- + baseline risk factor <sup>b</sup> -adjusted
<b>Men (N=3802, 69 events)</b>		
Height at baseline	0.94 (0.75, 1.19)	0.94 (0.81, 1.09)
Height at resurvey	0.91 (0.72, 1.15)	0.99 (0.78, 1.26)
Rate of absolute height loss between baseline and resurvey <sup>c</sup>	1.27 (1.03, 1.58)	1.24 (1.00, 1.53)
<b>Rate of proportional height loss between baseline and resurvey<sup>d</sup></b>	<b>1.27 (1.03, 1.58)</b>	<b>1.24 (1.00, 1.53)</b>
<b>Women (N=1615, 18 events)</b>		
Height at baseline	0.61 (0.39, 0.94)	0.65 (0.41, 1.03)
Height at resurvey	0.59 (0.38, 0.93)	0.64 (0.40, 1.03)
Rate of absolute height loss between baseline and resurvey	1.02 (0.66, 1.58)	0.93 (0.58, 1.50)
<b>Rate of proportional height loss between baseline and resurvey</b>	<b>1.02 (0.66, 1.58)</b>	<b>0.96 (0.60, 1.52)</b>

<sup>a</sup>Age at resurvey. <sup>b</sup>Adjusted for baseline measures of socio-economic status, smoking, total cholesterol, systolic blood pressure, body mass index and diabetes. <sup>c</sup>Units are cm per decade; comparison is 1 SD increase. <sup>d</sup>Units are percent reduction in height per decade; comparison is 1 SD increase. <sup>e</sup>Cox proportional hazards regression was used to compute these hazard ratios with accompanying 95% confidence intervals.

## Conclusion

In the present analyses, there was some evidence that loss of physical stature between survey and resurvey around a decade later was associated with an increased risk of CHD in men. This provides some support for the suggestion that height loss associated with pre-existing morbidity may contribute to the inverse relationship between a single measurement of height and later CHD reported in a number of studies.[13-15] We did not, however, make the same observations in women. This may be due to the low number of CHD events in this group. This notwithstanding, there were negative relationships of both baseline and resurvey height with incident CHD.

Results from the present cohort are consistent with those from the British Regional Heart Study of older men,[9] the only other study of which we are aware to have examined height loss and future CHD risk. Our findings also accord with a related literature on osteoporosis, a condition which has recently been postulated to have a shared aetiology with cardiovascular disease.[16] Thus, as well as having an unfavorable level of traditional risk factors for CHD (raised blood cholesterol, blood pressure and blood glucose, smoking), people with evidence of osteoporosis also experience higher rates of cardiovascular disease events than those with normal bone mineral density. However, given that the average absolute height loss in the Whitehall II study over a decade (0.52 cm in women, 0.35 cm in men) is much less pronounced than that seen in osteoporosis (>6 cm),[17] this is unlikely to be the sole explanation for the elevated CHD risk. That the rate of height loss is low in this population is likely to be due to the occupational nature of the cohort which, by definition, contains a greater proportion of healthy individuals than the general population (the so called 'healthy worker' effect). Of further mechanisms worthy of exploration, given the suggested association of vitamin D with both CHD[18] and loss of physical stature,[19] it is plausible that vitamin D levels mediate the height loss-CHD link.

In conclusion, our findings suggest that it is possible that reverse causality due to shrinkage may have contributed to the inverse association between a single measurement of height and later CHD.

## **What this paper adds ‘box’**

### **What is already known on this subject?**

- While several plausible biological mechanisms have been advanced for the association between greater physical stature and lower CHD risk in prospective cohort studies, the importance of one of the principal artifactual explanations – reverse causality due to shrinkage – remains unresolved.
- To explore this issue, studies with repeat measurements of height are required, however, to date, such data have been lacking.

### **What does this study add?**

- This is the first examination of CHD and height loss in women who typically experience a greater degree of decline in physical stature over time than men.
- Greater loss of physical stature between survey and resurvey was associated with an increased risk of CHD in men but not women
- These results suggest that reverse causality due to shrinkage may contribute to the inverse association between a single measurement of height and later CHD in other studies.

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