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Is leg length a biomarker of childhood conditions in older Chinese women? The Guangzhou Biobank Cohort Study

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ABSTRACT

Objective: In developed western populations longer legs have been shown to be a biomarker of better early childhood conditions. It was hypothesised that in transitioning populations better childhood conditions may bring forward puberty and thus decrease leg length, counteracting the overall positive effect of a favourable childhood environment on leg growth.

Design: Structural equation modelling was used to assess the interrelationship of age, education, father's job, age of menarche and leg length in a cross-sectional sample of 7273 Chinese women aged at least 50 years from the Guangzhou Biobank Cohort Study.

Results: Leg length had no significant association with education or father's occupation on bivariable testing. After including age of menarche in the model, education was associated with longer legs (0.45 cm longer per 10 years of education, 95% CI 0.20 to 0.71). Education was also associated with younger age of menarche (1.21 years younger per 10 years of education, 95% CI 1.09 to 1.34), which was in turn associated with shorter legs (0.23 cm shorter per year of menarche earlier, 95% CI 0.18 to 0.27).

Conclusions: In older Chinese women leg length is not a universal biomarker of childhood conditions, when proxied by her educational level and father's occupation. Nutritionally driven epigenetic influences operating over generations may constrain growth in very recently developed populations. Given the impact of childhood conditions on health, and the dearth of long-term records outside the industrialised world, a greater understanding of the influences on growth in the developing world is required.

Environmental factors throughout the life course have long been recognised as relevant to adult health.[1] Early life exposures have been shown to increase the risk of many adult chronic diseases.[2] Relationships between early life conditions and long-term health are most easily explored in established long-term prospective cohorts or by using record linkage to follow up historical cohorts. These are, however, scarce and limited resources that largely do not exist outside of postindustrial economies, which precludes potentially key evidence from countries with very different childhood exposures and patterns of adult disease. Biomarkers of childhood exposures that can be assessed in adults provide an alternative approach for elucidating relationships between childhood conditions and adult health within a reasonable time frame in more recently developed or developing populations.

Leg length has been demonstrated to be a reliable biomarker of better early childhood conditions,[3–5] in developed countries where improved living conditions over many generations since the Industrial Revolution have been reflected in gradual increases in height, mainly attributable to longer legs.[6] Moreover, improved childhood conditions have been reflected in increases in the tempo of sexual maturation[6 7] resulting in earlier puberty, although in women the secular trend may have plateaued at a physiological minimum.[6] Correspondingly low childhood socioeconomic status (proxied by own education or father's social class) is usually associated with shorter height,[8–11] although the association with older age of menarche may be more obvious in developing settings.[12–14] Outside of the postindustrialised world the historically more recent improvements in living standards mean that improved childhood conditions may affect both the tempo of maturation and the amount of growth, potentially making leg length a less sensitive marker of childhood conditions in these populations, because the higher levels of oestrogen associated with earlier puberty cause growth of the long bones in particular to cease.[15 16] Very sudden improvements in living conditions between generations can bring forward puberty and thereby decrease leg length, as seen in children adopted from developing to developed countries.[17 18] These children are typically growth restricted at adoption, then often experience catch-up growth that may trigger early puberty,[19] in which skeletal age advances beyond chronological age and skeletal growth ceases at an earlier chronological age than would otherwise occur. Premature termination of skeletal growth mainly affects the legs. To determine the validity of leg length as a biomarker of childhood conditions outside of long-term industrialised populations, we used data from Guangzhou, the capital of Guangdong province in southern China.

Sociohistorical context

China is currently experiencing very rapid economic growth. Before the establishment of The People's Republic of China (PRC) in 1949, however, living standards were similar to pre-industrial Europe.[20 21] Some growth around the treaty ports along the eastern seaboard (eg Shanghai and to a lesser extent Guangzhou) in the first half of the 20th century was reported,[22 23] but there was little industrialisation in Guangzhou.[24] Male height in southern China in the early 20th century was similar to height in France at its pre-industrial nadir.[25–28] Therefore for older adults currently living in Guangzhou, the stage of economic development during childhood was probably similar to pre-industrial or the very early stages of industrial development in Europe around the late 18th or early 19th century.

Hypothesis

Figure 1 shows the models used to investigate our hypothesis that the relationship between leg length and childhood conditions might be affected by age of menarche in this setting. First, components of height only were related to childhood conditions (model a). Second, childhood conditions impacted both leg length and age of menarche, and age of menarche in turn impacted leg length (model b).

MATERIALS AND METHODS

The Guangzhou Biobank Cohort Study is an ongoing collaboration between the Guangzhou No. 12 Hospital, and the Universities of Hong Kong and Birmingham, which was established to examine determinants of health prospectively, and has been described in detail elsewhere.[29] Briefly, recruitment of participants aged 50 years and over draws from the Guangzhou Health and Happiness Association for the Respectable Elders (GHHARE), a community social and welfare association unofficially aligned with the municipal government whose membership is open to anyone for a monthly fee of ¥4 (US50 cents). Approximately 7% of permanent Guangzhou residents aged 50 years and over are members of GHHARE, of whom 11% were selected for this study. Our participants have similar rates of diabetes and hypertension to a nationally representative urban sample of the same age.[29] Participants underwent a half-day detailed medical interview and a physical examination in 2003–2004. The Guangzhou Medical Ethics Committee of the Chinese Medical Association approved the study and all participants gave written, informed consent.

Components of height and age of menarche

Standing height and sitting height were measured to the nearest 0.1 cm in light clothing without shoes. One research nurse was allocated to height measurement throughout the study and followed a detailed protocol using one standard set of equipment and the same low stool for sitting height. Initial training was provided by the principal investigators. Leg length was taken as the difference between standing height and sitting height. Age of menarche was recorded in years.

Height in older individuals is not always a good estimator of stature at adulthood, as a result of shrinkage with age and ill-health, such as osteoporosis, which mainly affects the trunk. Leg length is less subject to change during adulthood. Age of menarche is potentially subject to random recall bias. Reliability was confirmed 6 months into recruitment by recalling 200 randomly selected participants. The intraclass correlation coefficient for age of menarche was 0.92. The kappa value for education was 0.90.

Childhood living conditions

Measures of childhood living conditions, such as diet, housing, sanitation or clothing, were not available for these women. In developing countries low family socioeconomic status reduces the child's educational attainment,[30] because of the expense of education and of foregoing an economic contribution to the household. China was similar to other developing countries before 1949, and social restructuring after the establishment of the People's Republic of China did not eliminate inequalities in education until possibly the Cultural Revolution,[31 32] when almost all these women had completed their education. We used the woman's highest school level reached and her father's occupation as proxies for childhood conditions. There is no commonly used classification for Chinese occupations. We classified occupations as manual (agricultural worker, factory worker, sales and service worker) and non-manual (military and police, administrator/manager and professional/technical).

Statistical analysis

Multiple linear regression was used to assess the trends in height and its components by age, education and age of menarche. Structural equation modelling (SEM) was used to assess the interrelationships between age, childhood living conditions, age of menarche and each component of height. We used the two models described previously in fig 1. First, we retained education, father's job and birth year as separate observed variables, with education a continuous variable representing the approximate number of years of education for each level of attainment, as in table 1. We used a weighted least squares estimate, because father's job was dichotomous. Second, we combined education, father's job and year of birth into a latent variable representing childhood conditions.

We examined whether relationships were consistent across age groups (<65 years and $\geqslant 65$ years), from the significance of interaction terms and the heterogeneity of effect across strata. Results were considered statistically significant when two-tailed $p<0.05$.

Almost half of the women (49.4%) were unable to give a classifiable father's occupation. Multiple imputation is the statistical gold standard in this situation; as the assumptions required for validity of a complete case analysis are a superset of those required for validity of a multiple imputation analysis.[33] Father's occupation was predicted on the basis of a flexible additive regression model with predictive mean matching[34] incorporating data on age, education, longest held occupation, current personal income, leg length, seated height and age of menarche. We imputed missing values 10 times and analysed the 10 complete datasets separately. We summarised the results into single estimated beta-coefficients with confidence intervals (CI) and p values adjusted for the missing data uncertainty.[33] For comparison we also carried out a complete case analysis and an analysis without father's occupation.

RESULTS

Of the 7349 women recruited, 22 were missing leg length and 54 were missing age at menarche, giving 99% (7273) with complete data on the variables of interest apart from father's job. The women were aged from 50 to 93 years, with a mean of 64.0 years and a standard deviation (SD) of 6.0 years. The mean age of menarche was 15.4 years (SD 2.1 years).

Table 1 shows the associations of age (expressed as birth years), education, father's job and age of menarche with height and its components. For simplicity the early ages of menarche (12 years or less) and the late ages of menarche (19 years and older) were grouped. Leg length had little relationship with age for those born up until 1949, although the very small number born after 1950 appeared to have longer legs. This difference was, however, not statistically significant. Education had little relationship with leg length for the majority of women (79.4%)

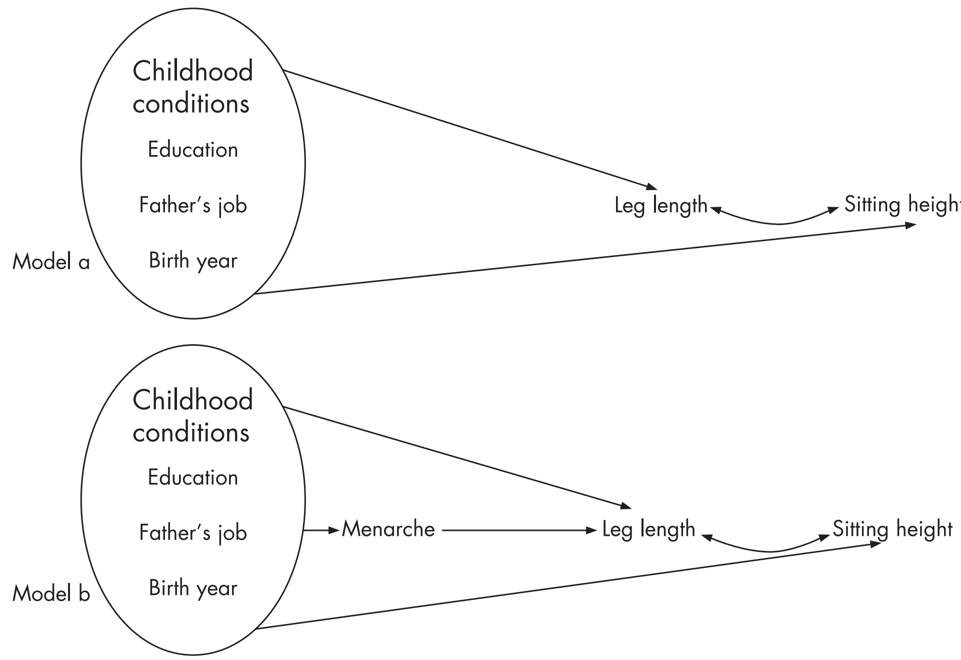


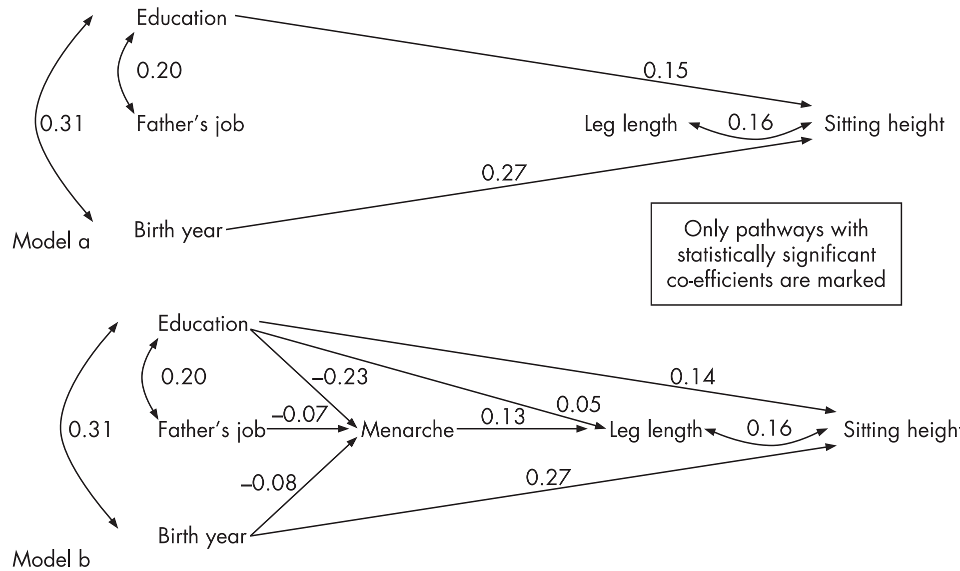
Figure 1 Possible models linking childhood conditions to components of height.

whose highest educational level was less than primary (17%), primary (40%) or junior middle school (22%). In these three groups leg length was almost identical and lowest in the middle group with primary education. For the minority of women with higher levels of education, however, leg length increased with education. Nevertheless, the overall linear trend was not

Table 1 Mean height and its components by age, education, father's job and age of menarche for 7273 women in the Guangzhou Biobank Cohort Study

	Proportion (%) in each group	Height (cm)	Leg length	Sitting height
Birth year				
1924 and earlier	0.9	149.3	70.2	79.1
1925–9	4.9	150.5	70.7	79.9
1930–4	18.3	151.6	70.7	80.9
1935–9	27.5	152.4	70.6	81.8
1940–4	25.0	153.1	70.5	82.6
1945–9	25.9	154.0	70.6	83.4
1950–>	0.9	155.6	71.3	84.3
p Value for linear trend*		<0.001	0.93	<0.001
Highest educational level (years)				
Less than primary (~0.5)	17.1	151.4	70.6	80.8
Primary (~6)	40.3	153.5	70.5	82.0
Junior middle school (~9)	22.1	153.2	70.6	82.6
Senior middle school (~12)	15.0	153.7	70.7	83.1
Senior technical college (~15)	3.2	154.4	70.8	83.5
University (~16)	2.4	154.3	71.0	83.3
p Value for linear trend*		<0.001	0.12	<0.001
Father's job				
Manual	76.2	152.7	70.6	82.1
Non-manual	23.8	152.9	70.5	82.4
p Value		0.64	0.41	0.07
Age of menarche (years)				
⩽12	6.4	152.1	69.6	82.5
13	14.7	152.7	70.2	82.5
14	15.2	152.8	70.4	82.4
15	18.1	152.5	70.4	82.2
16	17.2	153.1	70.4	82.3
17	11.7	153.2	70.7	82.1
18	10.8	152.7	71.1	81.7
19+	6.0	152.5	71.3	81.2
p Value for linear trend*		0.09	<0.001	<0.001

Figure 2 Structural equation models with corresponding correlation coefficients for models relating childhood conditions to components of height, without (model a) and with (model b) age of menarche included, for 7273 women in the Guangzhou Biobank Cohort Study.



statistically significant, nor was a comparison between the two most educated groups and the rest (p value 0.09). Father's job was not associated with leg length. In contrast, younger age and more education were associated with greater height and greater sitting height. In addition, younger age of menarche was statistically significantly associated with shorter legs and greater sitting height.

Figure 2 shows the interrelationships between childhood conditions, age and components of height, without age of menarche (model a) and including age of menarche (model b), from an SEM using observed variables. For clarity only pathways with statistically significant correlation coefficients ($p<0.05$) are marked and their correlation coefficients given. The corresponding regression coefficients with their 95% CI are in table 2 (model b only).

Without considering age of menarche (model a), leg length was unrelated to education, father's job or birth year, but increased sitting height was associated with more education and later birth year. After including age of menarche (model b), more education was significantly associated with longer legs: 0.45 cm longer per additional 10 years of education (95% CI 0.20 to 0.71). More education, a non-manual father and later birth year (ie younger age) were also associated with younger age of menarche. Age of menarche was 1.21 years younger (95% CI 1.09 to 1.34) per additional 10 years of education, 0.32 years younger (95% CI 0.16 to 0.48) for those with non-manual rather than manual fathers and 0.28 years younger per decade of birth later (95% CI 0.20 to 0.36). Younger age of menarche was in turn associated with shorter legs: 0.23 cm shorter (95% CI 0.18 to 0.27) per year of menarche earlier. The association of better childhood conditions with younger age of menarche, and in turn shorter legs, thus obscured the relationship between better childhood conditions and longer legs, which only became apparent when age of menarche was included (model b). There was no evidence of different associations by age group (<65 or ⩾65 years) in model b, in which p values for the interaction term of education with age group were more than 0.3 for menarche, more than 0.9 for leg length and greater than 0.5 for sitting height.

Models with childhood conditions as a latent variable dependent on education, father's job and year of birth produced broadly similar results. These models did not, however, fit well and were not investigated further.

Models using all participants with complete data produced similar results, as did models without father's occupation (see appendix 1).

DISCUSSION

In this cohort of women, better childhood conditions, proxied by own education and father's occupation, were associated with greater sitting height and younger age of menarche. Better childhood conditions were not apparently directly associated with leg length, because these same exposures were also associated with younger age of menarche, which resulted in

Table 2 Changes in age of menarche and components of height with education, father's job and age in 7273 Chinese women in the Guangzhou Biobank Cohort Study in the full model including age of menarche (model b)

	Age of menarche		Leg length		Sitting height	
	Difference (years) (95% CI)	Correlation coefficient	Difference (cm) (95% CI)	Correlation coefficient	Difference (cm) (95% CI)	Correlation coefficient
Education (per 10 years)	−1.21 (−1.34 to −1.09)	−0.23	0.45 (0.20 to 0.71)	0.05	1.16 (0.94 to 1.37)	0.14
p Value		<0.001		<0.001		<0.001
Father's job (non-manual compared with manual)	−0.32 (−0.48 to −0.16)	−0.07	−0.09 (−0.43 to 0.24)	−0.01	0.07 (−0.22 to 0.35)	0.01
p Value		<0.001		0.57		0.64
Birth year (per decade younger)	−0.28 (−0.36 to −0.20)	−0.08	−0.07 (−0.10 to 0.23)	0.01	1.47 (1.35 to 1.60)	0.27
p Value		<0.001		0.42		<0.001
Age of menarche (per year older)			0.23 (0.18 to 0.27)	0.13	−0.02 (−0.06 to 0.01)	−0.02
p Value				<0.001		0.18

CI, Confidence interval.

shorter legs. Once age of menarche was included in the structural equation model, higher levels of education were associated with longer legs.

Our observation that earlier menarche was associated with shorter legs is long known,[35] supported by evidence from large numbers of women,[36] and is biologically plausible, through the biphasic action of oestrogen. Low levels of oestrogen promote growth; higher levels cause the epiphyses to fuse and growth of the long bones in particular to cease.[15]

Our observation that higher socioeconomic status was associated with earlier menarche is consistent with observations from Hong Kong, which was largely peopled after 1945 by migrants from Guangzhou or the surrounding province of Guangdong. In girls from approximately the same birth years as this cohort, younger age of menarche was associated with higher parental socioeconomic status.[14]

On the other hand, our finding that the effect of better childhood conditions on leg length was masked by the same set of environmental exposures promoting earlier menarche is unique. To our knowledge no previous studies have examined the relationship between adult leg length, age of menarche and childhood conditions in societies at a similarly early stage of economic development as this cohort. We know of no studies investigating the validity of own education and father's occupation as proxies of childhood conditions in a similar setting. Childhood diet, clothing and housing or parental resources such as a bicycle, watch or sewing machine might be better proxies. We cannot rule out the possibility that our findings are a result of the inadequacies of our proxies of childhood conditions, although these proxies were associated with younger age of menarche, and intergenerational maintenance of privilege remains in China.[31 32 37]

Historically, trends in age of menarche and height have been "strikingly different",[6] with falls in age of menarche taking place over a shorter time span than increases in height. These different time trends at an ecological level are consistent with better living conditions preferentially promoting earlier sexual maturity at the early stages of economic development. In the early stages of industrialisation in the west in the late 18th and early 19th century height unexpectedly stagnated or declined, which has been interpreted as individual living conditions declining contrary to average levels,[38 39] but could also have been because better living conditions produced earlier sexual maturity rather than greater height.

The precise mechanisms controlling linear growth and the onset of puberty are poorly understood. Age and size at maturity are life history traits, with developmental plasticity and susceptibility to environmentally determined trade-offs.[40] Animal experiments show that maternal nutrition can impact growth and health over several subsequent generations.[41] Epigenetic mechanisms have evolved to maximise maternal–offspring co-adaptations, which in species in which the offspring require maternal resources postnatally would include the regulation of postnatal as well as prenatal growth.[42 43] Epigenetically determined growth regulation during early life growth phases could take several generations to "wear off". In the ethnically similar but economically developed population of Hong Kong, growth faltering has been observed during late infancy.[44]

We speculate that epigenetic influences operating in early life may restrain linear growth in women from very recently developed populations, making leg length a less good biomarker of early life conditions. Instead, biomarkers of childhood conditions may be epidemiologically stage specific, with leg length more sensitive at later stages of economic development, and age of menarche more sensitive at earlier stages. These speculations have corresponding implications for interpreting the impact of childhood conditions on cardiovascular risk. In recently developed populations, a lack of association between leg length and cardiovascular risk, as has been observed[45 46] (different from the protective effect in long-term industrialised countries),[47–51] does not necessarily imply that better childhood conditions are not protective. On the other hand, investigation of the impact of age of menarche on cardiovascular risk in these recently developed populations could provide key aetiological insights, in particular, if as in long-term industrialised countries early puberty is associated with increased cardiovascular risk.[52–55]

Limitations

There are a number of potential limitations. First, leg length may be more prone to measurement error than sitting height, as it was calculated as the difference between standing and sitting height, each with their own variances, which would attenuate associations, for which our large sample compensates. Second, women recalled age of menarche, with its usual caveat of reporting bias, and caution in its interpretation.[56] Random misclassification would again attenuate associations. Third, we used SEM, although one measure of childhood conditions was dichotomous. SEM is usually robust to violations of its assumptions in large samples. In addition, we could not obtain a well fitting SEM model with childhood conditions as a latent variable based on our proxies, possibly because what they represent is too disparate, hence our presentation of a model based on directly observed variables, with the advantages of simplicity and ease of interpretation. We did not have complete information on father's occupation, so we used multiple imputation, which uses all available data, preserves uncertainty from missing data,[57] minimises inclusion bias and increases statistical power.[33] Fourth, survival bias is possible. We found no effect modification by age group ($<$65 years and $\geqslant$65 years). Finally, our findings may be specific to this ethnic group, the

Policy implications

Research from long-term industrialised countries may not translate to other settings. Much more attention should be paid to the social and historical setting in which studies are carried out and how this might impact the findings.

What this study adds

- In developed western populations longer legs have been shown to be a biomarker of better early childhood conditions. In transitioning populations better childhood conditions could also bring forward puberty and with it decreased leg length
- In older Chinese women better childhood conditions proxied by father's job and education were unrelated to leg length, because these same exposures were also associated with earlier menarche
- Leg length may not be a universal biomarker of childhood conditions. Given the impact of childhood conditions on long-term health, and the dearth of long-term records outside the industrialised world a greater understanding of growth and development in the developing world is required

stage of epidemiological transition and inevitably to women. We collected no marker of age at sexual maturity in the men, such as timing of first nocturnal emission or voice change.

CONCLUSION

In a large cohort of older Chinese women, who are one of the first generations to experience economic development, age of menarche rather than leg length appeared to be a biomarker of childhood conditions, when proxied by own education and father's occupation. We speculate that epigenetic influences originating with nutrition in earlier generations may constrain growth. That leg length may not always be a good marker of childhood conditions has implications for interpreting the observed associations between longer legs and lower cardiovascular risk.

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Appendix 1
Complete case analysis

Analysis without using father's occupation

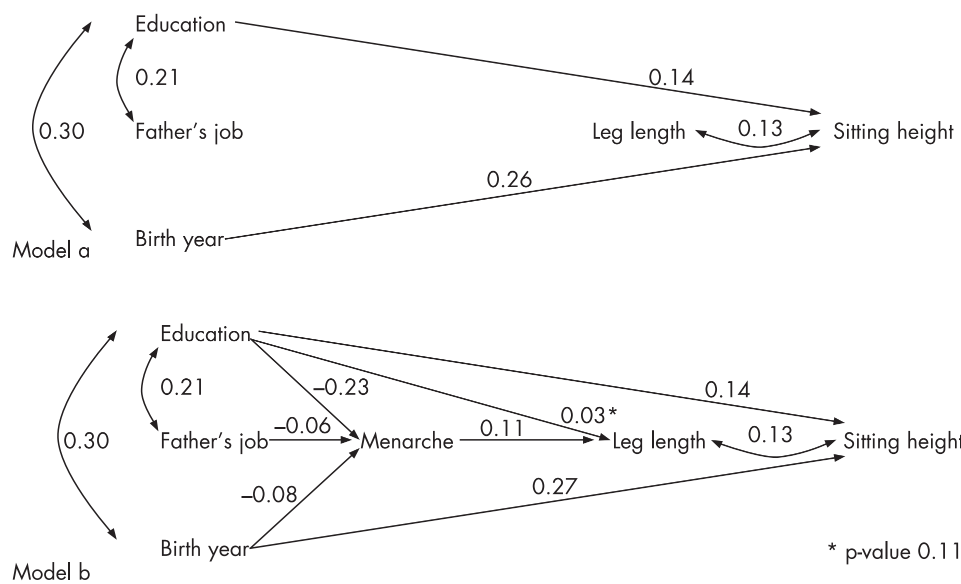

Figure A3 Structural equation models with corresponding correlation coefficients for models relating childhood conditions to components of height, without (model a) and with (model b) age of menarche included, for 3676 women with complete data in the Guangzhou Biobank Cohort Study.

Table A3 Changes in age of menarche and components of height with education, father's job and age for 3676 Chinese women with complete data in the Guangzhou Biobank Cohort Study in the full model including age of menarche (model b)

	Age of menarche		Leg length		Sitting height	
	Difference (years) (95% CI)	Correlation coefficient	Difference (cm) (95% CI)	Correlation coefficient	Difference (cm) (95% CI)	Correlation coefficient
Education (per 10 years)	−1.21 (−1.39 to −1.04)	−0.23	0.28 (−0.06 to 0.62)	0.03	1.15 (0.87 to 1.42)	0.14
p Value		<0.001		0.11		<0.001
Father's job (non-manual compared with manual)	−0.29 (−0.45 to −0.14)	−0.06	−0.07 (−0.36 to 0.23)	−0.01	0.10 (−0.15 to 0.34)	0.01
p Value		<0.001		0.67		0.42
Birth year (per decade younger)	−0.27 (−0.38 to −0.15)	−0.08	0.08 (−0.14 to 0.29)	0.01	1.42 (1.24 to 1.60)	0.27
p Value		<0.001		0.48		<0.001
Age of menarche (per year older)			0.20 (0.14 to 0.26)	0.11	−0.03 (−0.08 to 0.02)	−0.02
p Value				<0.001		0.22

CI, Confidence interval.

Figure A4 Structural equation models with corresponding correlation coefficients for models relating childhood conditions, proxied by education, to components of height, without (model a) and with (model b) age of menarche included, for 7273 women in the Guangzhou Biobank Cohort Study.

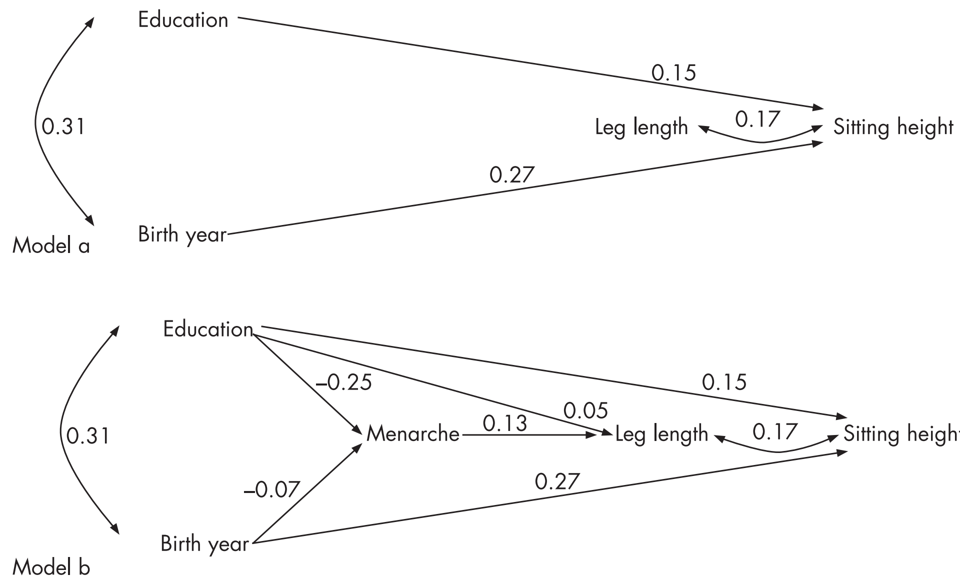

Table A4 Changes in age of menarche and components of height with education and age in 7273 Chinese women in the Guangzhou Biobank Cohort Study in the full model including age of menarche (model b)

	Age of menarche		Leg length		Sitting height	
	Difference (years) (95% CI)	Correlation coefficient	Difference (cm) (95% CI)	Correlation coefficient	Difference (cm) (95% CI)	Correlation coefficient
Education (per 10 years)	−1.29 (−1.41 to −1.17)	−0.25	0.43 (0.20 to 0.66)	0.05	1.17 (0.96 to 1.36)	0.15
p Value		<0.001		<0.001		<0.001
Birth year (per decade younger)	−0.26 (−0.34 to −0.18)	−0.07	0.07 (−0.08 to 0.22)	0.01	1.47 (1.35 to 1.59)	0.27
p Value		<0.001		0.35		<0.001
Age of menarche (per year older)			0.23 (0.18 to 0.27)	0.13	−0.03 (−0.06 to 0.01)	−0.02
p Value				<0.001		0.16

CI, Confidence interval.