Brief original contribution

Association between preterm birth and lower adult height in women

José G B Derraik*, Maria Lundgren, Wayne S Cutfield, Fredrik Ahlsson

* Author for correspondence: Dr José G B Derraik, Liggins Institute, University of Auckland, Private Bag 92019, Auckland, 1142, New Zealand; Email: jderraik@auckland.ac.nz.

List of abbreviations: BMI, body mass index; CI, confidence interval; Mpreterm, women born moderately preterm; SGA, small-for-gestational-age; Vpreterm, women born very preterm

ABSTRACT

We examined whether preterm birth was associated with changes in adult anthropometry in women. Data from the Swedish Birth Register were assessed on 201,382 women (born in 1973–1988) at a mean age of 26.0 years: 663 born very preterm (Vpreterm; <32 weeks of gestation), 8,247 born moderately preterm (Mpreterm; 32 to <37 weeks), and 192,472 born at term (37–41 weeks). Subgroup analyses were carried out within siblings or adjusting for maternal anthropometry. Statistical tests were two-sided. Decreasing gestational age was associated with lower height (-1.1 mm per week of gestation; $P<0.0001$), so that Vpreterm women were on average 12 mm shorter than Mpreterm ($P<0.0001$) and 17 mm shorter than Term ($P<0.0001$) women. Compared to Term women, odds of short stature (<155.4 cm) were 2.9 higher in Vpreterm and 1.43 higher in Mpreterm women. Subgroup analyses showed no differences between Mpreterm and Term women, but accentuated differences with women born very preterm. Amongst siblings (n=2,388) Vpreterm women were 23 mm shorter than those born at term ($P=0.003$), with a 20-mm difference observed in subgroup analyses (n=27,395) adjusting for maternal stature ($P<0.001$). There was a reduction in final height with decreasing gestational age, which was particularly marked in women born very preterm.

Keywords: adult; females; gestational age; premature birth; preterm; siblings; stature; women

INTRODUCTION

It has been estimated that 9.6% (1) to 11.1% (2) of all babies worldwide are born preterm (<37 weeks of gestation). However, rates vary considerably, being approximately 6% in Sweden but 18% in Malawi (2).

Preterm birth is a major cause of neonatal morbidity and mortality, particularly in poor countries (3). Further, there is increasing evidence of adverse long-term outcomes in children and adults born preterm (4-11). Prepubertal children born preterm were shown to have reduced insulin sensitivity compared to those born at term (4). Adults born preterm are at an increased risk of metabolic and cardiovascular diseases, displaying in particular increased adiposity, lower insulin sensitivity, and higher blood pressure (6-11).

Preterm birth also appears to alter the endocrine regulation of postnatal growth in childhood and adolescence, and preterm children were shown to be shorter and lighter than term controls throughout childhood (5, 12). However, data regarding final adult height in preterm survivors are scarce, particularly for women. In this study, we examined a large cohort of Swedish women assessed early in pregnancy to evaluate whether preterm birth was associated with changes in adult anthropometry.

METHODS

This study was approved by the Regional Ethical Review Board in Uppsala. The Swedish Birth Register contains data on over 99% of births in Sweden, and for the study period it had a low error rate for the main parameters of relevance, such as birthweight, date of last menstrual period, birth order, and classification as singleton or multiple (13). Information is prospectively collected during pregnancy from the first antenatal visit and subsequently forwarded to the Birth Register. This study examined data recorded during the first antenatal visit (mostly 10–12 weeks of gestation) on 303,301 singleton women born in 1973–1988 in Sweden, who gave birth in 1991–2009 and were aged ≥18 years. For women with two or more pregnancies in the study period, data were only included for the first recorded pregnancy. Exclusion criteria were non-Nordic ethnicity, extremely short stature (≤130 cm), being born small-for-gestational-age [SGA; <-2 standard deviation scores below the Swedish population mean for birthweight and/or birth length (14)], presence of congenital malformations (ICD-9 740–759 and ICD-10 Q0–Q99), and post-term birth (≥42 weeks of gestation). In addition, potential participants were only included if also born to a singleton mother aged ≥18 years at their first antenatal visit.

Anthropometric data were available on 268,208 women, but 33,724 women were either born post-term or lacked gestational age data. A further 33,102 women were excluded for failing to meet inclusion criteria. Thus, this study covers data on 201,382 women: 663 born very preterm (Vpreterm; <32 weeks of gestation), 8,247 born moderately preterm (Mpreterm; 32 to <37 weeks of gestation), and 192,472 born at term (Term; 37–41 weeks of gestation). The distribution of participants according to gestational age is shown in Web Table 1, illustrating the comparatively sparse number of women born at the lower end of the gestational age spectrum.

Weight and height were measured, although height was self-reported in some cases. Gestational age of the women at their birth (extracted from the Swedish Birth Register) was estimated from the date of the last menstrual period for the majority of participants, otherwise estimates were based on ultrasound scans. Short stature (<155.4 cm) was defined as height less than -2 standard deviations scores below the study population mean. Overweight was defined as body mass index (BMI) ≥25 kg/m^2 and obese as ≥30.

Statistical analyses

Data were compared using general linear regression models, including maternal ID as a random factor to identify sibling clusters. Continuous associations with gestational age were evaluated, but non-linear associations were not explored. Stratified analyses were performed comparing the 3 groups (Vpreterm, Mpreterm, and Term). Logistic regression models were run to evaluate binary outcomes (i.e. likelihood of short stature, overweight, or obesity).

Stratified analyses were also run within sibling groups. For these analyses, we only included those groups of siblings with discordant gestational ages, i.e. where at least one sibling was born at term and at least one other was Mpreterm or Vpreterm.

Models were run including confounding factors that are known to affect adult anthropometry, including age (15), birth order (16), as well as year of birth to account for population-wide secular trends. However, as adjusted and unadjusted results were nearly identical, only the unadjusted results are provided. The exceptions were models run within a subgroup of participants who had maternal anthropometric data, for which the results are provided after adjustment for the respective maternal parameter.

Analyses were performed in SAS v.9.4 (SAS Institute, Cary, USA). All tests were two-tailed with significance level maintained at 5%. Where applicable, results are expressed as odds ratios or ß coefficients with associated 95% confidence intervals (CI) in brackets.

RESULTS

Studied women had a mean age of 26.0 years (range 18 to 36 years). Lower gestational age was associated with lower stature among Swedish women [in cm, ß=0.113 (95% CI 0.096–0.129; *P*<0.0001). Thus, there was a progressive height reduction with decreasing gestational age (Figure 1), equating to an approximate 1.1 mm decrease in adult height for every one week decrease across the gestational age spectrum. As a result, Vpreterm women were on average 12 mm shorter than Mpreterm (*P*<0.0001) and 17 mm shorter than Term (*P*<0.0001) women (Table 1). In addition, Mpreterm women were 5 mm shorter than those born at term (*P*<0.0001; Table 1).

For every one week decrease in gestational age, the odds ratio of having short stature in adulthood was 1.10 higher (95% CI 1.08–1.12; p<0.0001). Consequently, compared to women born at term, the odds of short stature were 2.94 higher in Vpreterm (*P*<0.0001) and 1.43 higher in Mpreterm (*P*<0.0001) women (Web Table 2).

Lower gestational age was also associated with lower weight [in kg, ß=0.076 (95% CI 0.040–0.113; *P*<0.0001], but not with changes in BMI (p=0.36). Vpreterm women were 1.89 and 1.84 kg lighter than Mpreterm (*P*<0.001) and Term (*P*<0.001) women, respectively (Table 1). Mpreterm women had on average BMI that was 0.13 kg/m^2 higher than those born at term (*P*=0.006; Table

1). Further, there were increased odds of overweight and obesity in the Mpreterm group (Web Table 2).

Maternal anthropometry

Data were also analysed on a subgroup of 27,395 women with maternal anthropometric information. In this group, there was an attenuated association between gestational age and adult stature [in cm, ß=0.063 (95% CI 0.022–0.103; *P*=0.002), i.e. with 0.6 mm reduction in adult height per week decrease in gestational age. However, stratified analyses showed that while adjustment for maternal stature eliminated the difference between Mpreterm and Term women (2 mm; *P*=0.21), there was a more marked difference between women born very preterm and the others (Table 1). As a result, Vpreterm women were 18 mm shorter than Mpreterm (*P*=0.002) and 20 mm shorter than Term (*P*<0.001) women (Table 1).

Siblings

The above findings were corroborated by sibling analyses (Table 2). In this group (n=2,388), there were no differences between Mpreterm and Term women (*P*=0.62; Table 2). However, women born very preterm were 24 mm shorter than women born moderately preterm (*P*=0.002) and 23 mm shorter than those born at term (*P*=0.003; Table 2).

The within-sibling analyses and those adjusting for maternal anthropometry yielded no significant differences in weight or BMI between groups (Tables 1 & 2).

DISCUSSION

We observed that among Swedish women, height was reduced with decreasing gestational age, so that the odds of short stature were nearly 3-fold greater in women born very preterm compared to those born at term. However, within-sibling analyses and those adjusting for maternal stature showed that lower height was only observed amongst women born very preterm.

This seems to be the first study that aimed to specifically evaluate the association between preterm birth and final height in a large female population. The large data set also allowed for a more intricate assessment of adult height across the gestational age range in women. Previously, most studies have focused on those born preterm but of very low birth weight (rather than assessing the effects of gestational age *per se*). A prospective study in Australia followed a cohort of infants born extremely preterm (<28 weeks of gestation) until 18 years of age, observing a reduction in height *z* score in this group of -0.73 compared to term controls (12). Similar to our findings, studies on male conscripts in Sweden and Norway have observed that mean height at conscription increased with gestational age until term (17, 18). In the Swedish study, the risk of adult short stature (<166.3 cm) was nearly 3-fold higher in males born very preterm (<32 weeks of gestation) compared to those born at term (17). Data on women are scarce, but a recent small study in Finland on 92 adults at 25 years of age observed that women born preterm and of very low birth weight were on average 39 mm shorter than those born at term (19). A Swedish studied examined adult stature at first antenatal visit in association with SGA birth and yielded conflicting results (20); they observed that gestational age had little impact on final height, but, on the other hand, the adjusted odds ratio of short stature in preterm women was 1.71 times greater than that of women born 37–42 weeks of gestation (20). However, interpretation of the findings from the Finnish and Swedish studies is hindered by the inclusion of a large proportion of participants born SGA.

A strength of our study was that we were able to examine the associations between maternal anthropometry and familial characteristics on offspring outcomes. Maternal height for example, not only has a direct genetic effect on offspring height, but shorter mothers are more likely to give birth to a preterm child (21), which confounds the association between preterm birth and adult stature. Importantly, our analyses within siblings allowed us to examine possible genetic effects, while also accounting to some extent for possible environmental effects within individual families. Both analyses indicate that a long-term association with height seems to be particularly marked amongst women born <32 weeks of gestation. To put the 23-mm difference observed between very preterm and term siblings in perspective, women who were born during the 1959–1961 Chinese Famine (and exposed to under-nutrition early in childhood) experienced a reduction in adult height of 17 mm (22).

There is also a lack of data on adult body composition in association with gestational age at birth, as investigations have similarly focused on those born of very low birth weight (11). Here, we observed differences in the risk of overweight among the two preterm groups, suggesting that the factors associated with increased adiposity in adults born preterm previously seen (7) may differ in those born <32 weeks of gestation compared to those born moderately preterm.

This study is likely to be robust due to the evaluation of a very large and relatively homogenous cohort. For example, we excluded women born SGA, which is a known risk factor for adult short stature in women (20). However, this could have introduced some bias as very preterm infants born SGA are more likely to be misclassified as appropriate-for-gestational-age (23). This study has other limitations that need to be taken into account. Our analyses of siblings groups and those adjusting for maternal anthropometry need to be interpreted with caution, in light of the reduced number of included participants who were born very preterm. Our findings cannot be necessarily extrapolated to men due to commonly observed sexual dimorphism in association with early life programming (24), including preterm birth (7). Our cohort was comprised solely of Nordic women, so that our data may not be applicable to other ethnic groups. The proportion of women born preterm with missing anthropometric data was lower than that of women born at term, which could have theoretically introduced some bias. Gestational age for most women was estimated on the date of the last menstrual period, which is not as precise as ultrasound scans, but still relatively accurate to differentiate preterm and term births (25, 26). Although weight and BMI appear to change little in the first trimester of pregnancy (27), these parameters do not necessarily represent weight and BMI prior to pregnancy.

In summary, we observed a progressive reduction in final height with decreasing gestational age among Swedish women. However, associations with stature appear to occur mostly amongst women born <32 weeks of gestation. These women were 17 to 24 mm shorter and had odds of adult short stature nearly 3-fold greater than those born at term. Our findings indicate that the long-term associations with height and risk of overweight vary according to the severity of prematurity, which requires further investigation. Lastly, as our data cannot be readily applied to men, it would be of interest to ascertain whether there are contrasting long-term effects of preterm birth on anthropometry amongst adult men.

Author affiliations: Liggins Institute, University of Auckland, Auckland, New Zealand (José G B Derraik and Wayne S Cutfield); and Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden (Maria Lundgren and Fredrik Ahlsson).

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Table 1. Anthropometric data recorded in pregnancy (mostly 10–12 weeks) among Swedish women born very preterm, moderately preterm, or at term. Adjusted data have accounted for the respective maternal anthropometric parameter. All statistical tests were two-sided. Women were born in Sweden in 1973–1988, and anthropometric data were recorded in 1991–2009.

		Vpreterm [a]		**Mpreterm** [b]		**Term** [c]	
		Mean	95% CI	Mean	95% CI	Mean	95% CI
Unadjusted	n	663		8,247		192,472	
	Age (years) [d]	25.4 (3.9)		25.6 (4.0)		26.0 (3.9)	
	Height (cm)	165.6	165.1, 166.0	166.8 [h]	166.7, 166.9	167.3 [h,i]	167.2, 167.3
	Weight (kg)	65.61	64.64, 66.58	67.50 [g]	67.22, 67.78	67.45 [g]	67.39, 67.50
	BMI [e]	23.94	23.61, 24.26	24.24[f]	24.14, 24.33	24.09	24.07, 24.11
Adjusted	n	93		1,233		26,069	
	Age (years) [d]	22.2 (2.2)		22.2 (2.3)		22.3 (2.2)	
	Height (cm)	164.7	163.6, 165.8	166.5 [f]	166.2, 166.8	166.7 [f]	166.6, 166.7
	Weight (kg)	66.22	63.39, 69.05	67.61	66.83, 68.38	67.93	67.76, 68.10
	BMI [e]	24.40	23.43, 25.37	24.34	24.07, 24.60	24.42	24.37, 24.48

[a] Born very preterm: <32 weeks of gestation.
[b] Born moderately preterm: 32 to <37 weeks of gestation.
[c] Born at term: 37–41 weeks of gestation.
[d] Age data are means ± standard deviations
[e] Body mass index given as kg/m^2.
[f] $P<0.01$ vs Vpreterm.
[g] $P<0.001$ vs Vpreterm.
[h] $P<0.0001$ vs Vpreterm.
[i] $p<0.0001$ vs Mpreterm.

Table 2. Anthropometric data recorded in pregnancy (mostly 10–12 weeks) among siblings in a cohort of Swedish women born very preterm, moderately preterm, or at term. All statistical tests were two-sided. Women were born in Sweden in 1973–1988, and anthropometric data were recorded in 1991–2009.

	Vpreterm [a]		**Mpreterm** [b]		**Term** [c]	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
n	69		1,094		1,225	
Age (years) [d]	25.4 (3.7)		25.1 (3.9)		24.8 (3.9)	
Height (cm)	164.4	163.0, 165.9	166.8 [f]	166.4, 167.2	166.7 [f]	166.3, 167.0
Weight (kg)	64.61	61.45, 67.77	67.39	66.60, 68.18	67.10	66.35, 67.85
BMI [e]	23.96	22.90, 25.02	24.18	23.92, 24.45	24.13	23.88, 24.39

[a] Born very preterm: <32 weeks of gestation.
[b] Born moderately preterm: 32 to <37 weeks of gestation.
[c] Born at term: 37–41 weeks of gestation.
[d] Age data are means ± standard deviations
[e] Body mass index given as kg/m^2.
[f] $P<0.01$ vs Vpreterm.

Figure 1. Final height recorded in pregnancy (mostly 10–12 weeks) among 201,382 Swedish according to their gestational age (in completed weeks) at birth. Groups are indicated by shading: women born very preterm (white), moderately preterm (gray), or at term (black). Data are means and standard errors. Only gestational ages with more than 20 women are shown. Women were born in Sweden in 1973–1988, and height data were recorded in 1991–2009.