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Original Contribution

Association Between Preterm Birth and Lower Adult Height in Women

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We examined whether being born preterm was associated with changes in adult anthropometry in women. We assessed data on 201,382 women (born in 1973–1988) from the Swedish Birth Register. The mean age was 26.0 years. Of the women in our cohort, 663 were born very preterm (<32 weeks of gestation), 8,247 were born moderately preterm (at least 32 weeks but <37 weeks), and 192,472 were born at term (37–41 weeks). Subgroup analyses were carried out among siblings and also after adjustment for maternal anthropometric data. Statistical tests were 2-sided. Decreasing gestational age was associated with lower height (−1.1 mm per week of gestation; $P < 0.0001$), so that women who were born very preterm were on average 12 mm shorter than women who were born moderately preterm ($P < 0.0001$) and 17 mm shorter than women born at term ($P < 0.0001$). Compared with women who were born at term, those who were born very preterm had 2.9 times higher odds of short stature (<155.4 cm), and those born moderately preterm had 1.43 times higher odds. Subgroup analyses showed no differences between women born moderately preterm and those born at term but accentuated differences from women born very preterm. Among siblings (n = 2,388), very preterm 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) that were adjusted for maternal stature ($P < 0.001$). A shorter final height was associated with decreasing gestational age, and this association was particularly marked in women born very preterm.

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

Abbreviations: BMI, body mass index; SGA, small-for-gestational-age.

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, from approximately 6% in Sweden to 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 from preterm birth in children and adults (4–11). Prepubertal children who were born preterm have been shown to have reduced insulin sensitivity compared with those born at term (4). Adults who were born preterm are at a higher risk of metabolic and cardiovascular diseases, particularly 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 have been shown to be shorter and to weigh less than term controls throughout childhood (5, 12). However, data regarding final adult height in preterm survivors are scarce, particularly for women. In the present study, we examined a large cohort of Swedish women assessed early in pregnancy to evaluate whether preterm birth was associated with changes in adult anthropometric characteristics.

METHODS

This study was approved by the Regional Ethical Review Board in Uppsala. The Swedish Birth Register contains data on more than 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 birth (13). Information is prospectively collected during pregnancy starting at the first antenatal visit and subsequently forwarded to the Birth Register. In this study, we examined data recorded during the first antenatal visit (mostly at 10–12 weeks of gestation) on 303,301 singleton women who were born in 1973–1988 in Sweden, gave birth in 1991–2009, and were 18 years of age or older. For women with 2 or more pregnancies in the study period, we included data from the first recorded pregnancy only. 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 (*International Classification of Disease, Ninth Revision*, codes 740–759 and *International Classification of Disease, Tenth Revision*, codes Q0–Q99), and postterm birth (≥42 weeks of gestation). In addition, potential participants were only included if also born to a singleton mother who was 18 years of age or older at the first antenatal visit.

Anthropometric data were available for 268,208 women, but 33,724 women were either born postterm or lacked data on gestational age. A further 33,102 women were excluded for failing to meet inclusion criteria. Thus, the final study population comprised 201,382 women: 663 who were born very preterm (<32 weeks of gestation), 8,247 who were born moderately preterm (at least 32 weeks but <37 weeks of gestation), and 192,472 who were born at term (37–41 weeks of gestation). The distribution of participants according to gestational age is shown in Web Table 1 (available at http://aje.oxfordjournals.org/), 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 ages of the women at their births (extracted from the Swedish Birth Register) were estimated from the date of the mothers' last menstrual periods for the majority of participants; otherwise, estimates were based on ultrasound scans. Short stature was defined as height less than −2 standard-deviation scores below the study population mean (<155.4 cm). Overweight was defined as body mass index (BMI; weight in kilograms divided by height in meters squared) of 25 or higher; obese was defined as a BMI of 30 or higher.

Statistical analyses

Data were compared using general linear regression models in which we included maternal identification code as a random factor to identify sibling clusters. Continuous associations with gestational age were evaluated, but nonlinear associations were not explored. We performed stratified analyses to compare the 3 groups (women born very preterm, moderately preterm, and at term). Logistic regression models were run to evaluate binary outcomes (i.e., likelihood of short stature, overweight, or obesity).

Stratified analyses were also run among siblings. For these analyses, we only included those groups of siblings with discordant gestational ages, that is, those in which at least 1 sibling was born at term and at least 1 other was moderately or very preterm.

We ran models that included confounding factors that are known to affect adult anthropometric characteristics, including age (15) and birth order (16), as well as year of birth to account for population-wide secular trends. However, because the adjusted and unadjusted results were nearly identical, only the unadjusted results are provided. The exceptions were models run within a subgroup of participants with available maternal anthropometric data; for these models, we provided the results after adjustment for the respective maternal parameter.

Analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina). All tests were 2-tailed, with a significance level maintained at 5%. Where applicable, results are expressed as odds ratios or β coefficients with the associated 95% confidence intervals.

RESULTS

The women in our study cohort had a mean age of 26.0 years (range, 18–36 years). Lower gestational age was associated with shorter stature (measured in centimeters) among Swedish women (β = 0.113, 95% confidence interval: 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 1 week decrease in gestational age across the spectrum. As a result, women who were born very preterm were on average 12 mm shorter than those born moderately preterm ($P < 0.0001$) and 17 mm shorter than those born at term ($P < 0.0001$; Table 1). In addition, moderately preterm women were 5 mm shorter than those born at term ($P < 0.0001$; Table 1).

For every 1-week decrease in gestational age, the odds ratio of having short stature in adulthood was 1.10

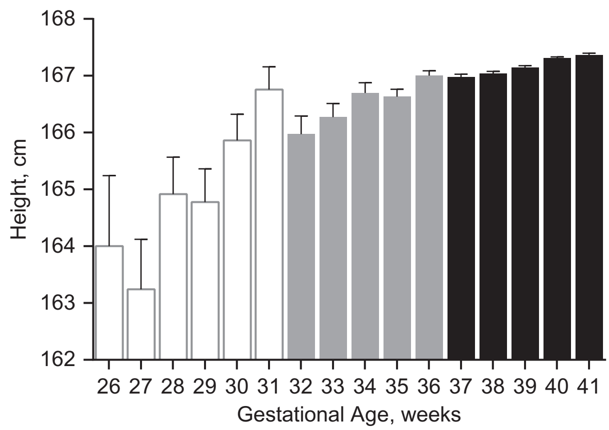

Figure 1. Mean final heights recorded during pregnancy (mostly at 10–12 weeks' gestation) among 201,382 Swedish women born in 1973–1988 according to their gestational age (in completed weeks) at birth, 1991–2009. Birth categories are indicated by shading: White indicates women born very preterm, gray indicates women born moderately preterm, and black indicates women born at term. Only gestational age categories with more than 20 women are shown. Bars, standard errors.

Table 1. Anthropometric Data Recorded During Pregnancy Among Women Born Very Preterm, Moderately Preterm, or at Term, Sweden, 1991–2009

Characteristic	Very Preterm[a]			Moderately Preterm[b]			At Term[c]		
	No.	Mean	95% CI	No.	Mean	95% CI	No.	Mean	95% CI
Unadjusted	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[e]	166.7, 166.9		167.3[e,f]	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[h]		23.94	23.61, 24.26		24.24[i]	24.14, 24.33		24.09	24.07, 24.11
Adjusted[j]	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[i]	166.2, 166.8		166.7[i]	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[h]		24.40	23.43, 25.37		24.34	24.07, 24.60		24.42	24.37, 24.48

Abbreviations: BMI, body mass index; CI, confidence interval.
[a] Less than 32 weeks of gestation.
[b] At least weeks 32 but less than 37 weeks of gestation.
[c] At 37–41 weeks of gestation.
[d] Data are expressed as mean (standard deviation).
[e] Two-sided $P < 0.0001$ versus women born very preterm.
[f] Two-sided $P < 0.0001$ versus women born moderately preterm.
[g] Two-sided $P < 0.001$ versus women born very preterm.
[h] Weight (kg)/height (m)^2.
[i] Two-sided $P < 0.01$ versus women born very preterm.
[j] Adjusted for the corresponding maternal parameter.

higher (95% confidence interval: 1.08, 1.12; $P < 0.0001$). Consequently, compared with women born at term, those born very preterm had 2.94 times higher odds of short stature in adulthood ($P < 0.0001$) and those born moderately preterm had 1.43 times higher odds ($P < 0.0001$; Web Table 2).

Lower gestational age was also associated with lower weight (β = 0.076, 95% confidence interval: 0.040, 0.113; $P < 0.0001$) but not with changes in BMI ($P = 0.36$). Women born very preterm were 1.89 kg lighter than those born moderately preterm ($P < 0.001$) and 1.84 kg lighter than those born at term ($P < 0.001$) (Table 1). On average, moderately preterm women had a BMI that was 0.15 higher than did women born at term ($P = 0.006$; Table 1). Further, there were increased odds of overweight and obesity in the moderately preterm group (Web Table 2).

Maternal anthropometric characteristics

We also analyzed data from a subgroup of 27,395 women for whom we had maternal anthropometric information. In this group, there was an attenuated association between gestational age and adult stature (β = 0.063, 95% confidence interval: 0.022, 0.103; $P = 0.002$); that is, there was a 0.6-mm decrease in adult height per each 1-week decrease in gestational age. However, stratified analyses showed that although adjustment for maternal stature eliminated the difference between women born moderately preterm and those born at term (2 mm; $P = 0.21$), there was a more marked difference between women born very preterm and the others (Table 1). As a result, women born very preterm were 18 mm shorter than those born moderately preterm ($P = 0.002$) and 20 mm shorter than those born at term ($P < 0.001$) (Table 1).

Siblings

The above findings were corroborated by sibling analyses (Table 2). In this group ($n = 2,388$), there were no differences between women born moderately preterm and those born at term ($P = 0.62$; 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 analyses among siblings and those adjusted for maternal anthropometric data yielded no significant differences in weight or BMI between groups (Tables 1 and 2).

DISCUSSION

We observed that among Swedish women, height was shorter in women born at lower gestational ages so that the odds of short stature were nearly 3-fold greater in women born very preterm compared with those born at term. However, analyses among siblings and those adjusted for maternal stature showed that lower height was only observed among women born very preterm.

Table 2. Anthropometric Data on Siblings Recorded During Pregnancies of Participants Who Were Born Very Preterm, Moderately Preterm, or at Term, Sweden, 1991–2009

Characteristic	Very Preterm[a] (n = 69)		Moderately Preterm[b] (n = 1,094)		At Term[c] (n = 1,225)	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
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[e]	166.4, 167.2	166.7[e]	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[f]	23.96	22.90, 25.02	24.18	23.92, 24.45	24.13	23.88, 24.39

Abbreviations: BMI, body mass index; CI, confidence interval.
[a] Less than 32 weeks of gestation.
[b] At least weeks 32 but less than 37 weeks of gestation.
[c] At 37–41 weeks of gestation.
[d] Data are expressed as mean (standard deviation).
[e] Two-sided $P < 0.01$ versus women born very preterm.
[f] Weight (kg)/height (m)^2.

To our knowledge, this present study is the first aimed at specifically evaluating 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 been focused on persons who were born preterm and had very low birth weights (rather than on assessing the effects of gestational age per se). In a prospective study in Australia, Roberts et al. (12) followed a cohort of infants born extremely preterm (<28 weeks of gestation) until 18 years of age and observed a lower z score for height in this group (−0.73) compared with term controls. Similar to our findings, results from studies of male conscripts in Sweden and Norway have indicated 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 with those born at term (17). Data on women are scarce, but in a recent small study in Finland of 92 adults at 25 years of age, researchers observed that women born preterm and of very low birth weight were on average 39 mm shorter than those born at term (19). Investigators in a Swedish studied examined adult stature at first antenatal visit in association with SGA birth and found 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 at 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 anthropometric and familial characteristics on offspring outcomes. For example, not only does maternal height have a direct genetic effect on offspring height, but shorter mothers are also more likely to give birth to a preterm child (21), which confounds the association between preterm birth and adult stature. Importantly, our analyses among siblings allowed us to examine possible genetic effects while also accounting to some extent for possible environmental effects within individual families. Results from both analyses indicated that a long-term association with height seems to be particularly marked among women born at less than 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 undernutrition 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 because investigations have similarly been focused on those born of very low birth weight (11). Here, we observed differences in the risk of overweight among the 2 preterm groups, which suggests that the factors underpinning the previously observed increase in adiposity in adults born preterm (7) may differ in those born at less than 32 weeks of gestation compared to those born moderately preterm.

This study is likely to be robust because of 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 because very preterm infants born SGA are more likely to be misclassified as appropriate for gestational age (23). The present study has other limitations that need to be taken into account. Our analyses of siblings groups and those adjusted for maternal anthropometric data 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 because of commonly observed sexual dimorphism in association with early life programming (24), including preterm birth (7). Our cohort was comprised solely of Nordic women, so our data may not be applicable to other ethnic groups. The proportion of women born preterm for whom anthropometric data were missing was lower than that of women born at term, which could have theoretically introduced some bias. For most women, gestational age was estimated based on the date of the mother's last menstrual period, which is not as precise as ultrasound scans but is still a relatively accurate way to differentiate between 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 appeared to occur mostly among women born at less than 32 weeks of gestation. These women were 17 to 24 mm shorter and had nearly 3-fold greater odds of adult short stature than did 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, because 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 anthropometric characteristics among adult men.

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REFERENCES

1. Beck S, Wojdyla D, Say L, et al. The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. *Bull World Health Organ*. 2010;88(1):31–38.
2. Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *Lancet*. 2012;379(9832):2162–2172.
3. March of Dimes, PMNCH, Save the Children, et al. *Born Too Soon: The Global Action Report on Preterm Birth*. Geneva, Switzerland: World Health Organization; 2012. http://www.who.int/pmnch/media/news/2012/201204_borntoosoon-report.pdf. Accessed November 21, 2016.
4. Hofman PL, Regan F, Jackson WE, et al. Premature birth and later insulin resistance. *N Engl J Med*. 2004;351(21):2179–2186.
5. Rowe DL, Derraik JG, Robinson E, et al. Preterm birth and the endocrine regulation of growth in childhood and adolescence. *Clin Endocrinol*. 2011;75(5):661–665.
6. Mathai S, Cutfield WS, Derraik JG, et al. Insulin sensitivity and β-cell function in adults born preterm and their children. *Diabetes*. 2012;61(10):2479–2483.
7. Mathai S, Derraik JG, Cutfield WS, et al. Increased adiposity in adults born preterm and their children. *PLoS One*. 2013;8(11):e81840.
8. Kajantie E, Osmond C, Barker DJ, et al. Preterm birth – a risk factor for type 2 diabetes? The Helsinki birth cohort study. *Diabetes Care*. 2010;33(12):2623–2625.
9. Keijzer-Veen MG, Dülger A, Dekker FW, et al. Very preterm birth is a risk factor for increased systolic blood pressure at a young adult age. *Pediatr Nephrol*. 2010;25(3):509–516.
10. de Jong F, Monuteaux MC, van Elburg RM, et al. Systematic review and meta-analysis of preterm birth and later systolic blood pressure. *Hypertension*. 2012;59(2):226–234.
11. Kajantie E, Hovi P. Is very preterm birth a risk factor for adult cardiometabolic disease? *Semin Fetal Neonatal Med*. 2014;19(2):112–117.
12. Roberts G, Cheong J, Opie G, et al. Growth of extremely preterm survivors from birth to 18 years of age compared with term controls. *Pediatrics*. 2013;131(2):e439–e445.
13. Cnattingius S, Ericson A, Gunnarskog J, et al. A quality study of a medical birth registry. *Scand J Soc Med*. 1990;18(2):143–148.
14. Niklasson A, Ericson A, Fryer JG, et al. An update of the Swedish reference standards for weight, length and head circumference at birth for given gestational age (1977–1981). *Acta Paediatr Scand*. 1991;80(8–9):756–762.
15. Sorkin JD, Muller DC, Andres R. Longitudinal change in height of men and women: implications for interpretation of the body mass index: the Baltimore Longitudinal Study of Aging. *Am J Epidemiol*. 1999;150(9):969–977.
16. Derraik JG, Ahlsson F, Lundgren M, et al. First-borns have greater BMI and are more likely to be overweight or obese: a study of sibling pairs among 26,812 Swedish women. *J Epidemiol Community Health*. 2016;70(1):78–81.
17. Tuvemo T, Cnattingius S, Jonsson B. Prediction of male adult stature using anthropometric data at birth: a nationwide population-based study. *Pediatr Res*. 1999;46(5):491–495.
18. Eide MG, Øyen N, Skjærven R, et al. Size at birth and gestational age as predictors of adult height and weight. *Epidemiology*. 2005;16(2):175–181.
19. Kajantie E, Strang-Karlsson S, Hovi P, et al. Insulin sensitivity and secretory response in adults born preterm: the Helsinki Study of Very Low Birth Weight Adults. *J Clin Endocrinol Metab*. 2015;100(1):244–250.
20. Lundgren EM, Cnattingius S, Jonsson B, et al. Prediction of adult height and risk of overweight in females born small-for-gestational-age. *Paediatr Perinat Epidemiol*. 2003;17(2):156–163.
21. Han Z, Lutsiv O, Mulla S, et al. Maternal height and the risk of preterm birth and low birth weight: a systematic review and meta-analyses. *J Obstet Gynaecol Can*. 2012;34(8):721–746.
22. Huang C, Li Z, Wang M, et al. Early life exposure to the 1959–1961 Chinese famine has long-term health consequences. *J Nutr*. 2010;140(10):1874–1878.
23. Hutcheon JA, Platt RW. The missing data problem in birth weight percentiles and thresholds for "small-for-gestational-age". *Am J Epidemiol*. 2008;167(7):786–792.
24. Gabory A, Roseboom TJ, Moore T, et al. Placental contribution to the origins of sexual dimorphism in health and diseases: sex chromosomes and epigenetics. *Biol Sex Differ*. 2013;4(1):5.
25. Haglund B. Birthweight distributions by gestational age: comparison of LMP-based and ultrasound-based estimates of

gestational age using data from the Swedish Birth Registry. *Paediatr Perinat Epidemiol*. 2007;21(suppl 2): 72–78.
26. Savitz DA, Terry JW, Dole N, et al. Comparison of pregnancy dating by last menstrual period, ultrasound scanning, and their combination. *Am J Obstet Gynecol*. 2002; 187(6):1660–1666.
27. Fattah C, Farah N, Barry SC, et al. Maternal weight and body composition in the first trimester of pregnancy. *Acta Obstet Gynecol Scand*. 2010;89(7):952–955.