Gestational age differences in health and development among young Swedish men born at term

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Background Although increased morbidity and mortality associated with pre-term birth and restricted fetal growth have been extensively studied, relatively little is known about variations in health outcomes among term births, because they are often assumed to be homogeneous.

Methods We examined variations in height, body mass index (BMI), systolic and diastolic blood pressure (SBP and DBP), and intellectual performance by gestational age and fetal ‘growth’ (birth weight for gestational age) among young Swedish men born at term (37–41 weeks of gestation). We also compared the magnitude of associations among 314 642 men from different families and among 72 212 full brothers from 35 215 families to assess whether the associations are explained by familial factors shared by siblings.

Results Gestational age in completed weeks was positively associated with height [0.11 cm, 95% confidence interval (CI): 0.09–0.13] and intellectual performance (0.01, 95% CI: 0.00–0.02) and negatively associated with SBP (−0.28 mmHg, 95% CI: −0.33 to −0.24), after controlling for birth weight, maternal age at the men’s birth, parity, family socio-economic position and family structure. The associations with height and SBP were observed also among brothers within families, suggesting that they are not explained by shared family characteristics. However, the positive association between gestational age and intellectual performance was no longer present within families. Birth weight for gestational age (z-score) was positively associated with height, BMI and intellectual performance and negatively associated with SBP. These associations were robust within families.

Conclusions Among young men born at term, fetal growth and even gestational age are independently associated with adult size, BP and cognitive ability. The extent to which shared family characteristics explain the associations varies across outcomes.

Keywords Gestational age, birth weight, height, body mass index, blood pressure, cognitive ability, developmental origins
HEALTH AND DEVELOPMENT BY GESTATIONAL AGE AMONG TERM BIRTHS

Introduction

Increased long-term morbidity and mortality associated with pre-term birth and restricted fetal growth have been extensively reported. It has been widely documented, e.g., that children born small for gestational age (SGA) or pre-term (<37 completed weeks) have elevated blood pressure (BP), insulin resistance, and lower cognitive ability, than their normal birth weight and term-born counterparts. Relative little is known, however, about variations in such outcomes among term infants, who are often assumed to constitute a homogeneous group. It is only recently that investigators have focused on whether such pregnancy outcomes, such as perinatal death, 5-min Apgar score and maternal delivery complications, vary by gestational age even in term births. Zhang and Kramer reported that both neonatal and post-neonatal mortality and neonatal morbidity vary by week of gestation among term births. We have also observed small positive associations between gestational age and intelligence quotient (IQ) among 6.5-year-old children born at term (37–41 completed weeks) with birth weight ≥2500 g.

One important issue in drawing inferences from observational studies of associations between gestational age or fetal growth with later health outcomes is residual confounding. Family characteristics are important determinants of pregnancy outcomes and of subsequent health and development. Data from siblings enable better control for family characteristics, as siblings share 50% of their genes, fixed maternal factors and home environment during childhood and adolescence. Thus, associations observed within siblings are less biased from residual confounding by unmeasured or poorly measured family characteristics shared by siblings. Several studies have compared the effects of birth weight within siblings to effects among non-siblings on type 2 diabetes, body composition, BP, and cognitive ability. However, most of the studies are based on twins; non-twin sibling-based studies of long-term outcomes are limited to BP and cognitive ability. In addition, such sibling-based studies have mostly focused on associations with birth weight and thus cannot distinguish effects of gestational duration and fetal growth. Our objectives, therefore, were to examine associations of both gestational age and fetal growth (as assessed by birth weight for gestational age) and adult height, body mass index (BMI), BP and intellectual performance in a large population-based cohort of Swedish young men and their full brothers who had been born at term.

Methods

Characteristics of this nationwide cohort and descriptions of the data have been published previously. In brief, using the unique National Registration Number assigned to each Swedish resident at birth, we obtained data by linking the Swedish Medical Birth Register, the Swedish Conscript Register, the Population and Housing Census of 1990 and the Swedish Multi-Generation Register. The Swedish Birth Register included information on 374,501 male infants born at term (37–41 completed weeks of gestation) between 1973 and 1981. To increase homogeneity within the study cohort, we excluded those born to mothers of non-Nordic nationality, men with congenital malformations and multiple births (n = 38,258). Of the remaining 336,243 individuals, 314,642 (94%) were conscripted between 1991 and 2000. Among the conscripted men, 72,212 (23% of the overall cohort) were full brothers from 35,215 families, including 33,484 families with two brothers, 1,680 families with three brothers and 51 families with four brothers.

The Medical Birth Register included data on gestational age estimated from the date of the last menstrual period, birth weight for gestational age which was standardized by Swedish birth weight references, maternal age and parity. All births are validated every year against the Swedish Register of Population and Population Changes, using the mothers’ and infants’ unique personal identification numbers. The Swedish Conscript Register contains information collected at the military service conscription examination, which is mandatory and enforced by law. Over 95% of men are conscripted at 18–19 years of age, and age at conscription has been shown not to differ by gestational age at birth. Men with known severe disability, congenital malformations or chronic diseases are not conscripted (~2–4% in each birth cohort). The registry was used to obtain data on weight, height, systolic BP (SBP) and diastolic BP (DBP) and intellectual performance score in young adulthood. The Multi-Generation Register was used to identify full brothers in the study population. The Population and Housing Census of 1990 was used to obtain information on households’ highest socio-economic and education categories and households’ family structure. These variables from the Population and Housing Census were classified according to recommendations set forth by Statistics Sweden. Within each household, we used the highest socio-economic category, which was classified in the following manner: unskilled blue-collar workers, skilled blue-collar workers, low-level white-collar workers, intermediate-level white-collar workers, high-level white-collar workers and self-employed. Households’ highest education was similarly classified into 9-year compulsory school, upper secondary school <3 years, upper secondary school 3 years, higher education <3 years and higher education ≥3 years. The family structure of the household was categorized as living with both biological parents, only living with biological mother, only living with biological father and living with neither biological parent.
Outcome measures
At conscription, men undergo a thorough health examination that measures weight, height and BP. Weight is measured in kilograms (in light indoor clothes) and height is measured in centimetres (without shoes). BP is measured after 5–10 min of rest in the supine position. If the measurement is considered elevated (SBP: $\geq 135$ mmHg or DBP: $\geq 85$ mmHg), a second measurement is taken, and the lower of the two measurements is recorded. Intellectual performance is measured using a time-limited test in four dimensions: logical/inductive, verbal, spatial and theoretical/technical. The test consists of 160 questions, 40 for each dimension. The resulting score ranges from 1 to 9 and is normally distributed, with a mean of 5 and standard deviation (SD) of 2. In the present study, data on intellectual performance, BMI, height and BP were available for 298,691 (95%), 294,721 (94%), 275,982 (88%) and 258,733 (85%) members of the study cohort, respectively.

Statistical methods
We first examined the association among gestational age, fetal growth (as reflected by the birth weight-for-gestational-age z-score) and the study outcomes in the overall cohort, taking into account clustering of siblings within families in the estimation of standard errors. We adjusted for fetal growth, maternal age and parity initially, and we further adjusted for family socio-economic characteristics and family structure in subsequent models. Gestational age was analysed both as a categorical variable (each completed week of gestation) with 40 weeks as the reference category, and as a continuous variable to be directly comparable to the family-based analysis. Fetal growth was analysed as a continuous variable.

We then conducted family-based analyses in families with at least two full brothers. Family-based analysis allows us to separate and simultaneously estimate within- and between-families effects. Between-family effects were estimated by the association of within-family means of gestational age across different families; those estimates represent the average differences in outcomes for each gestational week across men from different families. Within-family effects by associations with deviation from the family mean for each brother, and represent the additional difference in outcome per-gestational-week difference between brothers within the same family. If the association is largely explained by fixed maternal and family factors, then one would expect no association, or a considerably weaker association, within brothers (where these factors should be tightly controlled) compared with the association between men from different families. A generalized least-squares method was used to estimate the coefficients with restricted maximum-likelihood for estimating the variance parameters.

Results
Mean values of the health characteristics at conscription by gestational age are shown in Table 1; 5.5% of the men were born at 37 weeks of gestation, 12.6% at 38 weeks, 25.2% at 39 weeks, 33.2% at 40 weeks and 23.9% at 41 weeks.

Table 2 shows the crude and adjusted mean differences of the outcomes by gestational age in the overall cohort. Gestational age at birth was positively associated with height at conscription. Compared with young men born at 40 completed weeks, those born between 37 and 39 weeks were shorter, whereas no difference in mean height was observed among those born at 41 weeks. After adjusting for confounding factors, men born at 37 weeks were shorter by $0.34\text{cm} \ [95\% \text{ confidence interval (CI): } -0.46 \text{ to } -0.21]\] as were those born at 38 weeks (95% CI: $-0.43 \text{ to } -0.26$). Men born at 39 weeks were shorter by $0.18\text{cm} \ (95\% \text{ CI: } -0.25 \text{ to } -0.12)$ compared with those born at 40 weeks. On average, each completed week of gestation was associated with a $0.11\text{cm} \ (95\% \text{ CI: } 0.09 \text{ to } 0.13)$ increase in height. BMI was higher among men born at 37–38 weeks in the unadjusted analysis, but the association disappeared after adjusting for confounding factors. A negative association was observed between SBP and gestational age; on average, each additional week of gestation reduced SBP by $0.28\text{mmHg} \ (95\% \text{ CI: } -0.33 \text{ to } -0.24)$ after...
adjusting for potential confounding factors. However, mean DBP did not differ significantly by gestational age, except that those born at 38 weeks had higher DBP. Intellectual performance was also positively associated with gestational age. Compared with men born at 40 weeks, mean intellectual performance scores were lower among those born at 37 and 38 weeks by $-0.07$ (95% CI: $-0.10$ to $-0.03$) and

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>Height (cm)</th>
<th>BMI (kg/m²)</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
<th>Intellectual performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>$-0.21$ ($-0.32$, $-0.10$)</td>
<td>$0.06$ ($0.00$, $0.12$)</td>
<td>$0.69$ (0.49, 0.89)</td>
<td>$0.05$ ($-0.12$, $0.23$)</td>
<td>$-0.11$ ($-0.14$, $-0.08$)</td>
</tr>
<tr>
<td>38</td>
<td>$-0.17$ ($-0.25$, $-0.10$)</td>
<td>$0.04$ ($0.00$, $0.08$)</td>
<td>$0.57$ (0.44, 0.71)</td>
<td>$0.13$ ($0.01$, $0.26$)</td>
<td>$-0.04$ ($-0.06$, $0.23$)</td>
</tr>
<tr>
<td>39</td>
<td>$-0.13$ ($-0.19$, $-0.07$)</td>
<td>$-0.01$ ($-0.04$, $0.02$)</td>
<td>$0.23$ (0.13, 0.34)</td>
<td>$0.04$ ($-0.06$, $0.13$)</td>
<td>$-0.01$ ($-0.03$, $0.00$)</td>
</tr>
<tr>
<td>40 Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>41 Reference</td>
<td>$0.01$ ($-0.05$, $0.07$)</td>
<td>$0.00$ ($-0.03$, $0.03$)</td>
<td>$-0.27$ ($-0.38$, $-0.16$)</td>
<td>$0.07$ ($-0.03$, $0.17$)</td>
<td>$0.00$ ($-0.01$, $0.02$)</td>
</tr>
</tbody>
</table>

| $P$-value$^c$ | $<0.001$ | $0.037$ | $<0.001$ | $<0.001$ | $<0.001$ |
| Per week      | $0.07$ (0.05, 0.09) | $0.00$ ($-0.01$, $0.01$) | $-0.01$ ($-0.02$, $0.00$) | $-0.01$ ($-0.02$, $0.00$) | $-0.01$ ($-0.02$, $0.01$) |

$^a$Adjusted 1: adjusted for birth weight z-score.
$^b$Adjusted 2: additionally adjusted for maternal age at birth, parity, family socio-economic position and family structure (living with two biological parents/only one biological parent/neither biological parent).
$^c$The $P$-values for testing linear trend of the associations with gestational age.
BMI (kg/m²) Crude

Two biological parents/only one biological parent/neither biological parent).

1.97 cm (95% CI: 1.94–2) and by 0.30 kg/m² (95% CI: 0.27–0.32), respectively, per SD increase in birth weight z-score in the whole-cohort. These associations were slightly attenuated among brothers within families (1.53 cm, 95% CI: 1.45–1.61 for height; 0.22 kg/m², 95% CI: 0.18–0.27 for BMI). After controlling for potential confounding factors, birth weight for gestational age was inversely associated with SBP in the overall cohort (–0.17 mmHg per SD increase, 95% CI: –0.22 to –0.12) and among brothers (–0.25, 95% CI: –0.45 to –0.05). No difference in mean DBP by birth weight for gestational age was observed, however, after controlling for confounding factors. Intellectual performance scores were also positively associated with birth weight z-score after adjustment for confounding factors, both in the overall cohort and within brothers.

Discussion

We examined variations in height, BMI, BP and intellectual performance in early adulthood by gestational age and fetal growth among young men who had been born at term, and compared the magnitude of association within siblings with that among non-siblings. We observed small increases in height and intellectual performance and a decrease in SBP with each additional week of gestation in the overall cohort, even after adjusting for potential confounding factors. No associations were observed, however, with BMI or DBP. Analyses based on full brothers

Table 3 shows the within- and between-family mean differences in outcome by gestational week from the family-based analysis. Consistent with the results in the overall cohort analysis, variations by gestational age in height (positive association) and SBP (negative association) were found among brothers within the same family. Each additional week of gestation was associated with a 0.08-cm (95% CI: 0.04–0.13) increase in height and a 0.28-mmHg (95% CI: –0.37 to –0.13) decrease in SBP among full brothers. The positive association between gestational age and intellectual performance observed in the overall cohort was also observed within brothers in crude and birth weight-adjusted analyses. However, once we further adjusted for individual-specific (i.e. maternal age and parity at the offspring’s birth) and shared family factors, the positive association within brothers disappeared, mainly due to adjustment for parity.

Table 4 summarizes the associations with fetal growth, both in the overall cohort and in family-based analyses. Fetal growth was positively associated with all study outcomes except DBP. The patterns of association were similar in the two analyses, suggesting that the associations are not explained by shared familial factors. After controlling for potential confounding factors, height and BMI increased by 1.97 cm (95% CI: 1.94–2) and by 0.30 kg/m² (95% CI: 0.29–0.32), respectively, per SD increase in birth weight z-score.
Table 4  Mean differences in height, BMI, BP and intellectual performance score per SD of birth weight for gestational age z-score in the whole cohort and family-based analyses

<table>
<thead>
<tr>
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<th>Whole cohort</th>
<th>Family based</th>
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<tbody>
<tr>
<td></td>
<td>Crude</td>
<td>Adjusted 1a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>1.93 (1.91, 1.95)</td>
<td>1.43 (1.36, 1.49)</td>
</tr>
<tr>
<td>Adjusted 1a</td>
<td>1.93 (1.91, 1.96)</td>
<td>1.44 (1.37, 1.50)</td>
</tr>
<tr>
<td>Adjusted 2b</td>
<td>1.97 (1.94, 2.00)</td>
<td>1.53 (1.45, 1.61)</td>
</tr>
<tr>
<td>BMI Crude</td>
<td>0.29 (0.27, 0.30)</td>
<td>0.25 (0.21, 0.29)</td>
</tr>
<tr>
<td>Adjusted 1</td>
<td>0.29 (0.28, 0.30)</td>
<td>0.25 (0.21, 0.29)</td>
</tr>
<tr>
<td>Adjusted 2</td>
<td>0.30 (0.29, 0.32)</td>
<td>0.22 (0.18, 0.27)</td>
</tr>
<tr>
<td>SBP Crude</td>
<td>-0.17 (−0.21, −0.13)</td>
<td>-0.29 (−0.45, −0.13)</td>
</tr>
<tr>
<td>Adjusted 1</td>
<td>-0.17 (−0.21, −0.13)</td>
<td>-0.34 (−0.50, −0.18)</td>
</tr>
<tr>
<td>Adjusted 2</td>
<td>-0.17 (−0.22, −0.12)</td>
<td>-0.25 (−0.45, −0.05)</td>
</tr>
<tr>
<td>DBP Crude</td>
<td>0.05 (0.01, 0.08)</td>
<td>0.39 (0.24, 0.53)</td>
</tr>
<tr>
<td>Adjusted 1</td>
<td>0.05 (0.01, 0.08)</td>
<td>0.39 (0.24, 0.53)</td>
</tr>
<tr>
<td>Adjusted 2</td>
<td>0.04 (−0.01, 0.08)</td>
<td>0.02 (−0.15, 0.20)</td>
</tr>
<tr>
<td>Intellectual performance Crude</td>
<td>0.11 (0.11, 0.12)</td>
<td>0.01 (−0.01, 0.03)</td>
</tr>
<tr>
<td>Adjusted 1</td>
<td>0.11 (0.11, 0.12)</td>
<td>0.02 (−0.01, 0.04)</td>
</tr>
<tr>
<td>Adjusted 2</td>
<td>0.11 (0.10, 0.11)</td>
<td>0.08 (0.06, 0.11)</td>
</tr>
</tbody>
</table>

aAdjusted 1: adjusted for birth weight z-score.
bAdjusted 2: additionally adjusted for maternal age at birth, parity, family socio-economic position and family structure (living with two biological parents/only one biological parent/neither biological parent).

confirmed the associations with height and SBP; however, the positive association with intellectual performance in the overall cohort was attenuated and no longer significant in the fully adjusted analysis between brothers, suggesting that residual confounding may be responsible for the association with intellectual performance observed in the overall cohort. Men with higher birth weight for gestational age were taller, had higher BMIs, had lower SBP and scored higher on the intellectual performance test, even after controlling for potential confounding factors. These associations remained between brothers, suggesting that the differences in the study outcomes by fetal growth are not explained by shared familial factors and that part of the variation in these outcomes may originate in utero.

Comparison with other studies

Although numerous studies have examined long-term differences in adult health outcomes between pre-term, term and post-term births, very limited evidence exists concerning variations in outcome among term births. Consistent with our findings for fetal growth, previous studies have reported birth weight to be associated with height in adulthood.41,42 No previous studies, however, have examined differences in height by birth weight for gestational age within siblings. Though twins may experience different fetal growth patterns from those of singletons (as indicated by their lower birth weights compared with singletons), some twin studies have reported significant within-twin pair differences in height according to birth weight.27,28

Few studies have examined associations between gestational age and adult height. A large population-based study of Norwegian conscripts observed no independent effects of gestational age on adult stature and weight, but reported interaction effects between gestational age and birth length.43 To our knowledge, only Leger et al.44 examined variations in adult height by gestational age among ‘term’ (37–42 weeks) births and reported no association.

Numerous studies have reported higher SBP in children and adults who were born pre-term compared with those born at term,1,4,37,45 but few have investigated the association between gestational age and later BP in individuals born at term. Without restrictions to term births (i.e. across the entire gestational age distribution), gestational age has been inversely associated with BP in most1,30,46,47 but not in all studies.48 Leon et al.47 and Lawlor et al.30 investigated the association between gestational age and SBP using the same data sources as in our study. Leon et al.47 found an inverse association when analysing the overall cohort, while Lawlor et al.30 re-examined the association using siblings, as in our family-based analyses. However, both studies examined the association
across the entire distribution of gestational age, including individuals born pre-term or post-term. Our restriction to men who had been born at term (37–41 weeks) provides a ‘cleaner’ effect of gestational age in a more homogeneously ‘normal’ birth cohort.

It is widely recognized that individuals born small for gestational age or pre-term have lower cognitive ability than individuals born appropriate for gestational age or at term.\(^9,10,49\) Recent studies have demonstrated that birth weight is positively associated with cognitive ability across the entire distribution of birth weight, even within the normal range.\(^11,50\) Family-based approaches to the association between fetal growth and cognitive ability, however, have reported inconsistent results. The earliest study by Record et al.\(^51\) found that the association between birth weight and cognitive ability was attributable to differences in family factors, particularly socioeconomic characteristics, a finding supported by more recent studies.\(^36,52\) In contrast, other studies\(^33,35,54\) have found within-sibling differences in cognitive ability by birth weight. These inconsistent results may be due to differences in study populations or in measures of cognitive ability. While birth weight has been well studied in relation to cognitive ability, few studies have examined the association with gestational age among term births.\(^55,56\) We recently reported that cognitive ability at age 6.5 years increases with gestational age up to 40 weeks and decreases post-term in healthy, term-born Belarusian children.\(^15\) While the positive association among term births was robust with adjustment of maternal and family characteristics in our previous study without family-based analysis, the present study using full brothers suggests that the association might be due to residual confounding by family characteristics, which are better controlled for in family-based analyses.

Our results suggest that even among term births, gestational age affects adult height and BP independent of fetal growth, as has been observed in other studies with a wider range of gestational age (including pre-term births).\(^1,47\) They are also consistent with emerging evidence on length of gestation as an important determinant of major chronic health conditions, including cerebrovascular disease\(^57\) and insulin resistance,\(^5\) even among individuals with ‘normal’ fetal growth. Our study adds to the evidence by showing the association of length of gestation with adult stature and BP remaining after rigorous adjustment for potentially confounding family factors.

**Strengths and limitations**

Our study is based on a very large and representative sample of young Swedish men. The large sample size of our study provides not only highly precise effect estimates but also independent effects of gestational age and birth weight. The large nationwide databases allow us to identify men from the same family, enabling family-based analyses that separate within- and between-family associations. Comparing brothers within the same family is important because only a limited range of maternal and family characteristics were available to control as potential confounders in the data. Data on gestational age and birth weight were obtained from the prospectively collected national birth registry rather than by maternal report, and the result is thus not subject to recall bias. A validation study on the quality of data from the Swedish Medical Birth Registry confirmed the validity of data on gestational age, birth weight, maternal age and parity.\(^58\) Because the men in our study were born prior to routine ultrasound dating, gestational age was based on maternal report of her last menstrual period. However, as this information was obtained before completion of pregnancy, measurement errors should be non-differential. Measurement errors for outcomes are also possible, including rounding preferences in BP measures, as illustrated in a previous study based on the same data source.\(^36,47\) However, it is unlikely that such errors would differ by gestational age or between siblings. Our study is based only on men, and thus the associations we observed may not be generalizable to women. Moreover, the effects we observed remain susceptible to residual confounding by other maternal and family factors. While our family-based approach improves control for these factors, the improvement is limited to factors common to siblings. Thus, the effects we found within brothers might be explained by maternal and family determinants of gestational age and fetal growth that can vary from one pregnancy to another, such as smoking or family economic conditions.\(^17\)

In summary, gestational age in completed weeks was inversely associated with SBP and positively associated with adult height and intellectual performance independent of birth weight even among men born at term. The association with intellectual performance is, however, likely to be explained by shared family characteristics, as it is not observed among brothers within the same families. Although the associations observed in our study are small in magnitude, truly causal effects, even if small, could result in shifts of the entire population distribution of the outcomes.\(^59\) The recent decline in gestational age, largely the result of increased fetal surveillance and labour induction,\(^60–62\) underlines the potential importance of these effects for population health. Future studies should attempt to understand the pathophysiological mechanisms underlying the associations.

**Conflict of interest:** None declared.
KEY MESSAGES

- Relatively little is known about variations in later health outcomes by gestational age among term births since they are often assumed to be homogeneous.
- This study examined variations in height, BMI, blood pressure, and intellectual performance by gestational age and fetal growth (birth weight for gestational age) among young men born at term (37–41 weeks of gestation), comparing the associations among men from different families and among full brothers.
- Each additional week of gestation was associated with increased height and intellectual performance and decreased systolic blood pressure in the overall cohort. The associations with height and systolic blood pressure were also observed among full brothers, suggesting that the associations are unlikely to be explained by shared family characteristics.

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References


