Risks for Low Intellectual Performance Related to Being Born Small for Gestational Age Are Modified by Gestational Age

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ABSTRACT

OBJECTIVE. We sought to study whether the association between being born small for gestational age and risk for low intellectual performance was modified by gestational age.

METHODS. A population-based cohort study was conducted of 352 125 boys who were born between 28 and 43 completed weeks of gestation from 1973 to 1981 in Sweden. Risk for low intellectual performance at military conscription, estimated as odds ratios with 95% confidence intervals was measured.

RESULTS. Compared with men who were born preterm (28–36 weeks) and had normal birth weight for gestational age, men who were born preterm and had a very low birth weight for gestational age were not at increased risk for low intellectual performance. In contrast, men who were born preterm with a very short birth length or a very small head circumference for gestational age faced a near doubled risk for low intellectual performance compared with their appropriate peers. Among men who were born at term (37–41 weeks), risk for low intellectual performance was increased among those with very or moderately small birth weight, birth length, or head circumference for gestational age.

CONCLUSIONS. During early stages of gestation, growth in length and head circumference may be more important for intellectual development than weight increase. Future studies on size at birth and intellectual performance should consider also including anthropometric measurements other than birth weight.
Intellectual performance, cognitive function, and academic achievement are independently associated with both gestational age and measures of fetal growth. We showed previously that risks for low intellectual performance related to short gestational age and indicators of reduced fetal growth (low birth weight, short birth length, and a small head circumference for gestational age) remain after controlling for socioeconomic and familial factors.

It has been hypothesized that the impact of fetal growth restriction on the child’s long-term cognitive and motor development varies with gestational age at birth. A number of studies reported increased risks for low intellectual performance and poor cognitive development among growth-restricted infants who were delivered at or near term. Whether fetal growth restriction influences the long-term intellectual performance in preterm infants is still disputed. In the present nationwide Swedish study, we investigated whether the associations between anthropometric measurements at birth and risks for low intellectual performance in early adulthood are modified by gestational age.

METHODS

Data Sources
The methods of this nationwide Swedish cohort study are described in detail elsewhere. Briefly, we included information from 4 population-based registries: the Swedish Medical Birth Register, the Swedish Conscript Register, the Multi-Generation Register, and the Population and Housing Census of 1990. Record linkage was possible using the unique National Registration Number that is assigned to each Swedish resident at birth. We used the Medical Birth Register to collect data on mother’s age and parity and infant’s birth weight, birth length, head circumference, and gestational age. The Medical Birth Register was validated recently, and the quality of the variables that were included in the present investigation is considered high. The Swedish Conscript Register includes information about Swedish men who were conscripted for military service. The conscription examination is mandatory and enforced by law. The registry was used to collect data on intellectual performance at conscription. The Multi-Generation Register was used to identify full-brothers in the study population. The Population and Housing Census of 1990 was used to collect information on households’ highest socioeconomic and education categories and households’ family structure.

Study Cohort
Nonmalformed singleton male individuals who were born to Nordic mothers between 1973 and 1981 were identified in the Swedish Birth Register. The cohort was restricted to male individuals who were born between 28 and 43 completed weeks of gestation and were alive at 18 years. Of all 401,264 male individuals, 377,527 (94%) were conscripted between 1991 and 2000. Of the conscripted male individuals, 357,768 (95%) had information on intellectual performance. We analyzed only those with complete data on gestational age, birth weight, birth length, head circumference, and intellectual performance (n = 352,125; ie, 93% of all conscripted male individuals).

Measures
Birth weight, birth length, and head circumference for gestational age were standardized according to the Swedish birth weight, birth length, and head circumference standards and expressed in SD scores (SDS) for gestational age. More than 2 SDS below the mean birth weight for gestational age was defined as very low birth weight for gestational age, between −2 and −1 SDS as moderately low birth weight for gestational age, between −1 and 1 SDS as appropriate birth weight for gestational age, between 1 and 2 SDS as moderately high birth weight for gestational age, and >2 SDS as very high birth weight for gestational age. Definitions for birth length and head circumference followed the same procedure. Gestational age was estimated from the date of the last menstrual period and stratified into preterm (28–36 completed weeks), term (37–41 weeks), and postterm births (42–43 weeks). Growth in height was calculated by subtracting standardized birth length for gestational age (SDS) from standardized height (in SDS) at conscription.

At conscription, intellectual performance is measured through a time-limited test in 4 dimensions: logical/inductive, verbal, spatial, and theoretical/technical. The test consists of 160 questions, 40 for each dimension. The results on intellectual performance are presented as standard 9 (stanine) scores. Low intellectual performance was defined as a score of ≤2, which is considered to be associated with difficulties in coping with basic educational programs.

The variables from the Population and Housing Census were classified according to recommendations set fourth by Statistics Sweden. Within each household, we used the highest socioeconomic and education categories. The family structure of the household was categorized as 1 of the following: living with both biological parents, living only with biological mother, living only with biological father, and living with neither biological parent.

Loss to Follow-up
Birth weight was available for almost all male individuals (99.9%) in the study population (n = 401,264), irrespective of gestational age. Missing values for birth length and head circumference varied across gestation in
the study population. Among those who were born preterm (28–36 weeks), 2.2% had no information on birth length and 3.3% had no information on head circumference. Corresponding figures for those who were born at term (37–41 weeks) were 0.2% and 0.9%, respectively. Conscription rates varied slightly by gestation and by birth characteristics. Those who were born preterm had lower conscription rates than those who were born at term: 92% and 94%, respectively. Those who were born very small for gestational age (less than –2 SDS) had lower conscription rates than their appropriate peers, regardless of whether they were born preterm or at term. For example, among preterm-born male individuals, conscription rates among those who were born with very low (less than –2 SDS) and appropriate birth weight for gestational age (–1 to 1 SDS) were 90% and 93%, respectively. Similar results were found for birth length for gestational age. For head circumference for gestational age, there were no differences in conscription rates. Among conscripted male individuals, those who were born with a very low birth weight, very short birth length, or a very small head circumference for gestational age more often lacked measurements on intellectual performance compared with their appropriate peers. For example, among those who were born preterm with a very low birth weight for gestational age, 88% had measurements on intellectual performance, whereas among their appropriate peers, 93% had data on intellectual performance.

**Statistical Methods**
The cohort was analyzed with multiple logistic regression equations to adjust for correlation between full siblings. Risks were presented as odds ratios (ORs) with 95% confidence intervals (CIs). Multivariate logistic-regression analyses were tested in 2 models. In the first model, we adjusted only for maternal characteristics, whereas in the second model, we also adjusted for the influence of other anthropometric measures at birth. Included covariates are listed in the footnotes to the tables and have been described in detail elsewhere.*

**RESULTS**
In preterm births (28–36 weeks), the highest rates of low intellectual performance were found among male individuals who were born with a very small head circumference for gestational age (less than –2 SDS), a very short birth length for gestational age (less than –2 SDS), and a very high birth weight for gestational age (>2 SDS; Table 1). In term (37–41 weeks) and postterm (42–43 weeks) births, male individuals with very low birth weight, very short birth length, or a very small head circumference for gestational age had higher rates of low intellectual performance than male individuals with higher birth weight, longer birth length, and larger head circumference for gestational age, respectively. To investigate further whether the association between size at birth and intellectual performance varied by gestational age, we formally tested for interactions between gestational age and anthropometric measures at birth, using the categories presented in Table 1. Significant interactions were found between gestational age and birth weight for gestational age (P < .01), birth length for gestational age (P < .01), and head circumference for...
gestational age ($P = .03$). The analyses of risk for low intellectual performance related to birth weight, birth length, and head circumference for gestational age therefore were stratified by gestational age.

In the crude model and in the model adjusted for maternal factors, very and moderately low birth weights for gestational age were associated with increased risks for low intellectual performance, irrespective of gestational age (Table 2). After adjustments for maternal factors, the increase in risk for low intellectual performance associated with very low birth weight for gestational age was ~50% across all gestational age categories. However, when we also adjusted for birth length and head circumference for gestational age, very low birth weight for gestational age was no longer associated with an increased risk for low intellectual performance among male individuals who were born preterm (OR: 0.77; 95% CI: 0.49–1.19). Among male individuals who were born at term and postterm, very low birth weight for gestational age, after adjustment for birth length and head circumference for gestational age, was still associated with an increased risk for low intellectual performance.

Among male individuals who were born very short for gestational age, risk for low intellectual performance was more pronounced among preterm compared with term- and postterm-born male individuals, irrespective of whether we adjusted only for maternal factors or also adjusted for birth weight and head circumference for gestational age (Table 3). Among male individuals who were born preterm, we found that those who were very short for gestational age had an almost 80% increase in risk for low intellectual performance compared with male individuals with an appropriate birth length for gestational age (~1 to 1 SDS; Table 3, model 2). Among male individuals who were born very short for gestational age at term or postterm, corresponding increases in risks were substantially lower, 23% and 21%, respectively. Male individuals who were born preterm and were very or moderately long for gestational age were also at increased risk for low intellectual performance.

A very small head circumference for gestational age, similar to a very short birth length for gestational age, was foremost associated with risk for low intellectual performance in male individuals who were born preterm (Table 4). Compared with male individuals who were born preterm with an appropriate head circumference for gestational age, those who were born preterm with a very small head circumference for gestational age had a near doubled increase in risk for low intellectual performance, after adjustment for maternal factors and birth weight and birth length for gestational age. In contrast, among male individuals who were born at term, those who were born with a very small head circumference for gestational age experienced only a 24% increase in risk, whereas a very small head circumference for gestational age was not associated with risk for low intellectual performance.

### Table 2

<table>
<thead>
<tr>
<th>Birth Weight, SDS</th>
<th>Gestational Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preterm (28–36 wk)</td>
</tr>
<tr>
<td>Crude model</td>
<td></td>
</tr>
<tr>
<td>Less than $-2$</td>
<td>1.34 (1.01–1.79)</td>
</tr>
<tr>
<td>$-2$ to $-1$</td>
<td>1.59 (1.37–1.85)</td>
</tr>
<tr>
<td>$-1$ to $0$*</td>
<td>1.00</td>
</tr>
<tr>
<td>1 to 2</td>
<td>1.07 (0.92–1.25)</td>
</tr>
<tr>
<td>$&gt;2$</td>
<td>1.60 (1.27–2.00)</td>
</tr>
<tr>
<td>Adjusted model 1b</td>
<td></td>
</tr>
<tr>
<td>Less than $-2$</td>
<td>1.50 (1.09–2.08)</td>
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<tr>
<td>$-2$ to $-1$</td>
<td>1.58 (1.34–1.87)</td>
</tr>
<tr>
<td>$-1$ to $0$*</td>
<td>1.00</td>
</tr>
<tr>
<td>1 to 2</td>
<td>1.04 (0.88–1.23)</td>
</tr>
<tr>
<td>$&gt;2$</td>
<td>1.29 (1.00–1.67)</td>
</tr>
<tr>
<td>Adjusted model 2c</td>
<td></td>
</tr>
<tr>
<td>Less than $-2$</td>
<td>0.77 (0.49–1.19)</td>
</tr>
<tr>
<td>$-2$ to $-1$</td>
<td>1.34 (1.09–1.64)</td>
</tr>
<tr>
<td>$-1$ to $0$*</td>
<td>1.00</td>
</tr>
<tr>
<td>1 to 2</td>
<td>0.99 (0.82–1.20)</td>
</tr>
<tr>
<td>$&gt;2$</td>
<td>1.15 (0.82–1.62)</td>
</tr>
</tbody>
</table>

* Served as reference group.

b Adjusted for year of conscription, mother’s age at delivery, parity, household’s highest socioeconomic status, household’s highest education, and household’s family structure.

c Adjusted for all variables in adjusted model 1 and birth length and head circumference for gestational age.

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**Table 2** ORs of Low Intellectual Performance in Relation to Birth Weight for Gestational Age Stratified by Gestational Age: Men Who Were Born 1973–1981 and Conscripted for Military Service 1991–2000

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**Table 3**

- Among male individuals who were born preterm, we found that those who were very short for gestational age had an almost 80% increase in risk for low intellectual performance compared with male individuals with an appropriate birth length for gestational age (~1 to 1 SDS; Table 3, model 2). Among male individuals who were born very short for gestational age at term or postterm, corresponding increases in risks were substantially lower, 23% and 21%, respectively.
- Male individuals who were born preterm and were very or moderately long for gestational age were also at increased risk for low intellectual performance.

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**Table 4** Among male individuals who were born very short for gestational age, risk for low intellectual performance was more pronounced among preterm compared with term- and postterm-born male individuals, irrespective of whether we adjusted only for maternal factors or also adjusted for birth weight and head circumference for gestational age.
performance in male individuals who were born postterm (Table 4).

To investigate whether the effect of birth characteristics on risk for low intellectual performance was independent of postnatal growth, we also added BMI and growth in height as covariates to the final models presented in Tables 2 to 4. Among preterm-born male individuals, there was a slight increase in risk among male
individuals who were very short for gestational age (OR: 1.85; 95% CI: 1.22–2.81), whereas corresponding risk for those who were born very long for gestational age decreased (OR: 1.17; 95% CI: 0.78–1.75). These differences were largely attributable to the adjustment for growth in height. Risks for low intellectual performance decreased with increasing growth in height: those who are born very short for gestational age generally have a large growth in height, whereas those who are born very long for gestational age have small growth in height. We also tested including BMI and growth in height in the analyses of birth weight and head circumference for gestational age. However, results were similar to those presented in Tables 2 and 4 (data are available on request).

We also attempted to study the preterm births stratified into very preterm (28–31 weeks) and moderately preterm (32–36 weeks) births. However, the group of male individuals who were born very preterm was too small to permit meaningful analyses of birth characteristics and risk for low intellectual performance. The results were nonsignificant in all but 1 group: among very preterm–born male individuals, those who were born with a very small head circumference for gestational age (less than −2 SDS) had a nearly eightfold increase in risk for low intellectual performance (OR: 7.82; 95% CI: 1.56–39.13), compared with male individuals who were born with an appropriate head circumference for gestational age. The results found in the moderately preterm group were almost identical to those reported for the preterm group in Tables 2 to 4 (data are available on request).

**DISCUSSION**

The impact of a very small head circumference and a very short birth length for gestational age on risk for low intellectual performance seems to be more severe in earlier stages of gestation. In contrast, the increased risk for low intellectual performance related to a very low birth weight for gestational age seems to be restricted to term and postterm births, when adjusting for birth length and head circumference for gestational age.

It has been suggested that preterm-born infants with a low birth weight for gestational age may be especially vulnerable, as they are exposed to a short gestational period as well as restricted fetal growth. However, results from previous studies are partly conflicting, possibly as a result of differences in sample size, definitions of fetal growth restriction, range of gestational ages and birth weights, and duration of follow-up. Some studies reported that the importance of birth weight on neonatal and neurodevelopmental outcome was lower than that of gestational age. Other studies found no significant differences between preterm infants who were born with a low and appropriate birth weight for gestational age with regard to intelligence, neurodevelopmental outcome, and brain and mental development. In contrast, Hutton et al found that a low birth weight for gestational age predicted intelligence in childhood in preterm infants, whereas gestation did not. McCarton et al found that infants who are small for gestational age, irrespective of prematurity, are at increased risk for neurodevelopmental impairment compared with their appropriate peers. A recent study also suggested that intrapartum growth restriction has specific structural and functional consequences on cerebral cortical brain development in preterm-born infants, which could lead to impaired long-term neurodevelopmental outcome. Results from the present study indicate that birth length and head circumference for gestational age seem to predict cognitive function better than birth weight for gestational age among preterm-born infants.

When we included all 3 anthropometric measurements at birth in the adjusted models, we found that, among preterm-born male individuals, a short birth length and a small head circumference for gestational age but not a low birth weight for gestational age were associated with increased risks for low intellectual performance in young adulthood. Early studies have hypothesized that fetal length increases primarily in the second trimester, whereas fetal weight increases foremost during the third trimester. A recent study found that differences in abdomen circumference in utero between those who are born small and large at birth largely increases with increasing gestational age, whereas differences in femur diaphysis length and head circumference increase mainly during the second and early third trimesters. These and our results suggest that birth length and head circumference are better proxies of in utero growth restriction than birth weight for gestational age among preterm-born male individuals.

Previous studies have concluded, through 3-dimensional ultrasound, that head circumference is strongly correlated with brain volume. A small head circumference for gestational age in preterm-born infants therefore most likely is a sign of early fetal growth restriction of the brain. Preterm-born infants, especially very preterm–born infants, face a substantial risk for intracranial hemorrhage, which may be increased further if fetal growth is also affected. Preterm infants are also at high risk for white matter lesions, which are associated with reduced brain volume and later cognitive dysfunction. Studies of adolescents have also shown that brain abnormalities are more common among individuals who are born preterm compared with those who are born at term. Thus, a small head circumference for gestational age is more likely to be associated with pathologic prenatal brain development among preterm than term infants and to have a larger impact on intellectual performance later in life.

The study population was homogeneous, which reduces the influence of unmeasured confounding factors.
We also excluded male individuals who were born with congenital malformations. Although the overall con-
scription rate was high (94%), conscription rates varied
slightly by gestational age and anthropometry at birth:
slightly lower conscription rates were obtained among
preterm- compared with term-born male individuals
and among male individuals who were born small for
gestational age compared with their appropriate peers.
These and other findings suggest that we may have a
bias toward a healthy population and, if anything, could
have underestimated the associations among preterm
birth, fetal growth restriction, and risks for low intellec-
tual performance.

CONCLUSIONS
The present study concludes that impaired fetal growth
increases the risk for low intellectual performance across
all stages of gestation. However, it seems that during
early stages of gestation, skeletal growth and brain vol-
une (as measured by birth length and head circumfer-
ence) are more important for intellectual development
than increase in weight. As the time of onset of fetal
growth restriction may influence the long-term progno-
sis of intellectual performance, we suggest that future
studies within this field consider also including other
dimensions of size at birth, such as birth length and head
circumference.

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