Associations of Gestational Age and Intrauterine Growth With Systolic Blood Pressure in a Family-Based Study of 386 485 Men in 331 089 Families

Debbie A. Lawlor, PhD; Anna Hübinette, PhD; Per Tynelius, MSc; David A. Leon, PhD; George Davey Smith, DSc; Finn Rasmussen, PhD

Background—We conducted a family-based study to explore mechanisms underlying the associations of birth weight and gestational age with systolic blood pressure measured at 17 to 19 years of age.

Methods and Results—A record linkage study of 386 485 singleton-born men from 331 089 families was undertaken. Birth weight was inversely associated with systolic blood pressure within siblings, with a mean difference (adjusted for age at examination, examination center, and year of examination) within siblings per 1-SD difference in birth weight of −0.21 mm Hg (95% CI, −0.33 to −0.08) and between nonsiblings of −0.12 (95% CI, −0.16 to −0.08). Gestational age was inversely associated with systolic blood pressure within siblings (−0.18 mm Hg; 95% CI, −0.25 to −0.11, per week of gestational age) and between nonsiblings (−0.26 mm Hg; 95% CI, −0.29 to −0.24). Adjustment for socioeconomic position and maternal characteristics did not alter these within- or between-family associations. Furthermore, the associations were not affected by adjustment for paternal height, body mass index, or systolic blood pressure.

Conclusions—Our present findings suggest that the inverse associations of birth weight and gestational age with systolic blood pressure are not explained by confounding resulting from family socioeconomic position or other factors that are shared by siblings. Variations in maternal metabolic or vascular health during pregnancy or placental implantation and function may explain these associations. (Circulation. 2007;115:562-568.)

Key Words: birth weight ■ blood pressure ■ epidemiology ■ fetal development ■ pediatrics

A large number of studies have shown birth weight to be inversely associated with blood pressure, with 5 systematic reviews concluding that the magnitude of this association lies in the range of −1 to −2 mm Hg per 1 kg birth weight.1-5 More recently some studies have found that, independent of birth weight, having an earlier gestational age and/or preterm birth is associated with higher blood pressure,6-8 increased stroke risk,9,10 insulin resistance, and diabetes.11,12 The developmental origins hypothesis suggests that fetal undernutrition results in poor fetal growth and an earlier gestational age and that this fetal undernutrition programs (via effects on hormonal and organ development) elevated blood pressure in later life.7,13,14 Alternatively, it has been suggested that genetic variants with pleiotropic effects that influence both fetal growth and later blood pressure explain the association.15 Finally, some have suggested that the association is explained by publication bias, residual confounding, or inappropriate adjustment for contemporary body size.4,16

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Several investigators have compared the magnitude of the birth weight–blood pressure association in monozygotic to that in dizygotic twins to determine whether fetal genotype or nongenetic factors explain the association.17,18 A systematic review of these studies concluded that it was impossible to determine whether true differences existed because of the small sample sizes of individual studies and the variations between studies in the methods used to determine zygosity.17 A further problem with twin studies is the difficulty in assigning the correct birth weight to each individual within a twin pair.19 Twin studies could not provide insights into the mechanisms explaining the associations of gestational age with blood pressure because, by definition, twins have the same gestational age. Importantly, the relevance of associations in twins to the associations found in the general population of singletons is unclear given the very different fetal growth trajectories between twins and singletons.19,20

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Factors that influence birth size and gestational age can be broadly categorized into those that vary from one pregnancy to the next in the same mother (eg, fetal genotype, placental implantation and function, maternal age, parity, and pregnancy complications) and factors that are fixed for full siblings (eg, family socioeconomic background, maternal genotype, maternal pelvic size, and maternal exposures across her life course up to the birth of her first child).\(^6\) Sibling studies provide a useful method for distinguishing between fixed maternal/family characteristics and those factors that vary between full siblings in explaining the associations between perinatal exposures and later outcomes. Such sibling studies have been used to examine the mechanism underlying the association of birth weight with childhood intelligence,\(^22–25\) but to the best of our knowledge, only 2 previous studies have used this design to explore the association of birth weight with blood pressure.\(^21,26\)

In one of those studies, the association of birth weight with hypertension was similar within siblings and between nonsiblings in analyses that included 89 856 sibling sets.\(^26\) Associations across the blood pressure distribution were not assessed.\(^26\) In a second study, which included 600 sibling pairs, there were similar within- and between-family associations between birth weight and mean blood pressure.\(^21\) Neither of these studies examined family effects on the association of gestational age with blood pressure. The aim of the present study was to explore the mechanisms underlying the associations of birth weight and gestational age with systolic blood pressure in a population-based prospective record linkage study including 386 485 Swedish men from 331 089 families.

### Methods

The present study consists of all men born in Sweden between 1973 and 1984 who were still alive and completed their conscription medical examination (n = 413 683), which took place during 1990 to 2001. Date of birth of the index participant, mother’s age at birth, and the parents’ unique identity numbers (used to generate a family identification to identify full siblings) were extracted from the Swedish Multi-Generation Register. A linkage was made between these data and the Swedish Medical Birth Register,\(^27\) the Swedish Military Service Conscription Register, and the Population and Housing censuses of 1970, 1980, and 1990. The Regional Ethics Committee, Stockholm approved these linkages. We excluded multiple births, anyone with implausible extreme values, and anyone with missing data on any variables included in the present study.\(^6\)

After these exclusions, the study population comprised 386 485 men (93\% of eligible men).

Data on birth weight were measured by midwives or physicians shortly after birth, and other obstetric and perinatal factors were taken directly from the obstetric records and entered into the Medical Birth Register. Gestational age was assessed from the first day of the last menstrual period. The International Classification of Diseases, 9th revision, codes used to define a diagnosis of diabetes (either preexisting or gestational) during pregnancy were 250 and 648; those used to define a diagnosis of hypertension (preexisting or gestational, including preeclampsia or eclampsia) were 401 through 405 and 642.\(^6\)

During the years covered by the present study, it was a legal requirement that all Swedish men attend the Swedish military service conscription examination. Height and weight were measured using standard procedures with the men in underclothes and without shoes. Blood pressure was measured after 5 to 10 minutes of rest in the supine position. If the systolic blood pressure was ≥145 mm Hg and the diastolic blood pressure was between 50 and 85 mm Hg, no further measurements were made. If the measurements were outside these limits, a second measure was made, and the result of the second measure was entered into the register. For diastolic blood pressure, there was evidence of digit preference (heaping of values) to the nearest 10 mm Hg; this was less of a problem for systolic blood pressure, which tended to be rounded to the nearest 2 mm Hg.\(^6\) We therefore assessed only associations with systolic blood pressure.

Occupational social class of the parents was recorded in the 1970, 1980, and 1990 census records and was coded as manual, nonmanual, entrepreneur or farmer, and other. A household measure was created by taking the highest value of the father or mother. For those born in the 1970s, childhood social class was obtained from the 1970 census; for those born in the 1980s, it was obtained from the 1980 census. For all study subjects, social class also was taken from the 1990 census. Thus, we were able to adjust for family social class at 2 time points (the first around the time of birth or early childhood, and second around adolescence).\(^9\)

Birth weight z scores for gestational age (specific to each completed week) were derived using the total study population as the standard. To compare the within-sibling and between-nonsibling associations, we used random-effects linear regression models that take into account clustering within families.\(^21,29\) Each model involved running 2 regressions simultaneously. The first regression obtains the within-sibling association by regressing the difference in blood pressure between siblings who belong to the same family on their differences in birth weights or gestational age. The second regression obtains the between-nonsibling effect by regressing the mean blood pressure of sibling groups on their mean birth weight or gestational age. The random effects regression coefficients (combined coefficients) were then obtained as the weighted average of the within-sibling and between-nonsibling effects, each coefficient weighted by the inverse of its variance.\(^21,29\) This coefficient represents the overall association between birth weight or gestational age and systolic blood pressure in the cohort while taking into account possible nonindependence between siblings. The Hausman test was used to test whether the within-sibling and between-nonsibling associations differed from each other.\(^29\)

In the basic model, we adjusted for age at conscription examination, examination center, and year of examination.\(^6\) In our main analyses, we did not adjust for height and body mass index assessed at the same time as blood pressure because it has been argued that this adjustment is inappropriate.\(^16\) Because most previous studies have presented results adjusted for contemporary size, however, we did undertake these adjustments and present them in the present report for comparison with earlier studies.

It is established that the firstborn infant is smaller, by on average 200 g, than the second or subsequent infants, and it has been suggested that the association of birth weight with later outcomes may be stronger in firstborn compared with other infants, although few studies have formally tested this hypothesis.\(^30,31\) To examine whether parity influenced the associations examined here, we first tested whether the associations varied by parity in the whole cohort by undertaking stratified analyses (first, second, third, fourth, or greater completed pregnancy) and including an interaction term in our regression models. We then repeated the sibling-based analyses, including only those families in which 2 siblings were the firstborn and second-born. To determine whether our findings were influenced by individuals with extreme values of blood pressure, we repeated the analyses with those in the top and bottom 5\% of the distribution removed. The findings were not altered with these exclusions. Furthermore, we examined whether the associations were uniform...
across the distribution of blood pressure by examining them within each 10h of the distribution; the associations were uniform across the study sample blood pressure distribution.

The authors had full access to the data and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

The 386 485 men in this cohort belonged to 331 089 families; 103 548 men had at least 1 sibling within the cohort. Characteristics of those with at least 1 sibling in the cohort were similar to those for the cohort as a whole (Table 1). The mean age difference between the siblings was 3.0 years (SD, 1.3 years), with a range of 11 months to 8 years. For 94% of the families, all siblings were examined at the same examination center.

Table 2 shows the multivariable associations of birth weight and gestational age with systolic blood pressure within siblings and between nonsiblings, with these associations being unaffected by adjustment for indicators of family socioeconomic position (model 3). There was weak statistical evidence that the within-sibling inverse association between birth weight and systolic blood pressure was greater than the between-sibling inverse association (P for difference in effect=0.07 in the fully adjusted models) and that the opposite was true for the inverse association of gestational age with systolic blood pressure (ie, greater between nonsiblings than within siblings; P for difference in effect=0.02 in the fully adjusted model).

Of the 386 485 participants, 1339 (0.4%) had been exposed to maternal diabetes and 260 (0.1%) to maternal hypertension during their intrauterine period. Maternal diabetes during pregnancy was associated with greater birth weight (mean difference in birth weight z score comparing those whose mothers experienced diabetes with those whose mother did not from the random-effects model, 0.42; 95% CI, 0.37, 0.47), lower mean gestational age (−1.57 weeks; 95% CI, −1.65 to −1.48), and elevated systolic blood pressure

**TABLE 1. Characteristics of 386 485 Singleton-Birth Men Born in Sweden Between 1973 and 1984 and of 103 548 Men From Within This Cohort Who Have at Least 1 Sibling in the Cohort**

<table>
<thead>
<tr>
<th></th>
<th>Whole Cohort (N=386 485)</th>
<th>Participants With at Least 1 Sibling in the Cohort (N=130 548)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight, g</td>
<td>3603.7 (503.6)</td>
<td>3625.6 (494.6)</td>
</tr>
<tr>
<td>Gestational age, weeks</td>
<td>39.76 (1.55)</td>
<td>39.78 (1.51)</td>
</tr>
<tr>
<td>Age, y*</td>
<td>18.2 (0.3)</td>
<td>18.2 (0.3)</td>
</tr>
<tr>
<td>Height, cm*</td>
<td>179.9 (6.5)</td>
<td>179.9 (6.5)</td>
</tr>
<tr>
<td>BMI, kg/m²*</td>
<td>22.4 (3.2)</td>
<td>22.3 (3.2)</td>
</tr>
<tr>
<td>Systolic BP, mm Hg*</td>
<td>128.7 (11)</td>
<td>128.5 (10.9)</td>
</tr>
</tbody>
</table>

*Assessed at military conscription examination.

**TABLE 2. Mean Difference in Systolic Blood Pressure per Birth Weight z Score (SD) and per Week of Gestational Age Within Siblings and Between Nonsiblings**

<table>
<thead>
<tr>
<th></th>
<th>Difference Within Siblings</th>
<th>Difference Between Nonsiblings</th>
<th>P for Difference of Within Siblings and Between Nonsiblings</th>
<th>Combined (Overall) Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per birth weight z score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>−0.21 (−0.33 to −0.08)</td>
<td>−0.12 (−0.16 to −0.08)</td>
<td>0.10</td>
<td>−0.13 (−0.16 to −0.09)</td>
</tr>
<tr>
<td>Model 2</td>
<td>−0.24 (−0.36 to −0.11)</td>
<td>−0.12 (−0.16 to −0.08)</td>
<td>0.05</td>
<td>−0.13 (−0.17 to −0.10)</td>
</tr>
<tr>
<td>Model 3</td>
<td>−0.22 (−0.35 to −0.10)</td>
<td>−0.12 (−0.15 to −0.08)</td>
<td>0.07</td>
<td>−0.13 (−0.16 to −0.09)</td>
</tr>
<tr>
<td>Model 4</td>
<td>−0.22 (−0.35 to −0.10)</td>
<td>−0.12 (−0.16 to −0.08)</td>
<td>0.07</td>
<td>−0.13 (−0.16 to −0.09)</td>
</tr>
<tr>
<td>Per week of gestational age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>−0.18 (−0.25 to −0.11)</td>
<td>−0.26 (−0.29 to −0.24)</td>
<td>0.005</td>
<td>−0.26 (−0.28 to −0.23)</td>
</tr>
<tr>
<td>Model 2</td>
<td>−0.19 (−0.26 to −0.12)</td>
<td>−0.26 (−0.29 to −0.24)</td>
<td>0.01</td>
<td>−0.26 (−0.28 to −0.23)</td>
</tr>
<tr>
<td>Model 3</td>
<td>−0.19 (−0.26 to −0.12)</td>
<td>−0.25 (−0.27 to −0.23)</td>
<td>0.02</td>
<td>−0.25 (−0.27 to −0.23)</td>
</tr>
<tr>
<td>Model 4</td>
<td>−0.19 (−0.26 to −0.12)</td>
<td>−0.25 (−0.27 to −0.22)</td>
<td>0.02</td>
<td>−0.25 (−0.27 to −0.23)</td>
</tr>
</tbody>
</table>

Values are mm Hg; values in parentheses are 95% CIs. n=386 485 singleton-birth men from 331 089 families.

Model 1: adjusted for age at examination, examination center, and year of examination. Model 2: model 1 plus mutual adjustment for birth weight z score and gestational age. Model 3: model 2 plus adjustment for indicators of socioeconomic status (family occupational social class at birth and in later childhood/adolescence, maternal education, paternal education, maternal age, maternal parity). Model 4: model 3 plus adjustment for complications of pregnancy (maternal hypertension during pregnancy, maternal diabetes during pregnancy, antepartum hemorrhage, assisted delivery).
Maternal hypertension during pregnancy was associated with a lower birth weight (−0.31; 95% CI, −0.42 to −0.19), lower gestational age (−0.70 weeks; 95% CI, −0.89 to −0.51), and elevated systolic blood pressure (4.32 mm Hg; 95% CI, 3.01 to 5.63). Adjustment for these complications of pregnancy did not alter the inverse associations of birth weight or gestational age with systolic blood pressure (model 4, Table 2).

The results for birth weight in Table 2 are presented per SD (z score). The equivalent results expressed in terms of absolute birth weight indicate that within a family, if 1 sibling had on average a birth weight that was 1 kg greater than that of another sibling, his blood pressure at 18 years of age would be on average 0.49 mm Hg lower than that of the sibling with a lower birth weight (mean difference in systolic blood pressure, −0.49 mm Hg; 95% CI, −0.74 to −0.23). Furthermore, our results indicate that if the mean birth weight of all siblings in 1 family was 1 kg greater than the mean birth weight of all siblings in another family, the mean blood pressure in the first family will be on average 0.27 mm Hg lower than in the family with the lower birth weight (mean difference, −0.27; 95% CI, −0.34 to −0.19).

Body mass index and height assessed at the same time as blood pressure were positively associated with systolic blood pressure; change in systolic blood pressure per 1-SD-greater body mass index was 1.72 mm Hg (95% CI, 1.69 to 1.76) and per 1-SD-greater height was 1.02 mm Hg (95% CI, 0.90 to 1.15). With additional adjustment of the birth weight–systolic blood pressure association for the subject’s body mass index, the overall inverse association increased from −0.12 (model 4, Table 2) to −0.29 mm Hg per SD of birth weight (95% CI, −0.32 to −0.25). An increase in the inverse association also occurred with adjustment for height from −0.12 to −0.44 mm Hg per SD of birth weight (95% CI, −0.48 to −0.41). Adjustment for contemporary size resulted in similar increases in the within- and between-sibling associations of birth weight with systolic blood pressure. The inverse association of gestational age with systolic blood pressure was not affected by adjustment for body mass index or height.

For 112 292 (29%) of the 386 485 men in the main cohort, we had information on the fathers’ characteristics from the military medical examinations. The mean age of the fathers at the time of their examination was 18.7 years (SD, 0.8 years), mean height was 178.5 cm (SD, 6.2 cm), mean body mass index was 21.3 kg/m² (SD, 2.5 kg/m²), and mean systolic blood pressure was 127.1 mm Hg (SD, 11.1 mm Hg). Table 3 shows the correlations between fathers’ and sons’ characteristics in this subgroup. Within this subgroup, there were 95 651 families, with 16 645 individuals having ≥1 siblings in the cohort. Table 4 shows the effects of adjusting for paternal characteristics on the associations of birth weight and gestational age with systolic blood pressure in this subgroup with paternal data. These paternal characteristics are fixed within in each family, so the within-sibling associations could not be influenced by these adjustments. Additional adjustment of paternal characteristics had very little effect on the between-nonsibling associations (Table 4).

In the whole cohort, the associations of both birth weight and gestational age with systolic blood pressure were the same in firstborn, second-born, third-born, fourth-born, or greater (for interaction with either exposure and in all models, P>0.4). When the analyses were restricted to only firstborn and second-born (n=333 704 men from 294 443 families in the main analyses and n=103 965 men from 91 036 families in the analyses that also included adjustment for paternal characteristics), the associations were essentially the same as those presented in Tables 2 and 4.

**Discussion**

We have confirmed previous findings of an inverse association between birth weight and systolic blood pressure and added to the limited evidence of an independent inverse association of gestational age with systolic blood pressure.

In a previous publication based on a similar sample but with fewer birth cohorts and therefore participants, we also demonstrated inverse associations of birth weight and gestational age with systolic blood pressure. The present study advances these earlier publications by comparing associations within siblings with those between nonsiblings.

We found that the inverse associations of both birth weight and gestational age with later systolic blood pressure were present both within siblings and between nonsiblings. One previous study that included 600 sibling pairs also found within- and between-sibling associations of birth weight with mean systolic blood pressure. A previous study, which also used the Medical Birth Register and conscription data from Sweden but had fewer birth cohorts than we have included here and in which only associations of birth weight with hypertension were examined, noted that the odds ratio for high blood pressure at conscription per SD of birth weight was similar within siblings and between nonsiblings.

The presence of associations within siblings suggests that the associations we have examined are unlikely to be explained by maternal/familial characteristics that are very similar for full siblings because within siblings there will be full control for such characteristics. Factors that vary between siblings must explain the association. Our findings would be consistent with (1) fetal genetic variants that influence the exposures examined here (intrauterine growth and gestational age) and later blood pressure; (2) maternal behaviors that vary from one pregnancy to the next that influence fetal growth and later blood pressure; and (3) placental implantation.

**TABLE 3. Pearson Correlation Coefficients Between Fathers’ and Sons’ Characteristics**

<table>
<thead>
<tr>
<th>Fathers’ Characteristics</th>
<th>Systolic Blood Pressure</th>
<th>Body Mass Index</th>
<th>Height</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight</td>
<td>0.14</td>
<td>0.04</td>
<td>0.01*</td>
</tr>
<tr>
<td>Height</td>
<td>0.49</td>
<td>−0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>Body mass index</td>
<td>−0.02</td>
<td>0.28</td>
<td>0.05</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.04</td>
<td>0.04</td>
<td>0.12</td>
</tr>
</tbody>
</table>

*n=112 292. All measurements on both fathers and sons were done at the military conscription examinations when participants were 17 to 19 years of age. For all associations, P<0.001, except the one marked (*)P=0.005.*
tion and function, which vary between pregnancies and which influence fetal nutrition and hence growth and may result in programming of future blood pressure. With respect to this last explanation, maternal health, particularly the mother’s cardiovascular and metabolic health during pregnancy, might influence placental implantation and predict their own and their offspring’s future blood pressure.

In a previous family-based study, the between-sibling association of birth weight and systolic blood pressure attenuated with adjustment for both maternal and paternal blood pressures, with the effect of paternal blood pressure being somewhat stronger than that of maternal blood pressure.21 The authors interpreted the stronger and independent (of maternal blood pressure) association of birth weight and systolic blood pressure attesting to its importance in the programming of future blood pressure in offspring.

Maternal metabolic and vascular health may vary from one pregnancy to the next, which would affect fetal growth and gestational age. Both maternal diabetes and maternal hypertension during pregnancy were associated with offspring birth weight, gestational age, and later systolic blood pressure in this study. Adjustment for these maternal complications of pregnancy, however, did not alter the within-sibling or between-nonsibling associations. More subtle differences in maternal vascular function and metabolism between different pregnancies may influence both fetal growth and the offspring’s later blood pressure. Furthermore, it should be noted that we have obtained details on maternal diagnoses of diabetes and hypertension from routine clinical records; it is possible that some mothers remained undiagnosed and that we did not fully adjust for these conditions. Future studies with repeated measurements of maternal blood pressure and markers of lipid and glucose metabolism during pregnancy are required to determine their influence on both fetal growth and future blood pressure in offspring.

In a systematic review of all relevant studies, Huxley et al4 suggested that the reported inverse associations of birth weight with systolic blood pressure were exaggerated because of residual confounding, eg, by socioeconomic background, publication bias, and inappropriate adjustment for concurrent size. More recently, Tu et al16 have suggested that the exaggeration of the inverse association on adjustment for concurrent size indicates that most of this association can be explained by statistical artifact. Our present findings refute the suggestion that this association is explained by residual

### Table 4: Mean Difference in Systolic Blood Pressure per Birth Weight z Score (SD) and per week of Gestational Age Within Siblings and Between Nonsiblings With Adjustment for Father’s Characteristics

| Per birth weight z score | Difference Within Siblings (z) | Difference Between Nonsiblings (z) | P for Difference of Within Siblings and Between Nonsiblings | Combined (Overall) Difference z/
<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>−0.20 (−0.43 to 0.03)</td>
<td>−0.09 (−0.16 to −0.02)</td>
<td>0.60</td>
<td>−0.11 (−0.17 to −0.04)</td>
</tr>
<tr>
<td>Model 2</td>
<td>−0.20 (−0.43 to 0.03)</td>
<td>−0.15 (−0.22 to −0.08)</td>
<td>0.72</td>
<td>−0.16 (−0.23 to −0.09)</td>
</tr>
<tr>
<td>Model 3</td>
<td>−0.20 (−0.43 to 0.03)</td>
<td>−0.11 (−0.18 to −0.04)</td>
<td>0.63</td>
<td>−0.13 (−0.19 to −0.06)</td>
</tr>
<tr>
<td>Model 4</td>
<td>−0.20 (−0.43 to 0.03)</td>
<td>−0.10 (−0.17 to −0.03)</td>
<td>0.61</td>
<td>−0.11 (−0.18 to −0.05)</td>
</tr>
<tr>
<td>Per week of gestational age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>−0.19 (−0.31 to −0.07)</td>
<td>−0.26 (−0.31 to −0.22)</td>
<td>0.25</td>
<td>−0.26 (−0.30 to −0.22)</td>
</tr>
<tr>
<td>Model 2</td>
<td>−0.19 (−0.31 to −0.07)</td>
<td>−0.27 (−0.31 to −0.22)</td>
<td>0.20</td>
<td>−0.26 (−0.30 to −0.22)</td>
</tr>
<tr>
<td>Model 3</td>
<td>−0.19 (−0.31 to −0.07)</td>
<td>−0.26 (−0.31 to −0.22)</td>
<td>0.25</td>
<td>−0.26 (−0.30 to −0.22)</td>
</tr>
<tr>
<td>Model 4</td>
<td>−0.19 (−0.31 to −0.07)</td>
<td>−0.26 (−0.31 to −0.22)</td>
<td>0.25</td>
<td>−0.26 (−0.30 to −0.22)</td>
</tr>
</tbody>
</table>

Values are mm Hg; values in parentheses are 95% CIs. n = 112,292 singleton-birth men from 95,651 families.

Model 1: adjusted for age at examination, examination center and year of examination, birth weight, gestational age, indicators of socioeconomic position (family occupational social class at birth and in later childhood/adolescence, maternal education, paternal education, maternal age, maternal parity), and complications of pregnancy (maternal hypertension during pregnancy, maternal diabetes during pregnancy, antepartum hemorrhage, assisted delivery), ie, equivalent of model 4 in Table 2. Model 2: model 1 plus father’s height. Model 3: model 1 plus father’s body mass index. Model 4: model 1 plus father’s systolic blood pressure.
confounding by familial socioeconomic background and are consistent with some studies that have been able to adjust for socioeconomic position across the life course in this association.37 A recent cross-cohort comparison48 and large prospective cohort study39 suggested that publication bias does not fully explain a weak inverse association, consistent with our findings. Our present study demonstrates that there is a weak inverse association of systolic blood pressure on birth weight that does not depend on adjustment for concurrent size (We have not adjusted for concurrent size in our main analyses).

Our present study has the advantage of a large sample size, but some limitations need to be acknowledged. Measurement error, particularly in the assessment of systolic blood pressure, is likely to be larger than in studies that use standardized research protocols, and this may have resulted in an underestimate of the true magnitude of association between birth weight and gestational age with systolic blood pressure.6 It is unlikely that measurement error will differ between siblings and nonsiblings; therefore, any bias will not have influenced our sibling analysis. This is supported by the finding that within-sibling variation accounts for 53% of the total variation in systolic blood pressure in this cohort, which is comparable to other family-based studies with research standard measures of blood pressure in which the contribution of within-sibling variation to total variation is between 50% and 70%.

Blood pressure was assessed with the men in a supine position. Although this technique should not affect the results presented here, we should note that it may have resulted in a lower mean blood pressure than would have been found if measurements had been conducted with the participants seated. Assessment of gestational age was based on maternal report of her last menstrual period, which has been shown to slightly underestimate true gestational age.43 Because information on last menstrual period was has been shown to slightly underestimate true gestational age and clearly before assessment of offspring blood pressure, it will be nondifferential; as with measurement error in blood pressure, we cannot see any reason why this would bias our comparison of within- and between-sibling effects. We know that the individuals whom we have defined as full siblings were born to the same mother and registered as having the same father. We have no means of directly determining true paternity, however. Our present study was conducted in Swedish men, and the results are not necessarily generalizable to women.

The magnitude of the associations reported in the present study is small. Birth weight and gestational age are likely to be acting as proxies for the real intrauterine exposures (eg, fetal nutrition related to placentaion and/or maternal cardiovascular and metabolic health) that influence later blood pressure and therefore cannot provide information on the true magnitude of any effect of the primary causal risk factors. Furthermore, a recent large study demonstrated amplification of the association between birth weight and blood pressure with increasing age.39 In that study, the simple sex-adjusted association in those <25 years of age at the time of systolic blood pressure assessment (equivalent to our population) was −0.08 mm Hg (95% CI, −1.3 to 1.1) per 1 kg birth weight, whereas in those who had their blood pressure assessed at ≥55 years of age, it was −3.9 mm Hg (95% CI, −6.7 to −1.1).49 Thus, the associations we reported in the present study, with blood pressure assessed at mean age of 18 years, may become stronger as the cohort ages.

Our present findings suggest that the inverse associations of birth weight and gestational age with later blood pressure are not explained by confounding resulting from family socioeconomic position, maternal skeletal size, or factors from across the earlier part of a mother’s life course. The most likely explanations are that variations in maternal metabolic or vascular health (beyond frank diabetes or hypertension) during pregnancy and/or placental implantation and function explain the associations of birth weight and gestational age with later blood pressure. Future studies should aim to directly examine these associations.

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Disclosures
None.

References
A large number of studies have shown birth weight to be inversely associated with blood pressure, with 5 systematic reviews concluding that the magnitude of this association lies in the range of −1 to −2 mm Hg per 1 kg birth weight, but mechanisms underlying this association are unclear. The present family-based study was conducted to explore possible mechanisms underlying this association. A record linkage study was done of 386,485 singleton-born men from 331,089 families. Birth weight was inversely associated with systolic blood pressure within siblings, with a mean difference (adjusted for age at examination, examination center, and year of examination) within siblings per 1-SD difference in birth weight of −0.21 mm Hg (95% CI, −0.33 to −0.08) and between nonsiblings of −0.12 mm Hg (95% CI, −0.16 to −0.08). Gestational age also was inversely associated with systolic blood pressure within siblings (−0.18 mm Hg; 95% CI, −0.25 to −0.11 per week of gestational age) and between nonsiblings (−0.26 mm Hg; 95% CI, −0.29 to −0.24). Adjustment for socioeconomic position and maternal characteristics did not alter these within- or between-family associations. Furthermore, the associations were not affected by adjustment for paternal height, body mass index, or systolic blood pressure. These findings suggest that the inverse associations of birth weight and gestational age with systolic blood pressure are not explained by confounding as a result of family socioeconomic position or other factors that are shared by siblings. Further research is merited to determine whether variations in maternal metabolic or vascular health during pregnancy, placental implantation and function, or other factors explain these associations.
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